nature portfolio

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Last updated by author(s): Nov 18, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection

Data were collected using scripts from our public repository: https://github.com/owkin/fedeca.
Most of our scripts are python-code except for YODA preprocessing is done in R (https://github.com/owkin/fedeca/blob/main/experiments/yoda/yoda_preprocessing.R)
We rely on the following open-source libraries, whose versions we list below.
Commented pinned versions are only there as references but should not matter too much as long as the versions are compatible with the ones that are not commented.

"substrafl==0.46.0",
"numpy==1.26.4",
"pandas",#==2.2.3
"pre-commit",#==4.0.1
"scipy",#==1.13.1
"seaborn",#==0.13.2
"opacus",#==1.4.0
"lifelines",#==0.29.0
"git-python",#==1.0.3
"build",#==1.2.2.post1
"torch==1.13.1",
"scikit-learn==1.2.1",
"pydantic", #==2.23.4

"indcomp==0.2.1",
"hydra-core",#==1.3.2
When in doubt, we advise the user to open an issue in our repository and to refer to the repository as the source of truth.

Data analysis

FedECA is available as a Python package on Github (https://github.com/owkin/fedeca) for non-commercial use.
The code in this repository follows best practices such as continuous integration (CI), thorough code testing (coverage of code at 82% on commit 480fa75), deployed documentation using Github pages as well as the use of pre-commit hooks to help manage the repository's evolution.
The availability of the code not only ensures the reproducibility of the results presented in this article as well as the possibility to audit its implementation, but also opens the possibility for other research teams to perform real-world federated ECA.
Indeed, a user can launch FedECA running the exact same code either in-RAM for simulations, or on a real deployed substra network in real conditions by modifying the backend type, as shown in Listing Supplementary Listing S1.
The FedECA repository contains a quickstart as well as detailed documentation and comments, which should allow easy replication.
All quantitative figures in this article with synthetic data can be reproduced by following instructions in experiments/README.md. The associated yaml configurations provide all hyper-parameters that were used.
The use of modern generator-based random seeds further ensures the reproducibility of the results.
For experiments on 10 centers replication involves deploying a substra network, which require some development operations (DevOps) capabilities. However details in section 6.5.1 should be sufficient to reproduce the results. The associated experiment script is defined in real world runtimes.yaml.
For experiments on YODA data, we install the fedeca package within the YODA platform, split the data in such a way that the control arm and the treatment arm are in two separate groups, and run fedeca with bootstrap variance estimation. Scripts used to preprocess the data and run the experiments are available in the yoda folder in the fedeca repository.
For experiments on metastatic pancreatic adenocarcinoma data, we use the fedeca package unaltered on commit b6474e5 after having registered the data in the Substra platform. Obfuscated versions of the scripts that ran on the deployed platform and that were used to generate the related figures in the article are available in the pdac folder in the fedeca repository. Where by "obfuscated" we mean that dataset hashes or urls in this script were converted to random strings so they cannot be mapped to any of the original data or servers.
The nature of this last experiment is such that replications require data access which might be restricted, see Section 7. However once access to data is obtained and federated network is deployed all experiments should be easily reproduced thanks to the above scripts.
Further questions can be addressed to the corresponding author J.O.d.T. through the creation of github issues or via direct e-mail.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Synthetic data used in this study can be re-generated using the scripts provided.
For the first example with real patient data, data access should be requested to the Yale University Open Data Access (YODA) Project. Detailed procedure to request data access is provided on YODA website https://yoda.yale.edu/how-request-data.
For the second example with the federated research network of FFCD, IDIBGI and PanCAN, the data is under restricted access and are not freely available as specific clearance from the ethics committee and compliance with local regulations is required to access data from each center. Data from PanCAN is available to qualified researchers by submitting a proposal for review at https://spark.sbgenomics.com/. Data from FFCD and IDIBGI can also be made available upon reasonable request. Specific conditions and restrictions of access to the datasets are to be discussed directly with the main investigators in each center: J.-B. B. for FFCD, R. C. for IDIBGI.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender

Biological sex was used as a covariate in the study on metastatic pancreatic cancer data. Gender information was not collected. Summary statistics of sex are given for every patient arm that we consider in Supplementary Tables S5, S6 and S7

