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FAIR compliant metabolomics profiling of population-based studies

Whitepaper

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FAIR compliant metabolomics profiling of population-based studies

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Summary

Multi-omics analyses are becoming a leading favorite for researchers interested in the biochemical characterization of large-scale epidemiological cohorts. While genome-wide association studies (GWAS) have been and continue to be applied for large cohorts, metabolite panels are attracting growing attention in population-based studies. Thanks to these approaches, epidemiological cohort studies at the scale of hundreds of thousands, or even millions of samples, are no longer an unsurmountable challenge.

This article classifies different metabolomics approaches using the FAIR principles for scientific data (i.e. findability, accessibility, interoperability and reusability), with a spotlight on data quality. Additionally, we discuss the scientific impact of a solution to scale analysis quickly and reliably.

1. Introduction

Recent advances in omics research have enabled many researchers to carry out comprehensive characterization of large epidemiological cohorts [1,2]. Over the last decade, GWAS and metabolomics have grown in popularity, with the number of publications featuring metabolomics jumping from about 1,500 in 2010, to nearly 9,000 in 2020. Similarly, around 650 cohort studies were analyzed using metabolomics in 2020 compared to around 50 in 2010.

The sample size in epidemiological studies has also vastly increased. Several long-term large cohort studies are currently in progress, including the 'UK Biobank' (United Kingdom), the 'Nationale Kohorte' (Germany), the 'Tohoku Medical Megabank Project' (Japan) and the 'Cohen Veterans Cohort' (USA) to name a few. Moreover, several countries have established literal mega-cohorts with sample sizes of tens to hundreds of thousands of participants. Researchers no longer see genetics as the only factor relevant to studying the development of complex traits and diseases: metabolomics is equally important. Combined studies have proven particularly useful when examining the interaction of genetic factors, biomarker panels, the environment and their impact on the cause of diseases [3].

Biological analyses of large sample sets require a broad analyte coverage and methodological robustness to deliver reliable and meaningful results. A comprehensive panel is required for a functional

overview of the study population. Methods and data must be sustainable and of high quality, to enable longitudinal data analysis, reanalysis in different contexts, and pooling of different independent datasets. Most importantly, these methods need to be accessible and scalable: the technology must be broadly proven to allow analysis of a large number of samples in a cost-efficient and timely manner. Overall, the ideal approach needs to adhere to the FAIR principles of findability, accessibility, interoperability and reusability.

2. Metabolomic approaches

Established techniques available for large scale studies

The metabolome can be analyzed using different approaches. Targeted approaches can be applied either fully or semi-quantitatively, while untargeted approaches are mainly explorative, and generally not quantitative.
Mass spectrometry in combination with liquid chromatography (LC-MS) or gas chromatography (GC-MS) is the most commonly used method, representing more than 80% of all published metabolomics studies [4]. Segers and colleagues have reviewed LC-MS and GC-MS in metabolomics in detail [5].

Up to 20% of metabolomic studies used Nuclear Magnetic Resonance (NMR), which is a quantitative and reproducible technology, useful for metabolite and lipid profiling and quantification. It is cost-effective and free of batch effects with no burdensome sample preparation steps. Based on a lipoprotein assay, the NMR assay represents a multiplexing panel with known parameters from clinical chemistry [4]. In total, more than 20 metabolites can be analyzed using NMR, plus various metabolite ratios and lipoprotein particles, such as LDL and VDL [6]. NMR has a lower sensitivity, hence the number of analytes is significantly smaller than with MS-based approaches. For this reason, NMR and LC-MS are often used together to combine the "best of both worlds".

Capillary electrophoresis mass spectrometry (CE-MS) has matured in recent years, used mainly for untargeted profiling but also for limited targeted approaches [7; 8]. It is less reproducible than reversed phase LC-MS but can deliver complementary metabolite coverage.

Targeted, fully quantitative metabolomics approaches can identify and quantify several hundred metabolites with reliable precision (low coefficient of variation (CV)). Semi-quantitative targeted methods offer relative quantification, such as fold-changes. Untargeted metabolomics is a powerful tool for exploratory approaches, for example, to profile samples in order to detect as many metabolites as possible and identify

What is FAIR?

