Opinion Paper

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Preanalytical quality improvement – an interdisciplinary journey

<https://doi.org/10.1515/cclm-2022-0117>

Received February 22, 2022; accepted February 23, 2022;

published online March 7, 2022

Abstract: Since the beginning of laboratory medicine, the main focus was to provide high quality analytics. Over time the importance of the extra-analytical phases and their contribution to the overall quality became evident. However, as the initial preanalytical processes take place outside of the laboratory and mostly without its supervision, all professions participating in these process steps, from test selection to sample collection and transport, need to engage accordingly. Focusing solely on intra-laboratory processes will not be sufficient to achieve the best possible preanalytical quality. The Working Group for the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has provided several recommendations, opinion papers and scientific evidence over the past

years, aiming to standardize the preanalytical phase across Europe. One of its strategies to reach this goal are educational efforts. As such, the WG-PRE has organized five conferences in the past decade with the sole focus on preanalytical quality. This year's conference mainly aims to depict the views of different professions on preanalytical processes in order to acquire common ground as basis for further improvements. This article summarizes the content of this 6th preanalytical conference.

Keywords: errors; integrated diagnostics; interdisciplinary; laboratory medicine; preanalytical phase; quality; standardization.

Introduction

Imagine suffering from a health issue, needing medical treatment. You go to see the doctor either in the hospital or

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in primary care. Most probably your blood will be collected for further analysis. Imagine further that your report comes back from a ISO15189 accredited laboratory, with false positive or false negative results, obviously without you or the treating physician knowing of this circumstance. The consequences might range from mild to catastrophic. This scenario is not uncommon and emphasizes two things: (1) Laboratory tests are vital for the majority of medical decision making, as the current pandemic clearly demonstrates [1], and (2) even if the analytical quality complying with the highest standards, errors may occur in many extra-analytical process steps [2]. While the room for improvement is limited in the analytical phase, it is a wide scope to improve the preanalytical phase [3].

One aspect that contributes massively to the discrepancies in error rates between these two phases is that the former one is under meticulous control of the laboratory while the latter one is not. The extra-analytical phases are prone to error since its standardization and surveillance are far more difficult since more non-laboratory professions are involved [4]. Physicians, nurses, carriers/porters etc. need to be educated. However, from their point of view the additional task of adhering to several guidelines and recommendations regarding blood collection, storage and transport hamper the focus on their core duty. Therefore, an understanding among all involved professions need to be achieved to be able to improve the overall laboratory quality.

The Working Group for the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) has made it its goal to provide the necessary documents for preanalytical standardization [5–12] (a complete list can be found at <https://www.eflm.eu/site/pubsearch/WG-PRE>). Additionally, the WG organizes conferences every two years focusing solely on preanalytical topics. This year the 6th preanalytical conference under the title “Preanalytical Quality – An interdisciplinary journey” will be held online from 15th to 18th of March 2022 due to the raging pandemic. This collective article anticipates and summarizes the concepts expressed in the various lectures of this conference and follows the previous four opinion papers that were published by the EFLM WG-PRE upon the preceding conferences [13–16].

What is new in the pre-analytical phase?

Most preanalytical studies in the past were focused on understanding the mechanisms and effects of various pre-analytical errors and the frequency of these errors. This led to

the understanding of the problems magnitude. It became evident that preanalytical phase is the most vulnerable part of the total testing process and that we as a profession have the responsibility to address this issue with great care. What was not so obvious at that time was the link between preanalytical errors and patient outcome. For sure, every improvement in preanalytical phase will not necessarily lead to the reduction of the frequency of diagnostic errors and better patient outcome. The key question for us is therefore to understand which preanalytical errors have major contribution to patient outcome and how to manage those errors [17, 18]. High quality outcome studies are needed, which employ evidence-based metrics to measure not only the effects of various preanalytical errors on test results, but also on the patient outcome and healthcare expenses. Future studies need to be designed, executed and reported in a standardized manner in order to increase their transparency and comparability, to assure transferability of results and demonstrate to what extent various preanalytical sources of variability may or may not affect medical decision making, quality of patient care and associated costs. The role of WG-PRE in the future shall therefore be to propose recommendations for standardized performing and reporting of preanalytical studies. One such recommendation has recently been published for stability studies and surely more will follow soon [6].

