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SHORT COMMUNICATION

Towards quality assurance and quality control in untargeted metabolomics studies

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Abstract
We describe here the agreed upon first development steps and priority objectives of a community engagement effort to address current challenges in quality assurance (QA) and quality control (QC) in untargeted metabolomic studies. This has included (1) a QA and QC questionnaire responded to by the metabolomics community in 2015 which recommended education of the metabolomics community, development of appropriate standard reference materials and providing incentives for laboratories to apply QA and QC; (2) a 2-day 'Think Tank on Quality Assurance and Quality Control for Untargeted Metabolomic Studies' held at the National Cancer Institute's Shady Grove Campus and (3) establishment of the Metabolomics Quality Assurance and Quality Control Consortium (mQACC) to drive forward developments in a coordinated manner.

Keywords Quality assurance (QA) · Quality control (QC) · Community engagement · Test materials · Reporting metrics

1 Introduction

Metabolites have many important biological roles [for example, (Drenos et al. 2016; Kaddurah-Daouk and Weinshilboum 2015)] and the study of metabolites by advanced analytical and informatic platforms is defined as metabolomics. There are numerous sub-specialties in the field of metabolomics; for example, metabolomics investigations of drug response are often referred to as 'pharmacometabolomics'. Two general types of approaches can be applied depending on the study objectives, either discovery-based (untargeted) studies which have the objective to investigate hundreds or thousands of known and unknown metabolites to generate targets for further investigation, or targeted metabolomic studies which are focused on the investigation of a small subset of metabolites of known biological relevance though assays and studies can integrate untargeted and targeted studies, for example see (Davies et al. 2014). QA and QC processes are hugely important to ensure that the data acquired and reported in scientific publications and housed in data repositories are of high quality and are analytically reproducible. These processes relate to the procedures applied in preparation for data acquisition (QA) and during/after data acquisition (QC) [for example, (ISO9000 2015)]. QA processes include staff training, standard operating procedures, instrument maintenance and calibration, as well as other processes. QC processes include use of measured data from standard/certified reference materials and quality control samples to address the veracity of experimental data as well as other processes. For targeted studies, there is a long history of defined criteria for QA and QC processes, reporting of data quality for biological samples and standard reference materials and for assessment and reporting of data quality [for example, FDA 2001)]. However, these criteria

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and biological samples are not routinely applied, are not available, or otherwise inappropriate for untargeted studies but are urgently required to enable the quality of these studies to be peer reviewed and accepted in the scientific community (Bouhifd et al. 2015). Without well-defined QA and QC procedures for untargeted metabolomics, harmonization across laboratories and multi-laboratory studies become nearly impossible. A recent example from the lipidomics research community has demonstrated how standard reference materials can be applied for community harmonization including QA and QC (Bowden et al. 2017).

A QA and QC questionnaire responded to by the metabolomics community in 2015 provided four key recommendations as shown in Table 1 (Dunn et al. 2017).

2 Think Tank on quality assurance and quality control for untargeted metabolomic studies

Following up on these recommendations, a two-day 'Think Tank on Quality Assurance and Quality Control for Untargeted Metabolomic Studies' was held on October 19–20, 2017 at the National Cancer Institute's Shady Grove Campus in Rockville, MD, USA. The four organizers were Drs. Richard Beger (Food and Drug Administration, USA), Dan Bearden (National Institute of Standards and Technology, USA), Warwick Dunn (University of Birmingham, UK) and Krista Zanetti (National Cancer Institute, USA). Fifty internationally recognized experts in metabolomics and QA/QC processes were invited from the United States, Europe, and Australia with scientists and stakeholders from instrument manufacturers, commercial laboratories, and government and academic institutions invited. 38 of the invited experts attended including NIH Program Staff. The application area focus was on human and biomedical investigations with a goal to communicate and integrate with other application areas (e.g. in toxicology with the "MEtabolomics standaRds Initiative in Toxicology (MERIT)" funded consortium). The objectives of the Think Tank were to:

1. Identify and prioritize the types of test materials that are needed in the field of metabolomics for QA/QC in untargeted studies
2. Identify the most useful metrics for assessing study and data quality for untargeted metabolomic studies
3. Identify and prioritize processes to ensure appropriate reporting of QA/QC data.

The Think Tank had presentations from leading experts to initiate discussions, followed by facilitated breakout sessions where small groups of attendees answered six different questions. Each attendee had the opportunity to provide input for each of the questions posed. Following the breakout sessions, the information gathered was collated and reported to the larger group. The information was then prioritized through an open voting process that allowed for each attendee to weigh in equally with other attendees. The questions posed and priorities identified are outlined in Table 2.

Following the breakout groups, the attendees identified the overall priorities to address current gaps in the use of QA and QC processes in untargeted metabolomics. The consensus was that there is merit in starting with a set of simple priorities and then increasing their complexity. The consensus priorities are listed below:

1. *Publish a workshop report* to communicate the meeting proceedings to the metabolomics community and allow new members to join the consortium.
2. *Publish a white paper* which could include: (1) metabolomics practices with a focus on QA/QC procedures; (2) an emphasis on the use of QC samples as best practices and give examples of current use; (3) a discussion of metabolomics QA/QC being a developing principle, the need to develop standards, and the need for the wider community to be involved in the process; and (4) a description of the QC procedures performed in experienced labs to begin a community dialogue on the topic.
3. *Engage scientific journals* to report that the community believes that good, documented QC practices, including analysis of QC samples, should be part of the acceptance criteria for publication.