In 2016, the "FAIR Guiding Principles for scientific data management and stewardship" were published in the journal Scientific Data [31]. The authors intended to provide guidelines "to improve the Findability, Accessibility, Interoperability, and Reuse of digital assets". To meet the requirements of FAIR compliance metabolomic data must fulfill the following criteria:

Findable — Data need to be uploadable to data repositories

Accessible — The repository should be visible for the scientific community and publicly available

Interoperable — Uploaded data require a harmonized format and common units to enable shared data from different sources

Reusable — Data must be comparable, with long-term validity and independent of time

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significant unknowns. The disadvantages of untargeted metabolomics are its low sensitivity and non-quantitative nature.

Although the majority of published metabolomics papers utilize untargeted methods, it is surprising that only a handful of novel metabolites were discovered and identified in recent years [9]. The majority of identified metabolites are already included in targeted solutions. The promises and pitfalls of untargeted metabolomics are well described by Gertsman and Barshop [10].

Reproducibility and expectable analytical robustness

Data from untargeted approaches are often based on individual protocols and approaches. With protocols and instrumentation subject to regular change, the comparison of data across platforms, laboratories and countries can be challenging. By contrast, method standardization in targeted metabolomics such as biocrates' kit-based methods allow data to be methodologically preserved and fully shareable.

The FAIR aspects of interoperability and reusability pose particular complexities for untargeted or semi-quantitative targeted metabolite assays. As many metabolites exist in a continuum in body fluids, clinical translation and application of non-quantitative data is challenging. Targeted methods are more stable, fully shareable and data generation can be scaled over different laboratories, which are able to run the same kits or perform the same assays. In clinical and analytical practice, reproducibility is demonstrated by ring trials.

For these reasons, targeted solutions with large metabolite panels tend to be the better option for large-scale studies, due to the quantitative nature of the data, high reproducibility, and the cost-effectiveness and ease with which data can be shared and combined between laboratories in different countries, and even across time.

3. biocrates targeted metabolomics kits

Standardized, fully quantitative and FAIR-compliant profiling

The FAIR principles demand that data is "Findable, Accessible, Interoperable and Reusable." These are fundamental to determining the research data, infrastructures and frameworks required for new studies.
With nearly two decades of experience as a mass-spectrometry solution provider, biocrates is a global leader for targeted metabolomics technology. Over the years, biocrates has successfully developed standardized and fully quantitative ready-to-use platforms to map various biochemical pathways.
The MxP® Quant 500 kit is biocrates' most comprehensive product for metabolic profiling, offering a rapid and unique approach for the quantification of up to 864 data points, comprising analytes, sums and ratios from 26 metabolite classes, containing small molecules, polar and neutral lipids. The coverage spans microbiome-derived metabolites and enables the study of membrane composition, cellular signaling, bioenergetic processes, functional microbiomics and host-microbiome-nutrition interaction.
The targeted technology itself has a proven track record with more than 1,000 publications in peer-reviewed journals. This includes many large cohort studies in neurology, oncology, cardiovascular diseases and microbiome studies.

biocrates kits generate highly reproducible data across platforms, laboratories, and time. The technology enables cohort studies that require scalability and harmonized data formatting, requiring a small sample volume of just 10 µL, and applicable to many biological matrices.
This not only enables researchers and clinicians to make reliable lab-to-lab comparisons, but so far has enabled more than 100 core facilities around the world to contribute to scalable, integrated

and exchangeable data across different cohort studies. Moreover, biocrates kit researchers hold total ownership of their metabolomic data and are supported to be completely FAIR compliant.

Standardizing metabolomics

The reproducibility and standardization of biocrates' approach to targeted metabolomics has been proven by three internationally recognized and peer reviewed ring trials [11; 12; 13]. Data standardization could be confirmed even across different mass spectrometry platforms, including inter-laboratory comparability, quality assurance and scalability.

