EV-TRACK: transparent reporting and centralizing knowledge in extracellular vesicle research

EV-TRACK Consortium*

We argue that the field of extracellular vesicle (EV) biology needs more transparent reporting to facilitate interpretation and replication of experiments. To achieve this, we describe EV-TRACK, a crowdsourcing knowledgebase (http://evtrack.org) that centralizes EV biology and methodology with the goal of stimulating authors, reviewers, editors and funders to put experimental guidelines into practice.

EVs have emerged as having important (patho)physiological roles, and as such they have been the focus of intense study over the past decade[1–4]. Despite substantial progress, the complexity and challenges associated with EV research remain considerable[5]. EVs released from different cell types (and even from a single cell type) are heterogeneous in size and in protein, nucleic acid and lipid content[6–9]. The isolation of EV populations is frequently complicated by the presence of contaminants with comparable features[10,11]. Different isolation methods enrich for single or multiple EV subtypes with diverse composition and variable purity, thus identifying method-dependent EV content and function[6–11]. Each detection and characterization method has its own accuracy and precision in measuring EVs[12,13]. Still, functional studies on EVs vastly outnumber those focusing on EV biology and methodology (**Supplementary Fig. 1**).

In EV research, as in any field, the implementation of different methods requires validated controls and adequate reporting of experimental parameters. Failure to follow these principles can result in data that are difficult to interpret and reproduce[14]. Similar to minimal information checklists in other fields[15–17], the International Society for Extracellular Vesicles (ISEV) introduced minimal informations for studies on EVs (MISEV) guidelines[18,19]. Nevertheless, EV research is unfolding at a rate that impedes widespread adoption of these guidelines.

We convened an international consortium to develop the EV-TRACK knowledgebase, which records experimental parameters of EV-related studies. EV-TRACK implements a bottom-up community consensus approach and encourages researchers to upload published and unpublished experiments and provide feedback. It is a unique resource that was developed to (i) create an informed dialog among researchers about relevant experimental parameters, (ii) improve the rigor and interpretation of experiments studying EVs, and (iii) record the evolution of EV research. The final goal of the EV-TRACK consortium is to facilitate standardization of EV research through increased systematic reporting on EV biology and methodology.

Creation of the EV-TRACK knowledgebase

Currently, the EV-TRACK knowledgebase comprises methodological specifications of 1,226 EV-related articles published in 2010–2015 (**Supplementary Fig. 2**). Publications that included multiple sample types or isolation methods were separated into multiple entries, resulting in 1,742 experiments (**Supplementary Methods**). For each experiment, we completed a checklist of 115 parameters—based partially on the MISEV guidelines[19]—relating to sample type, preanalytical variables, isolation protocol and characterization method (**Supplementary Table 1**). Data were curated before inclusion in the knowledgebase, which can be accessed freely at http://evtrack.org.

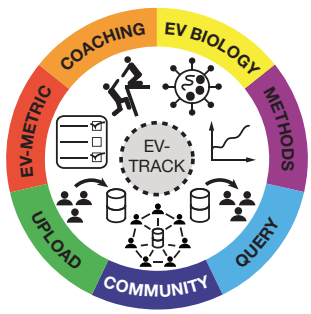

Figure 1 | The seven enabling features of the EV-TRACK platform.

EV research practices

To assess current practices in EV experiments, we performed an in-depth analysis of the data in the EV-TRACK knowledgebase. This revealed widespread heterogeneity in EV isolation methods and inconsistent implementation and reporting of important experimental parameters, including isolation methods and characterization of EV size, composition and purity (**Supplementary Fig. 3**).