Preanalytical challenges and solutions in long distance sample transport

As mentioned in the introduction, sample transportation is a critical preanalytical process step, potentially impacting test results. It is therefore critical that samples sent to the laboratory for testing arrive in good quality and that they arrive with a full audit trail of the conditions they have been transported in, to enable laboratory staff to provide the correct interpretation and advise for the best patient care. There are various possible mechanisms of sample transport, from manual, through pneumatic tube systems, road vehicle, drone, robot, post and finally long distance using planes, trains or boat [19, 20]. For all of these possibilities it is important that each mechanism is fully verified, to ensure sample suitability for the requested analytes. Additionally, in order to allow a complete transport audit trail, data loggers, tracking temperature, g-forces and time should accompany the samples [21]. In addition to details about the conditions samples are exposed to, it is also important to ensure that all packaging is safe and there is no risk of the packaging

impacting on sample integrity or from other forms of contamination [22].

Impact of preanalytical phase on SARS-CoV2 testing

During the Covid19 pandemic, nasopharyngeal swabs sample collection (NSSC) for laboratory testing has become crucial. Healthcare professionals describe this type of sample collection as simple procedure when compared with others procedures, such as tracheal intubation, broncho-aspiration, or peripheral insertion of central catheters [23]. However, preanalytical factors such as the type of swab used, inadequate collection or transportation may lead to false negative test results and the subsequent consequences of viral spread [24]. Marty et al. properly showed how to obtain an NSSC with detailed demonstration regarding the use of personal protective equipment during the procedure, however, omitting details regarding swab types [25]. The swabs for collecting biological specimens are cylindrical rods around one end of which, the tip, is wrapped a wad of fiber with hydrophilic properties, to allow rapid absorption of sufficient quantity of specimen. These fibers consist of materials such as rayon or cotton.

Stable adherence of the fiber wrapped around the tip of the rod is generally achieved by gluing. This type of swab allows a recovery of only 40% of the biological material, thus reducing analytical sensibility and increasing the chance of false negative results. Alternatively, another type of swab may be used, with short nylon fibers that are arranged in a perpendicular fashion. This arrangement results from a process called flocking, where the fibers are sprayed onto the tip of the swab, while it is held in an electrostatic field. This technology allows a recovery of up to 90% of the biological material, increasing sensibility and minimize false negative results [26].

However, the cotton swabs are widely employed for NSSC, mainly in undeveloped countries. As a consequence, poor sample quantity may lead to reduced analytical quality and may jeopardize patient safety.

PREDICT – a checklist for preventing preanalytical diagnostic errors in clinical trials

Uncertainties within the extra-analytical phase of the total testing process, especially including preanalytical

activities, continue to challenge quality and reliability of the total testing process [27]. The research arena, an essential part of science and medicine, is not logically exempted by the risk that mishandled preanalytical procedures may generate a dramatic impact on the endpoints and outcomes of the research, which may then translate into inappropriate development and/or validation and/or certification and/or clearance of medical therapies and devices [28]. Owing to such increasing awareness, the EFLM WG-PRE has developed and endorsed a dedicated checklist aimed at prevention of preanalytical diagnostic errors in clinical trials (PRE-DICT) [8], which is especially aimed at addressing many important aspects from collection to preparation for testing of blood specimens in clinical trials. Therefore, this checklist targets specific preanalytical aspects, those more vulnerable to (human) errors, and thus encompassing test selection, patient preparation, along with blood samples collection, handling, preparation, transportation, storage and retrieval before testing. All these key aspects shall be proactively evaluated before designing and developing clinical trials, formally implemented within all standard operation procedures (SOPs) available to the staff, with specific focus on the fact that protocol deviations shall be highlighted and recorded, for preventing that unreliable test results may jeopardize results and evidence emerged from clinical trials.

IT solutions aiding in preanalytical process optimization (A.I.)

In spite of many successful approaches to decrease errors in the total laboratory process, still some areas remain, showing high error rates. Trying to categorize these areas, most of them are to be found at interface processes between patient, clinician and the laboratory, such as inappropriate test requests (over-/underuse), neglected results, incorrect interpretation of results, missing or inappropriate follow-up testing and other [2].