The ring trial for the largest targeted metabolite panel is currently in progress. This includes 13 laboratories worldwide, including Duke University, University of Alberta, Stanford University, Tohoku University, with the Helmholtz Center in Munich as the coordinating institution. The robustness of this technology demonstrated by these ring trials was evident by the inter-laboratory precision of <10% variance for high-abundant metabolites and <25% variance for more than 80% of all analyzed metabolites in the kit. Absolute quantification, time preserved, with forward and backward comparability is now proven for three generations of biocrates kits: AbsoluteIDQ® p150, AbsoluteIDQ® p180 and MxP® Quant 500. It will also apply to future kit generations currently under development.

biocrates' decentralized multi-lab approach offers both economic and scientific benefits. Pooling scientific infrastructure means research can be conducted using existing instruments, knowledge and staff. This reduces costs and optimizes investments in other equipment, while generating additional insights.
biocrates' cutting-edge technology is best suited for clinical translation and interpretation, particularly biomarker discovery and validation. It supports the integration of multi-omics quantitative data, such as metagenomics, proteomics or genomics, to complement available clinical data.

4. A multi-cluster approach for large population-based cohorts

The biocrates kit technology is designed to study and combine large sample sets in a 96-well format. Analyses are quality-controlled, with the data quality best described as "diagnostic-like" (for details please refer to section 7). Furthermore, the reproducibility of the data has been demonstrated in several international ring trials. This allows data pooling from different laboratories and different instrument platforms and enabling the analytical throughput to be modularly scaled.

Each kit has the capacity to measure up to 80 samples in a single run, leading to an annual throughput of up to 6,000 samples on a single LC-MS platform. This output can be scaled up according to the user's requirements, either through integrating several laboratories into an analytical network, or through utilization of several instruments in one laboratory ("instrument cluster").
An instrument cluster based on three LC-MS platforms would be able to measure up to 800 samples per week, resulting in 35,000 samples per year (Fig. 1).

For larger sample sets, such as population-based studies, instrument clusters of analytical networks can be combined. For instance, a combination of four three-instrument clusters could lead to an overall throughput of up to 150,000 samples per year.

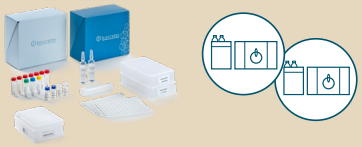
Such multi-clusters can be run independently in different laboratories. Figure 2 illustrates such a potential setting for the cohorts of the EPIC network.

This novel multi-cluster solution enables researchers to use reproducible metabolomics for large population cohorts. Data can be generated by pooling results from multiple laboratories, or by splitting

Conventional approach
1 study, 1 laboratory, 1 instrument

6,000 samples p.a.

Core laboratory approach
1 study, 1 laboratory, multiple instruments



13,000 samples p.a.

Cluster approach
Increasing throughput by splitting workflow to 3 instrument cluster processing samples parallelly (+ optional backup)

35,000 samples p.a.

Multi-cluster approach
Maximized throughput by applying the splitted workflow to 4 instrument clusters

150,000 samples p.a.

Fig. 1: An overview on the biocrates cluster approach for population-based studies: the sample throughput can be easily scaled to the user's requirements.