The 1,742 experiments that are recorded in EV-TRACK report 190 unique isolation methods and 1,038 unique protocols to retrieve EVs from biofluids (**Supplementary Tables 2** and **3**). Differential ultracentrifugation (dUC) is the most popular method (45% of all experiments), but with variable parameters selected by researchers, even for experiments handling a similar sample type. For cell culture supernatant (n = 813 experiments using dUC), 218 unique combinations of centrifugation steps and final pelleting times are recorded, along with a

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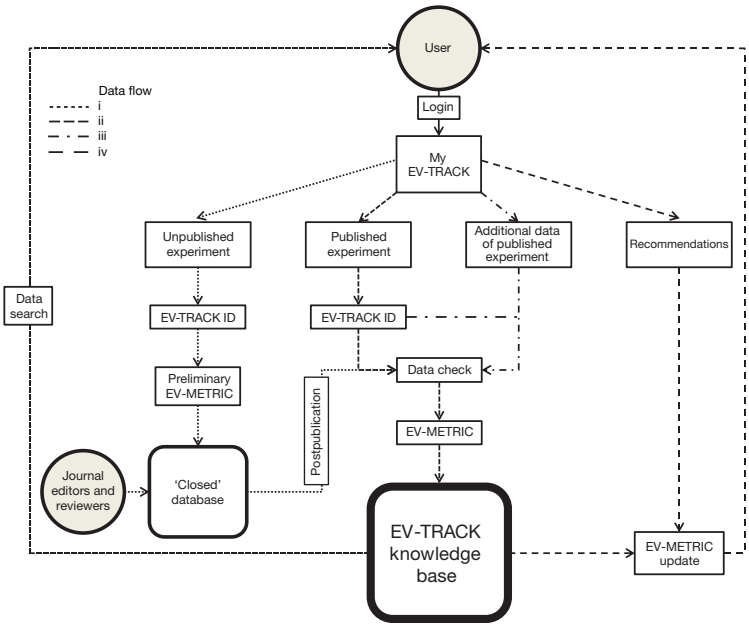

Figure 2 | Implementation of the EV-TRACK knowledgebase. A flowchart demonstrating four different data flows available to registered EV-TRACK users. (i) Study authors are able to upload prepublication data. Upon upload, an EV-TRACK ID is assigned, and preliminary EV-METRIC is calculated based on the specified parameters. Upon publication, the data submitted in EV-TRACK are curated by the EV-TRACK administrators, the final EV-METRIC is calculated, and the experiment(s) is(are) included and searchable in the public knowledgebase. (ii) Data of published experiments that are submitted to EV-TRACK can immediately be curated and included in the main database. (iii) Unpublished data of an experiment can be added to increase reporting transparency. (iv) EV-TRACK users can provide recommendations which will be considered together with data from the knowledgebase to update EV-TRACK and EV-METRIC.

wide variety of rotor types ($n = 43$). While the ratio of *k*-factor to pelleting time should be constant to pellet objects with a similar sedimentation coefficient[20], this is not the case (**Supplementary Fig. 4**). Overall, nearly all dUC experiments report on *g*-forces and durations of different UC steps (96%); only 28% of experiments report on rotor type. In just over 18% of experiments, a density gradient was implemented to obtain or at least validate results, with 30% and 60% of these reporting rotor type or EV density, respectively. Use of density gradients decreases over time, for the period we analyzed, and is accompanied by increased implementation of commercial isolation methods (**Supplementary Fig. 5**). Alternative but less frequently recorded isolation methods include immunoaffinity capture[6,21] (2.2%) and size-exclusion chromatography[22] (5.6%).

17% of experiments provide no characterization of EVs; in 29% and 39% of experiments characterization was limited to protein or particle analysis, respectively. Unbiased characterization of EV proteins by proteomics is performed in 16% of experiments. In 55% of experiments only an antibody-based assay was included to detect EV proteins. 21%, 25%, 26% and 29% of these experiments report the presence of 1, 2, 3 or >3 proteins, respectively. Tree maps reveal CD63, CD9, CD81, PDCD6IP (Alix) and TSG101 as the most commonly evaluated EV-enriched proteins (**Supplementary Fig. 6**). Evaluation of contaminating proteins in EV preparations is done in 17% of experiments and typically limited to organellar proteins. When antibodies are used, clone or catalog number and dilution factor are reported in 14% of experiments. Preparation of lysis buffers is detailed in 29% of experiments. 18% of experiments include both qualitative (electron microscopy (EM) or atomic force microscopy (AFM)) and quantitative (EM, nanoparticle-tracking analysis (NTA), dynamic light scattering (DLS), tunable resistive pulse sensing (TRPS), high-resolution flow cytometry (hrFC)) particle analysis. Transmission electron microscopy (TEM), NTA and DLS are the most used particle analysis methods (used in 41%, 17% and 6% of experiments, respectively). Immuno-EM is performed in 10% of experiments, with CD63 as the most frequently evaluated protein (36%). EV size, as measured by EM image analysis, is reported in 3% of experiments. Alternative but less frequently recorded particle analysis methods are cryo-EM, scanning-EM, TRPS, AFM and hrFC (used in a total of 11% of the recorded experiments).