To address these interface errors, new technological and IT solutions need to be adopted. Many of such technological assists are already available, such as the earlier mention data-loggers to track sample transportation, or devices to standardize or even perform sample collections [7]. For the more complex processes at the interfaces, software solutions using artificial intelligence (AI) are probably the best way forward. Such systems are already in use in different medical fields like radiology, ophthalmology,

genetics, cardiology and others [29] as well as in specific areas of laboratory medicine where image recognition is the main mode of sample testing, like hematology [30]. In other, more complex areas, in which results from anamnesis, physical examination, laboratory tests, preexisting condition etc., are need for valid diagnostics and interpretation, AI could support by calculating smart algorithm. Nevertheless, relevant issues, legal and medical, need to be addressed before AI models can become a reliable tool to optimize diagnostic quality in pre- and postanalytics.

Implementation of pre-labelled barcode tubes and the GeT-System in a general hospital for the exact documentation of the time of venous blood sample and improvement of sample quality

In an endeavor to improve sample quality at the Department of Laboratory Medicine of the General Hospital Steyr, pre-labelled barcoded tubes (Greiner Bio-One GmbH, Austria or BD, NJ, USA) were introduced in late 2016 [31]. The accompanying software “Greiner eHealth Technology (GeT) System” supports the use of these tubes and documents the various steps in the preanalytical (e.g. exact time of blood collection) and postanalytical phases. The GeT System interacts with the Laboratory Information System, providing the possibility to issue a warning on the report accompanying the result of time sensitive parameters, in case the according timespan between sample collection and analysis exceeded the parameters standards. Two years after implementation, the influence of the pre-barcoded tubes in combination with the GeT System on samples quality was evaluated. The “total number of preanalytical errors divided by the total number of tubes” and “the number of patient misidentification errors divided by the total number of venipunctures” as was used quality indicators.

Between the years 2016 and 2018 a 29% reduction pre-analytical errors (0.44% and 0.32% of all tubes) was observed, mainly due to a decrease of hemolytic samples. Patient identification errors decreased by 53% (51 in 2016 and 24 in 2018). These findings supported the initial intent when implementing pre-barcoded tubes and the GeT system, namely to increased patient safety by reducing preanalytical errors. Apart from allowing an automated documentation of the correct time of blood collection, this new system showed a high user satisfaction at acceptable costs.

How to include your clinicians in the preanalytical process – a toolbox

Clinical laboratory initiatives that impact the preanalytical phase are doomed to fail in the absence of sufficient communication among all relevant stakeholders. Effective methods to involve non-laboratory physicians in the pre-analytical process include (1) ensuring adequate clinical laboratory representation on hospital standing committees, (2) encouraging collegial relationships with strong communication between clinical laboratory faculty/staff/trainees and other clinical partners, (3) creation of a laboratory test formulary committee to address test stewardship [32], and (4) close partnership in the creation of protocols with interventionists who perform complicated sampling procedures [33]. The COVID-19 pandemic has created barriers to initiating some of these interventions, as social distancing and workplace safety measures have removed opportunities for both formal and informal communication. The pandemic has also shown, however, that communication with clinicians, for example in coordinating workflows for rapid COVID-19 assessments prior to procedures, is critical for safe and effective work in these new and challenging times.

Willingness of clinicians to collaborate with lab specialists in improving test requesting

Numerous studies have shown the misuse of laboratory resources [34–36]. Since most published viewpoints on this topic, including demand management as possible solution, reflects only those from laboratory specialists and not those of clinicians, the EFLM WG-PRE decided to survey both clinicians’ and laboratory specialists’ views. Hence, two surveys were distributed to laboratory specialists and clinicians from 9 European countries. Seventy-two responses from laboratory specialists and 78 from clinicians were analyzed [37].

Answers showed that 76% of clinicians believed improving test requesting would enhance patient safety and half of the clinicians reported regular contact with laboratory specialists. However, only 19.2% reported participating in multidisciplinary groups on appropriateness of test requesting, while another 35.9% did not participate in such rounds, but were willing to. Six percent of clinicians stated that such groups did not exist in their setting, but over 80% of the latter would be willing to participate in case such groups were to be implemented. When asked who’s role in the choice of test

portfolio ought to predominate, both clinicians and laboratory specialists valued their own opinion over the others while agreeing that health care management should have the least influence on this decision.