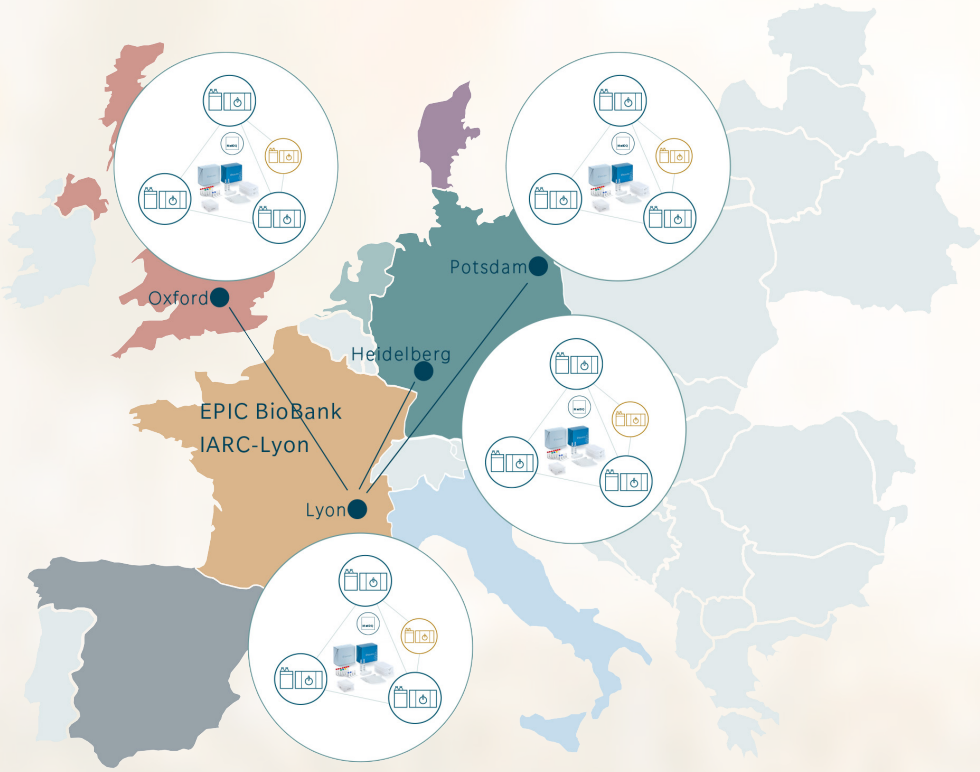


Fig. 2: EPIC consortium with study centers in Oxford (UK), Potsdam (Germany), Heidelberg (Germany) and Lyon (France). The EPIC Bio-Bank is located at IARC in Lyon (France).

sample analyses on a multiple instrument cluster from the same laboratory. Applying this approach, epidemiological cohort studies of up to one million samples can become reality.

5. Metabolomics in major epidemiological studies

Application of biocrates kit solution in large cohort studies

biocrates kit solutions have contributed successfully to prominent cohort studies such as the 'Alzheimer's Disease Neuroimaging Initiative' (ADNI), 'Baltimore Longitudinal Study of Aging' (BLSA), the FENLAND Study, 'Kooperative Gesundheitsforschung in der Region Augsburg' (KORA), 'European Prospective Investigation into Cancer and Nutrition' (EPIC), 'Tohoku Medical Megabank' (TMM)' and others (Figure 3).

Both the ADNI and BLSA studies focus on neurodegenerative diseases. Prof. Rima Kaddurah-Daouk and Prof. Madhav Thambisetty demonstrated that metabolic alterations were stage-specific during progression of Alzheimer's disease and could possibly be explained by a malnutrition of the brain [14, 15]. Similarly, microbiome-derived secondary bile acids were shown by Prof. Rima Kaddurah-Daouk to play an active role in Alzheimer's and other neurodegenerative diseases and are associated to progression of disease [16].

In the FENLAND, KORA and EPIC studies, the groups of Prof. Claudia Langenberg, Prof. Annette Peters, and Prof. Rudolf Kaaks respectively showed that branched-chained amino acids play a causal role in type-2 diabetes [17]. The risk prediction for myocardial infarction (Framingham Score) was shown to be significantly improved by metabolic markers [18], and such markers were also linked to the prediction of cancer occurrence [19].