The heterogeneity revealed by this analysis demonstrates the need for reporting guidelines to improve evaluation and reproducibility of EV experiments. We were motivated by these findings to develop the EV-METRIC, described below and in **Box 1**, **Figure 3**, to improve the completeness of methodological reporting of EV-based experiments.

Using the EV-TRACK platform

The EV-TRACK platform comprises seven enabling features to assist researchers (**Fig. 1**).

Upload. Researchers can upload EV experiments through an online interface. As part of each upload, experimental parameters including sample type, preanalytical variables, isolation protocol and characterization method are recorded. Each annotated experiment receives a unique identifier, the EV-TRACK ID (**Fig. 2**). Unpublished EV experiments are contained in a 'closed' section of the database, only accessible to the study authors, editors and reviewers. After acceptance, study authors can modify the submission to reflect what is reported in the peer-reviewed manuscript, and they can add the PubMed identifier.

The annotation of experiments will be publicly accessible after curation by the EV-TRACK administrators. Study authors are notified when experiments are uploaded to EV-TRACK. They can then add more detailed descriptions of experiments reported in the original publication (e.g., UC specifics, antibody details, EM images). These postpublication adaptations will be flagged to distinguish them from the peer-reviewed parameters. To ensure data integrity, modifications to any entry can be requested for consideration by the EV-TRACK administrators based on what is reported in the corresponding peer-reviewed article.

EV-METRIC. EV experiments get assigned an EV-METRIC based on the reported experimental parameters (**Box 1**, **Fig. 3**). This metric assesses whether enough information has been provided to interpret and reproduce the experiment. It consists of nine components that stipulate validation experiments and experimental parameters

that our consortium argued to be indispensable for unambiguous interpretation and independent replication of EV experiments. Some of the challenges are not unique to the EV field and have been discussed previously[14,23]. Other components (sections 2 and 3 on protein and particle analysis) are included in the MISEV guidelines[19].

The EV-METRIC reflects reporting in an experiment according to the version of the metric at the time of uploading. However, the metric is necessarily dynamic, meaning that its defining components can change as the field evolves. We have developed it primarily to pave the way toward standardized EV research; it is not our intention to impede studies on EVs that are rare or poorly described. When submitting data to EV-TRACK, authors have the option to indicate why one or more components of the EV-METRIC were not adhered to, which will be displayed as a note together with the EV-METRIC summary.

Query. Users can query the database for articles using a range of search parameters The query results list is accompanied by an overview of the most common EV isolation protocols and EV-enriched proteins. For each experiment, the EV-METRIC, its percentile across other annotated experiments

BOX 1 THE EV-METRIC

We extracted nine relevant experimental parameters that we condensed into a single metric, the EV-METRIC. It represents a checklist to assess the completeness of reporting of generic and method-specific information necessary to interpret and reproduce the experiment (**Supplementary Table 5**). The EV-METRIC describes the type of information that should be provided for EV experiments in three sections.