	under "Biological gender". For YODA experiments neither sex nor gender is used. We refer the reader to the original YODA trials documentation.
Reporting on race, ethnicity, or other socially relevant groupings	We access to all data in a retrospective fashion. Patient recruitments were done either in the well regulated context of clinical trials or through patient care in hospitals. We do not use any information about race, ethnicity or social grouping.
Population characteristics	We describe the population characteristics of the different cohorts in the Methods section of the article
Recruitment	Patients were recruited either through the clinical trials described in the study or through patient care. In both case in this study we access to this data retrospectively.
Ethics oversight	The ethics of this retrospective study on clinical data collected during care and from past clinical trials were validated for each institution according to corresponding local regulations. We list below the corresponding statements from each of the participating cancer centers. Regarding FFCD data, the study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) requirements and Good Clinical Practice guidelines; it received authorization from the French national medicines agency (ASNM), and independent ethics committee (number 214-R18 and 14-12-79 respectively for PRODIGE 35 and PRODIGE 37). The study was both registered in clinicaltrials.gov (NCT02352337 for PRODIGE 37 and NCT02827201 for PRODIGE 35) and EudraCT 2014-004449-28. For IDIBGI data the study was approved by the Comitè d'Etica d'Investigaciò amb Medicaments CEIM ` GIRONA the 8th of August 2023 (Acta 11/2023) under reference CEIM code 2023.165 with principal investigators ADELAIDA GARCIA VELASCO and ROBERT CARRERAS TORRES and SANOFI-AVENTIS SA as promoter. Finally for PanCAN data the sponsor of the IRB was the Pancreatic Cancer Action Network (# KYT001) the IRB reference is 20192301, study 1265508 with main investigator Matrisian, Lynn.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample size in all experiments refers to the number of patients. The real-world experiments are observational studies hence no a priori calculation of effect size was performed. All patients that met the inclusion/exclusion criteria described below were included. In both real-world experiment settings, the sample size is comparable to that of some of the reference works cited.
Data exclusions	YODA experiment: First, the inclusion/exclusion criteria of both trials were aligned, patients in NCT02257736 with present visceral metastases at randomization were excluded to match the exclusion criterion of NCT00887198. Then a group of variables of patient's baseline characteristics were chosen for propensity-weighting based on literature review as well as on their availability in both trials. The chosen covariates are age, body-mass index (BMI), eastern cooperative oncology group (ECOG), brief pain inventory (BPI) score and bone-metastasis-only. Supplementary Figure S4 provides a CONSORT-like diagram of exclusion criteria. Metastatic pancreatic adenocarcinoma: The FFCD data consists of a subset of two clinical trials: PRODIGE 35 [124] and PRODIGE 37 [125] that respectively compare the first line efficacy of, for PRODIGE 35, 6 months of FOLFIRINOX (arm A), 4 months of FOLFIRINOX followed by leucovorin plus fluorouracil maintenance treatment for controlled patients (arm B), and a sequential treatment alternating gemcitabine and fluorouracil, leucovorin, and irinotecan every 2 months (arm C) and for PRODIGE 37: alternately receive gemcitabine + nab-paclitaxel for 2 months then FOLFIRI.3 for 2 months in arm A, or gemcitabine + nab-paclitaxel alone until progression in arm B. We use both the FOLFIRINOX arm B (n = 92) and the gemcitabine + nab paclitaxel arm A from PRODIGE 37 with (n = 61). The inclusion criteria of this new subset is thus metastatic pancreatic adenocarcinoma patients with a performance status eastern cooperative oncology group (ECOG) of either 0, 1 or 2. We select patients with the same inclusion criteria treated with FOLFIRINOX or gemcitabine + nab-paclitaxel from clinical practice data from IDIBGI and PanCAN. In PanCAN we find n = 101 patients treated with FOLFIRINOX and n = 94 with gemcitabine + nab-paclitaxel patients that meet the criteria totalling n = 195 patients out of 199 originally available excluding ECOG 3 and 4. We note that in PanCan, 2 patients are censored at the time the study starts therefore their data is not informative for the Cox model fitting but might still be useful for the estimation of the propensity model. In IDIBGI we find n = 22 patients treated with FOLFIRINOX and n = 144 with gemcitabine + nab-paclitaxel. For each patient we access the following covariates: age at diagnosis, ECOG performance status, biological gender and whether or not patients have liver metastasis following the literature [126] and restrictions due to data availability for each covariate in each center. We present baseline characteristics for each of the centers in Supplementary Table S7,Supplementary Table S5 and Supplementary Table S6 respectively for FFCD, IDIBGI and PanCAN.

	We then filter these patients to remove non-informative patients, i.e., patients with missing treatment or survival information. The final full distributed cohort consists of n = 514 patients (n = 153 for FFCD, n = 166 for IDIBGI and n = 195 for PanCAN).
Replication	For experiments on metastatic pancreatic cancer data results were consistent with a vast body of literature on FOLFIRINOX vs gemcitabine +nab paclitaxel that we cite. For experiments on YODA data similarly we compare results with the literature in Table 1.
Randomization	This study is concerned only with external control arms analyses which are by definition not randomized.
Blinding	The study is not blinded as this is an external control arm analysis and knowledge on the treatment assigned to each patient is necessary.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT02352337, NCT02827201, EudraCT 2014-004449-28, NCT02257736, NCT00887198.
Study protocol	Study protocols should be available online following the provided trial registration numbers. We are using this data in a retrospective fashion and thus the work presented in this article is entirely independent of any original study protocols.
Data collection	Data collection details are to be found in original analyses we use this data in a retrospective fashion.
Outcomes	We use Overall Survival in our study as our primary clinical endpoint for the metastatic pancreatic cancer. We use radiographic progression-free survival (rPFS) endpoint for the metastatic prostate cancer data analysis.

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A