In conclusion, given the willingness expressed by both sides, a proactive attitude should be adopted to facilitate this type of collaboration. As it is the laboratory specialist's core task to acquire knowledge on available analytes, their appropriateness as well as their preanalytical and analytical biases, this profession should initially provide a suggestion on laboratory testing policies and agree with clinicians prior to implementation.

The impact of preanalytical factors on results – a clinicians view on what this means to clinicians and patients

The Get It Right First Time (GIRFT) program is a clinically led national program in England that studies clinically important variation across multiple specialties. In the Pathology program we have reframed the preanalytical phase using the term “Clean In”, which sees the problem from the perspective of the patient rather than the perspective of the laboratory [38]. We considered questions, universally true, even for high quality service. These include: (1) are the tests appropriate? (2) are samples collected, labelled and stabilized appropriately? (3) do samples get to the point of testing on time?

We have chosen a variety of metrics that can be compared across labs that start to shine a light on the variation that occurs at this preanalytical stage across all pathology disciplines. For example, we have looked at inter-laboratory variation in

- requesting rates of different analytes
- proportion of requests that have accurate patient identifier
- proportion of potassium results that are non-numeric
- difference in mean potassium between February and July
- end to end turnaround time

In our report we describe several examples of excellence to tackle these issues. For instance, we looked at how some labs facilitate requesting of the correct tests aligned to the clinical question being asked; how some have improved phlebotomy; how some have stabilized samples outside the lab; how transport can be improved.

We believe that our report could act as a catalyst for wider change.

Interdisciplinary improvement of the preanalytical phase: nurses point of view

An important goal of good nursing care is to reduce errors and prevent complications [39, 40]. Research show that students and newly trained nurses have deficiencies in performing practical skills such as venous blood specimen collection. Hence, we investigated nursing students' phlebotomy performance after training and before attending their internship. Thirty-two nursing students were observed and filmed during training at the clinical training center, documenting the procedure on standardized observation protocols.

We found a large variation in students' performance. After the training, phlebotomy performance accuracy increased in respect to information procedures (39% adherence), identification procedures (83% adherence) and tourniquet procedures (22% adherence). Hence, there is a need to describe, verbalize and to communicate the student's level of competence with clinical supervisors at the clinical placements to ensure patient safety. Clinical supervisors have to know about the student's level of practical skill performance before taking over and continue with the training. Additionally, nursing students and newly qualified nurses should pass an according standardized exam before entering internship.

Integrated diagnostics: the future for laboratory medicine?

Currently, the scenario of *in vitro* and *in vivo* diagnostics can be summarized using the “silo metaphor”, where laboratory medicine, pathology and radiology are three conceptually separated diagnostic disciplines, which will increasingly share many comparable features. The substantial progresses in our understanding of biochemical-biological interplays that characterize many human conditions, coupled with extraordinary technical advances, are now generating important multidisciplinary convergences, leading the way to a new frontier, called integrated diagnostics [41]. The COVID-19 pandemic has highlighted the need for more and better integration of not only between all laboratory medicine sub-disciplines, including pathology, but also imaging [42].

The convergence of imaging, pathology and laboratory tests with advanced information technology, has an enormous potential for revolutionizing diagnosis and therapeutic management of human diseases, including those causing the largest number of worldwide deaths (i.e. cardiovascular disease, cancer and infectious diseases). In addition, the use of artificial intelligence and machine learning tools may pave the way to personalized medicine and better clinical outcomes for individual patients and populations [29]. This, in turn, requires innovative education and training programs to enable future laboratory professionals to effectively work as members of integrated and multidisciplinary teams [43].

Conclusions

These collected abstracts nicely show that Preanalytical Quality Improvement goes far beyond correct sample collection. Starting at the appropriate test selection, over thoughts on integrated diagnostics and closer collaboration with clinicians to the implementation of A.I. technology, the trend to intensify interdisciplinary strategies becomes more than obvious. Hence, laboratory specialists are encouraged to pro-actively engage with other disciplines, either diagnostic or clinical, and to embrace new technology as an inevitable tool, aiding our daily life and contributing to better patient care.

Research funding: None declared.

Author contribution: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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