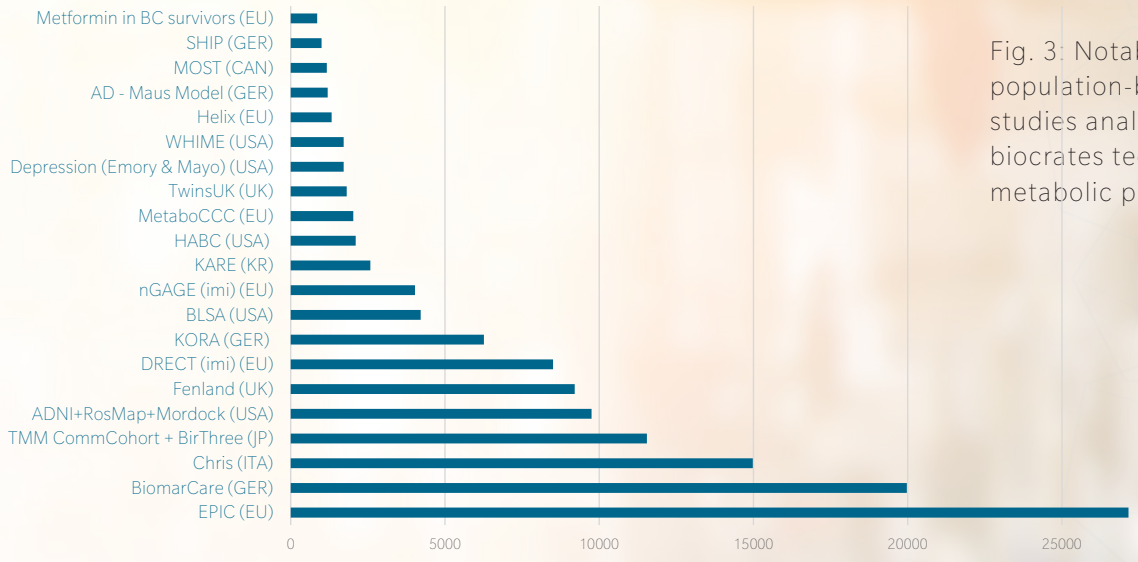


Fig. 3: Notable population-based studies analyzed by biocrates technology for metabolic phenotyping

6. Inter-cohort data comparisons and multi-omics integration

Accelerating insights and advancing the understanding of health

Table 1: Successful demonstrations of pooling and replication of data across independent cohorts

Cohorts	Brief	Literature
EPIC KORA CARLA	– EPIC: relationships between diet, nutritional status, lifestyle and environmental factors, and the incidence of cancer and other chronic diseases – KORA: new insights into the causes, development and consequences of cardiovascular disease, diabetes as well as lung diseases and allergies – CARLA: risk factors for cardiovascular disease in an urban elderly East-German population	[20] [4] [21]
FENLAND EPIC	– FENLAND: interaction between environmental and genetic factors in determining obesity, type-2 diabetes, and related metabolic disorders – EPIC: relationships between diet, nutritional status, lifestyle and environmental factors, and the incidence of cancer and other chronic diseases	[22]
ADNI ROS MAP	– ADNI: Biomarkers for prediction and characterization of Alzheimer's disease – ROS/MAP: prospective studies of aging and dementia with detailed, longitudinal cognitive phenotyping during life and a quantitative, structured neuropathologic examination after death	[16]
BLSA ADNI	– BLSA: To characterize the many aspects of the aging process and learn how people can successfully adapt to aging – ADNI: Biomarkers for prediction and characterization of Alzheimer's disease	[23]
TMM CommCohort TMM BirThree	– TMM CommCohort: Population-based cohort to study how genetic factors and environmental factors affect disease risk – TMM BirThree Cohort: Family-based cohort, birth and three-generation cohort to study how genetic factors and environmental factors affect disease risk – jMorp Reference Panel	[24]
KORA KARE	– KORA new insights into the causes, development and consequences of cardiovascular disease, diabetes as well as lung diseases and allergies – KARE: Biomarkers for type-2 diabetes	[25]
BLSA TMCS	– BLSA: To characterize the many aspects of the aging process and learn how people can successfully adapt to aging – TMCS: metabolomics biomarkers for common diseases and disorders related to environmental and genetic factors	[26]