Section 1: isolation method

A. Density gradient, at least as validation of results attributed to EVs

B. EV density

C. Ultracentrifugation specifics: *g*-forces, duration, rotor type (conditional)

Density gradient centrifugation separates EVs and non-EV structures based on differences in buoyancy, making it currently the only isolation method that eliminates the majority of contaminants[6,10,11,21,30–33]. It should at least be implemented to validate an EV experiment (i.e., to confirm presence of the molecule(s) of interest and/or attributed functions in the EV fraction of the gradient). Subsequent reporting of the equilibrium density of gradient fraction(s) containing the EVs allows identification and comparison of different EV subtypes[6–8]. In case EVs are isolated through differential ultracentrifugation, rotor type, applied *g*-forces and duration of centrifugation steps should be specified to allow interpretation and replication of the protocol (**Supplementary Table 5**)[20,34].

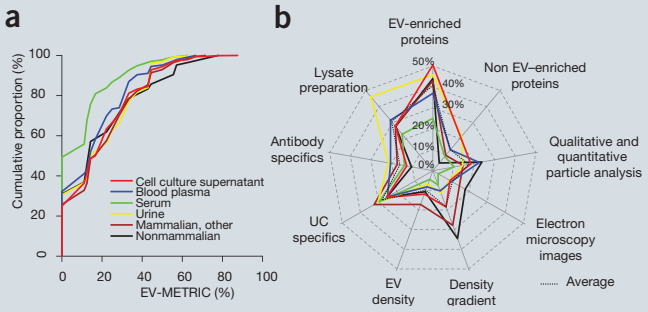

Figure 3 | Using the EV-METRIC to evaluate transparent reporting in EV research. (**a**) Cumulative frequency plots showing the cumulative proportion of experiments achieving a certain EV-METRIC. (**b**) Spider chart representing the percentage of experiments that adhere to each of the respective EV-METRIC parameters for indicated biofluids. Color codes for biofluids are identical in **a** and **b**, with the addition of the average as a black dotted line in **b**.

Section 2: protein analysis

A. Analysis of three or more EV-enriched proteins

B. Assessment of a non-EV-enriched protein

C. Antibody specifics and dilution (conditional)

D. Lysis buffer composition (conditional)

In addition to EV density, recent evidence shows that combinations of differentially enriched proteins can discern EV subtypes[8,10,26,29,35]. Reporting on the presence of multiple (three or more) proteins in the EVs of interest, whether via biochemical assays or omics approaches, is therefore included in the EV-METRIC. Given the current lack of a consensus on proteins that can be considered EV subtype 'markers', we did not include a priori restrictions on proteins that should be evaluated. Reporting on the absence of one or more proteins in EV preparations is a way of evaluating contamination by non-EV entities[10,18]. In case antibody-based assays are used, reporting their details (reference, provider, clone, dilution) is a general requirement in biochemical research[23]. If EVs are lysed for protein analysis, reporting on the composition of the lysis buffer and conditions of the lysate preparation allows interpretation of western blot bands.

Section 3: particle analysis

A. Quantitative and qualitative analysis

B. Widefield and close-up electron microscopy image

Close-up and widefield images obtained by electron microscopy or similar methods (e.g., AFM) allow evaluation of both EV morphology and the presence of non-EV structures[36–38]. Particle yield can be determined by quantitative analysis of EM pictures, bulk (DLS) or single-particle methods (e.g., NTA, TRPS, hrFC)[13,37].

Since most of the EV-METRIC's experimental parameters are poorly reported as identified by EV-TRACK data mining, experiments generally had low EV-METRICs (**Fig. 3** and **Supplementary Table 6**). A cumulative plot reveals that less than 6% of experiments obtain an EV-METRIC above 50% (**Fig. 3a**). Moreover, almost 30% of experiments fail to adhere to a single EV-METRIC component. The average EV-METRIC across all biofluids is 20%, and the maximum lies at 88%. Experiments on serum-derived EVs generally have the lowest metric, with the average being 11% ($P < 0.001$, Kolmogorov–Smirnov test). A spider chart (**Fig. 3b**) shows that some of the EV-METRIC parameters are reported relatively more often (EV-enriched proteins, UC specifics, lysis buffer composition) than others (non-EV-enriched proteins, EV density, EM images, antibody specifics).

and raw annotation data can be consulted. EV-TRACK querying allows EV researchers to find and compare specific information of published experiments with their own unpublished data. All published experiments are accessible without the need for registration.