Table 1 Four recommendations as defined from a 2015 questionnaire responded to by the metabolomics community (Dunn et al. 2017) and which were used to develop the agenda for the Think Tank on Quality Assurance and Quality Control in Untargeted Metabolomics Studies

Recommendation
Appropriate agencies and the Metabolomics Society should provide guidance on quality assurance processes and their review and develop consensus processes through specialist meetings and reports
To provide education to the metabolomics community, with an emphasis on early career scientists, on usage of quality materials, and to provide continuing education to ensure these good practices continue
To communicate with the metabolomics community to define the types and volumes of Standard Reference Materials required
Recognizing the need to provide further incentive for laboratories to improve overall QA/QC practices, expert panels should be convened to develop workable, practical QA/QC recommendations and guidelines

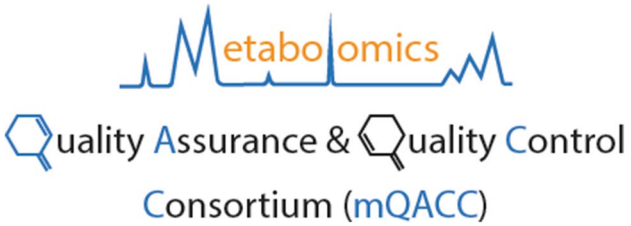
Table 2 Breakout session questions and recommended actions identified at the Think Tank on Quality Assurance and Quality Control in Untargeted Metabolomics Studies

Question	Recommended actions
What are the current gaps that should be addressed to establish widespread best practices for QA in untargeted metabolomics?	• Document complete experimental processes and reporting from study design to data analysis • Focus is not just analytical but study protocols • Training and education, different for researchers and users new to the scientific discipline versus experienced researchers in the discipline • Define the best practices and those that should be avoided in sample collection, processing and storage
What are the current gaps that should be addressed to establish widespread best practices for QC protocols in untargeted metabolomics?	• Obtain buy in from scientific journals, companies, software developers, database developers, and funders • Define best QC practices • Need agreement and to encourage/enforce QC practices • Educate community about QC procedures
What is needed to establish QC acceptance criteria reporting across the wider community?	• Establish minimum acceptance criteria, including creating a broad-based scoring system [For example, one QC scoring scheme could include: (i.e. 0 = none, 1 = pooled, 2 = pooled and SRM)] • Create reporting standards/SOPs for the entire analytical process
What should be the minimum QA and QC reporting standards for publications and databases?	• Define acceptance criteria [e.g. scoring system (or explain why criteria were not met)] • QC metadata should be reported (e.g. sample order, QC sample reference material used) and define elements under each category with adequate details for reproducibility
What are the key characteristics of high-availability test material sample types for metabolomics?	• Develop test materials for inter-laboratory comparisons • Quantitative/semi-quantitative comparisons • Inexpensive materials • Same sample for all technologies—must cover wide range of characteristics • Develop key data quality metrics for each platform and test material
What best use practices should be established for test material samples by the community?	• Define best practices • Need consensus, including when you run the test material and timing of use, to allow for data harmonization • Context dependent (i.e., highly dependent on matrix) • Determine if test materials should be accompanied by SOPs • Test materials should be used in conjunction with other QC samples • Use for lab qualification, instrument qualification, training

4. *Document and subsequently publish* the complete experimental procedure for metabolomics, including the QC practices
5. *Establish a community forum* to discuss the development of reference standards, and interlaboratory comparison exercises.
6. *Engage the community* to identify key reference materials that need to be developed.
7. *Form a steering committee* and larger scientific advisory board.
8. *Identify funding opportunities* to hold meetings and continue the group discussion and planning.
9. *Organize workshop(s) on QA/QC at the Metabolomics Society* meeting to promote community engagement in these efforts.

3 Establishment of the Metabolomics Quality Assurance and Quality Control Consortium (mQACC)

Following the inaugural meeting, the group has continued to be active, and ultimately established the metabolomics Quality Assurance and quality Control Consortium (mQACC). The establishment of the consortium will provide a structure for the Think Tank participants to not only continue these efforts, but expand them to include the broader metabolomics community. The consortium logo is shown below and further information is available at https://epi.grants.cancer.gov/Consortia/mQACC/.



Author contributions All authors contributed equally to the preparation of this manuscript.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest to disclose. The authors declare no competing financial interests. The views presented here do not necessarily reflect those of the U.S. Food and Drug Administration. Views expressed in this article are those of the authors and do not necessarily represent views or policies of the US EPA. Mention of products or trade names does not indicate endorsement of by the US EPA. Any use of trade, firm, or product names is for descriptive purposes only and does not imply endorsement by the U.S. Government.

Research involving human and animal participants No research involving human or animal participants is included.

Informed consent No research involving human participants is included and no informed consent was therefore collected.

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