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; BLSA, Baltimore Longitudinal Study of Aging; CARLA, Cardiovascular Disease, Living and Ageing in Halle; EPIC, European Prospective Investigation into Cancer and Nutrition; KARE, Korea Association Resource; KORA, Kooperative Gesundheitsforschung in der Region Augsburg; MAP, Rush Memory and Aging Project; ROS, Religious Orders Study; TMCS, Tsuruoka Metabolomics Cohort Study; TMM BirThree, Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study; TMM CommCohort, Tohoku Medical Megabank Project Community-Based Cohort Study

Case study

Multi-Omics Integration – Enhancing GWAS with Metabolomics

Circulating levels of small molecules or metabolites are highly heritable, but the impact of genetic differences in metabolism on human health is not well understood. Prof. Langenberg and her team performed a genome-wide meta-analysis of 174 metabolite levels across six cohorts and identified 499 (362 novel) genome-wide significant associations at 144 (94 novel) genomic regions (mGWAS). They were able to show that inheritance of blood metabolite levels in the general population is characterized by variation in transporter and enzyme encoding genes.

Most identified genes were known to be involved in biochemical processes regulating metabolite levels, and to cause monogenic inborn errors of metabolism linked to specific metabolites. In addition, mGWAS enabled the efficient discovery of genetic regulators of human metabolism. The resulting clinical insights led to a better understanding of impaired insulin secretion and type-2 diabetes risk, and a potential new diagnostic approach for degenerative retinal disease [27]

7. Quality of data

Details on data quality assurance and technical validation

Data quality is integral to clinical insights. In cohort studies, the highest quality data is obtained by applying the MxP® Quant 500 kit within a quality-controlled system. Quality controls and standard operating procedures (SOPs) should cover every aspect from sampling to results within an entire scientific consortium.
The MxP® Quant 500 kit and kit-plate layout are designed with the standard rules for LC-MS in mind. With a 96-well format and a workflow controlled by proprietary MetIDQ® software, each kit can typically analyze 80 samples. Sixteen wells of each plate are designated for blank, kit-based calibration standards/curves, including quality control (QC) samples in low, medium and high concentration ranges. Isotope-labeled internal standards are pre-placed into each sample and reagent-well for each analysis, to control sample preparation.

Each analyzed kit plate undergoes a technical intra-plate validation. Performance analysis based on the MetIDQ® software verifies the actual performance of the applied quantitative procedure with defined acceptance criteria.
Both the kit and MetIDQ® software are set up according to standard rules as applied in diagnostic-clinical settings. Replicates of the QC samples are included after every 20th sample (and in no less than triplicates on each plate), and calibration curves are measured at the beginning and the end of each plate analysis. biocrates' standardized approach makes it easy to compare metabolome analysis and technical validation of study cohorts requiring more than one kit.

As an additional measure to be FAIR-compliant, we recommend introducing study/cohort-specific pool quality controls (SPQC) and standard reference materials (SRMs) [14; 28; 16; 29; 30].

SPQC samples from each matrix (plasma, serum, urine and stool) can be created from aliquots from the whole cohort or a representative part of the cohort, and should be included in triplicate on each plate. The SPQCs need to be accessible for all consortium partners who will be producing data. The SPQC represent the 'study average' and can be

used to assess intra- and inter-batch precision and accuracy, so batches can be adjusted if required [14]. To monitor accuracy, studies should include SRMs that are relevant for each matrix, such as NIST SRM-1950.

WebIDQ® – The collaboration platform for metabolomics laboratories

The next generation of biocrates' cloud-based software, WebIDQ®, will include new features to simplify data exchange and accessibility between cohort owners. Consortia will be able to jointly access and contribute to data sets using state-of-the art data security. The software will improve the kit workflow, combining advanced new features for data analysis and interpretation and an improved user experience.

Finally, because the practical guidance for implementation in each laboratory impacts data quality and throughout, biocrates has developed a kit-specific comprehensive LC-MS instrument suitability test that confirms instrument performance readinesss before samples are being analyzed. This test can reduce re-analyses significantly [13; 31]. Please do not hesitate to contact us to submit any questions or remarks, or to find out more about how biocrates kits can support your large population-based studies.

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