Coaching. By facilitating the search and comparison of EV-related publications, EV-TRACK familiarizes EV researchers with relevant experimental parameters.

Methods. The EV field is rapidly evolving with new methods to isolate and characterize EVs. Community annotation enables identification of these methods and helps to monitor if and when experimental guidelines are required.

EV biology. Beyond experimental parameters, EV-TRACK systematically catalogs biochemical and physical characteristics of EVs. This will provide insights into the basics of EV biology, such as the identification of EV subsets and optimal protocols to isolate them.

Community. EV-TRACK aims to increase standardized reporting of experimental parameters using a community consensus approach. Registered EV-TRACK users will be involved in future decision making on EV-TRACK and its EV-METRIC by submitting their recommendations.

Discussion and future perspectives

Our analyses reveal that a large number of publications on EVs contain insufficient information for unambiguous interpretation or replication of experiments. We established the crowdsourcing EV-TRACK platform as a next step toward increasing experimental rigor, enhancing biological knowledge, and creating timely and mature minimal information checklists.

EV-TRACK data mining identified a need to guide EV researchers in specific aspects of EV isolation and characterization, which led us to develop the EV-METRIC. Although the EV-METRIC's experimental parameters are currently poorly reported, we believe that the application of this system will not impose an unrealistic burden on researchers. It is meant as an incentive to report parameters that hitherto often remained unreported. In 81% of examined experiments, an increase of the EV-METRIC would already have been achieved by increased reporting, without additional analyses (**Supplementary Table 4**).

The EV-METRIC is applicable to the majority of EV experiments in literature. However, we recognize that it can be challenging to adhere to certain components of the metric, for example if samples are difficult to obtain or limited in volume. The EV-METRIC is not meant to restrict the study of EVs in such cases, and EV-TRACK allows the transparent discussion of any issues that might render the EV-METRIC less suitable. If possible, we propose for these studies that researchers validate the most appropriate method on a test sample.

The diversity and constant evolution of the EV research field, including constant methods development, requires the EV-METRIC to be dynamic. Systematic cataloguing of isolation and characterization methods, experimental parameters and information on EV subtypes by EV-TRACK will fuel future iterations of the metric. For example, combinations of isolation methods are likely required to explore the full range of EV subtypes with immunoaffinity capture and size-exclusion chromatography to complement the use of density gradients[6,22]. Technological progress will allow isolation-independent identification and characterization of EVs in different biofluids (e.g., hrFC[24] or microfluidics devices[25,26]). The use of quantitative technologies such as NTA, TRPS and hrFC will drive the inclusion of additional method-specific guidelines in the EV-METRIC[12]. We hope that future work will establish guidelines for analysis of the RNA content of EVs, since this is highly affected by the purity of an EV preparation[10,27,28], as well as for EV treatments in cell culture and/or animal models[29].

The widespread implementation of EV-TRACK and EV-METRIC will depend on the scientific community at large. We recommend that funding organizations, editors and editorial board members encourage reviewers to implement EV-TRACK and EV-METRIC to adequately identify potential limitations in EV-related grant applications and manuscripts. As such, the EV-TRACK consortium aims to increase experimental rigor in order to help the EV field to mature and reach its full potential.

Data availability statement. All data that were collected during the course of this study and that support its findings are available online at http://evtrack.org.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

J.V.D., P.M., O.D.W., J.V. and A.H. designed the study and analyzed and interpreted the data. J.V.D., P.M., P.A., G.B., J.G., B.G., A.F.H., S.M., E.N.M.N.-'t.H., L.O., M.W.P., S.S., J.V.S., C.T., G.V.N., M.W., K.W.W., O.D.W., J.V. and A.H. discussed and prepared the manuscript. J.V.D., P.M., J.A., O.D.W., J.V. and A.H. developed the online tool. All authors annotated data and approved of the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

