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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	All information collected for this registrational trial is stored in proprietary databases owned and curated by the sponsor of the study using Data Management, Clinical Operations and Biostatistics experts. As we report results of a registrational trial, regulatory agencies request to control data collection and distribution by the sponsor.
Data analysis	SAS and R were used, and the mansucript states the software versions used.

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

The results presented are part of a registrational trial registered on clinicaltrials.gov and submitted to regulatory agencies for clearance of the TriVerity test. Therefore, data cannot be made available at this time.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	As part of the study protocol and the data collection the term sex was used throughout but not gender.
Population characteristics	All relevant covarites incl age, race, ethnicity and medical history were recorded in detail and are reported in the manuscript.
Recruitment	Recruitment occurred in the emergency departments of participating sites (all Prinicpal Investigators are co-authors and have approved the manuscript) using detailed inclusion and exclusion criteria that are reported in the Methods section of the manuscript. Site staff was trained intensively to ensure adherence to the study protocol. Time of enrollment and enrollment numbers by site are reported in the manuscript. There was no selection bias, as we did not employ enrichment or other tool enrollment of convenience samples. Inclusion criteria are very broad and sites are geogpraphically distributed over the US and 1 site in Europe avoiding introduction of bias.
Ethics oversight	As we enrolled patients at 22 sites there were a vast number of local clinical-site IRBs at academic medical centers. Several sites used their local and the central IRB (Advarra) that cleared the study protocol before enrollment of patients at the respective site.

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	we used statistical analysis (power calculation) incorporating the accuracy of Triverity and prevalence of bacterial infection, viral infection and severe illness (the three readouts of the test and primary endpoints of the study. Approximately 400 sample for each of the three readouts was calculated resulting in a target enrollment of 1200.
Data exclusions	There were no exclusions performed for the eligible patient population.
Replication	not applicable as this was a clinical study enrolling almost 1500 patients.
Randomization	As the study was non-interventional trial no randomization was performed.
Blinding	As described in the Methods section clinical adjudicators (establishing the ground truth for infection status) were blinded to the results of the TriVerity test throughout the study. Data collection and analysis was performed by biostatisticians at the sponsor exclusively. Biostatisticians were kept blinded to the results of the TriVerity test until final analysis was done.

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

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	NCT04094818 (clinicaltrial.gov
Study protocol	The full study protocol is owned by the sponsor of this registrational trial and can therefore not be accessed. The Methods section contains a description of the key parts of the study protocol.
Data collection	Data collection was perfromed at clinical sites enrolling patients by clinical research staff throughout the study duration. Data collection was also performed at central laboratories (where testing of frozen samples occurred). Clinical adjudication was performed by selected investigators. All data fro the above mentioned sources were entered into a secure electronic database (medrio) which ws then used for statistical analysis via SAS and R. The Methods section has a detailed description of the data collection.
Outcomes	In the study protocol the primary outcomes were pre-defined based on the TriVerity test result readout: 1) accuracy of TriVerity for the diagnosis of, 1) bacterial infection, 2) viral infection, both compared to clinically-adjudicated infection status, and 3) accurate prediction of the risk of clinical deterioration (need for mechanical ventilation, vasopressors and/or renal replacement therapy) within 7 days These pre-defined endpoints were maintaied throughout the study and biostatistical analysis. The Methods section has a detailed description of the outcomes and how these were assessed.