1. Melo, S.A. *et al. Nature* **523**, 177–182 (2015).
2. Peinado, H. *et al. Nat. Med.* **18**, 883–891 (2012).
3. Yáñez-Mó, M. *et al. J. Extracell. Vesicles* **4**, 27066 (2015).
4. Biller, S.J. *et al. Science* **343**, 183–186 (2014).
5. Tkach, M. & Théry, C. *Cell* **164**, 1226–1232 (2016).
6. Kowal, J. *et al. Proc. Natl. Acad. Sci. USA* **113**, E968–E977 (2016).
7. Brouwers, J.F. *et al. Proteomics* **13**, 1660–1666 (2013).
8. Willms, E. *et al. Sci. Rep.* **6**, 22519 (2016).
9. Tosar, J.P. *et al. Nucleic Acids Res.* **43**, 5601–5616 (2015).
10. Van Deun, J. *et al. J. Extracell. Vesicles* **3**, 24858 (2014).
11. Kalra, H. *et al. Proteomics* **13**, 3354–3364 (2013).
12. Maas, S.L. *et al. J. Control. Release* **200**, 87–96 (2015).
13. Rupert, D., Claudio, V., Lässer, C. & Bally, M. *Biochim. Biophys. Acta* **1861**, 3164–3179 (2016).
14. Begley, C.G. & Ellis, L.M. *Nature* **483**, 531–533 (2012).
15. Brazma, A. *et al. Nat. Genet.* **29**, 365–371 (2001).
16. Taylor, C.F. *et al. Nat. Biotechnol.* **25**, 887–893 (2007).
17. Bustin, S.A. *et al. Nat. Methods* **10**, 1063–1067 (2013).
18. Witwer, K.W. *et al. J. Extracell. Vesicles* **2**, 20360 (2013).
19. Lötvall, J. *et al. J. Extracell. Vesicles* **3**, 26913 (2014).
20. Cvjetkovic, A., Lotvall, J. & Lässer, C. *J. Extracell. Vesicles* **3**, 23111 (2014).
21. Tauro, B.J. *et al. Methods* **56**, 293–304 (2012).
22. Böing, A.N. *et al. J. Extracell. Vesicles* **3**, 23430 (2014).
23. Anonymous, *Nature* **515**, 7 (2014).
24. van der Vlist, E.J., Nolte-'t Hoen, E.N., Stoorvogel, W., Arkesteijn, G.J. & Wauben, M.H. *Nat. Protoc.* **7**, 1311–1326 (2012).
25. Im, H. *et al. Nat. Biotechnol.* **32**, 490–495 (2014).
26. Shao, H. *et al. Nat. Med.* **18**, 1835–1840 (2012).
27. Chevillet, J.R. *et al. Proc. Natl. Acad. Sci. USA* **111**, 14888–14893 (2014).
28. Hill, A.F. *et al. J. Extracell. Vesicles* **2**, 22859 (2013).

29. Dhondt, B., Rousseau, Q., De Wever, O. & Hendrix, A. *Cell Tissue Res.* **365**, 621–641 (2016).
30. Bobrie, A., Colombo, M., Krumeich, S., Raposo, G. & Thery, C. *J. Extracell. Vesicles* **1**, 18397 (2012).
31. Zonneveld, M.I. *et al. J. Extracell. Vesicles* **3**, 24215 (2014).
32. György, B. *et al. Blood* **117**, e39–e48 (2011).
33. Rødahl, E., Iversen, O.J. & Dalen, A.B. *Scand. J. Immunol.* **20**, 21–26 (1984).
34. Livshits, M.A. *et al. Sci. Rep.* **5**, 17319 (2015).
35. Groot Kormelink, T. *et al. Cytometry A* **89**, 135–147 (2016).
36. Coleman, B.M., Hanssen, E., Lawson, V.A. & Hill, A.F. *FASEB J.* **26**, 4160–4173 (2012).
37. Arraud, N. *et al. J. Thromb. Haemost.* **12**, 614–627 (2014).
38. Höög, J.L. & Lötvall, J. *J. Extracell. Vesicles* **4**, 28680 (2015).

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