Review

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The preanalytical phase – from an instrument-centred to a patient-centred laboratory medicine

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Abstract: In order to guarantee patient safety, medical laboratories around the world strive to provide highest quality in the shortest amount of time. A major leap in quality improvement was achieved by aiming to avoid preanalytical errors within the total testing process. Although these errors were first described in the 1970s, it took additional years/decades for large-scale efforts, aiming to improve preanalytical quality by standardisation and/or harmonisation. Initially these initiatives were mostly on the local or national level. Aiming to fill this void, in 2011 the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) working group "Preanalytical Phase" (WG-PRE) was founded. In the 11 years of its existence this group was able to provide several recommendations on various preanalytical topics. One major achievement of the WG-PRE was the development of an European consensus guideline on venous blood collection. In recent years the definition of the preanalytical phase has been extended, including laboratory test selection, thereby opening a huge field for improvement, by implementing strategies to overcome misuse of laboratory testing, ideally with the support of artificial intelligence models. In this narrative review, we discuss important aspects and milestones in the endeavour of preanalytical process improvement, which would not have been possible without the support of the *Clinical Chemistry and Laboratory Medicine* (*CCLM*) journal, which was one of the first scientific journals recognising the importance of the preanalytical phase and its impact on laboratory testing quality and ultimately patient safety.

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How it all began

As early as 4,000 BC, analyses of human urine samples have been documented by Babylonian and Sumerian physicians [1]. A long time has passed since then and many analytical innovations have finally led to today's diagnostic possibilities. In modern healthcare settings, a sheer endless variety of laboratory tests can be performed with astonishing accuracy and quality in record turnaround times, building the basis of the majority of medical decisions [2]. Currently laboratory medicine has the lowest error rates among medical diagnostic disciplines, with a six-sigma level of >4 [3]. Aiming for even higher quality, it soon became evident that the majority of errors within the total testing process are to be found within the preanalytical phase [4–6].

In the 1970s attentive observers, such as Walter Guder, who many colleagues consider to be the founder of preanalytical science, found that despite high analytical quality, test results were varying, depending on influencing variables prior to the analysis [7]. The term "preanalytic" was then introduced by Statland et al. in 1977 [8].

Neglecting the obvious importance of these findings, it took another 15–20 years for laboratories to acknowledge at least intra-laboratory preanalytical influencing factors [4]. Over the following years laboratories expanded their search for errors onto the extra-laboratory preanalytical processes. Today a more patient-centred approach is emerging, aiming to avoid all test related errors, potentially leading to wrong, missed or delayed diagnosis (Figure 1). Similarly, the scientific interest in preanalytics developed continuously from the late 70s until today (Figure 2).

Why all that fuzz?

Errors within the preanalytical phase are numerous and can be categorised into sample collection, sample transportation and sample preparation/processing prior to

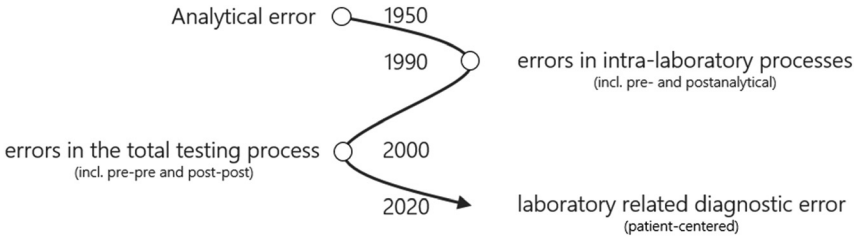

Figure 1: Evolution of focus on errors in the total testing process over time. Adapted from ref. [9].

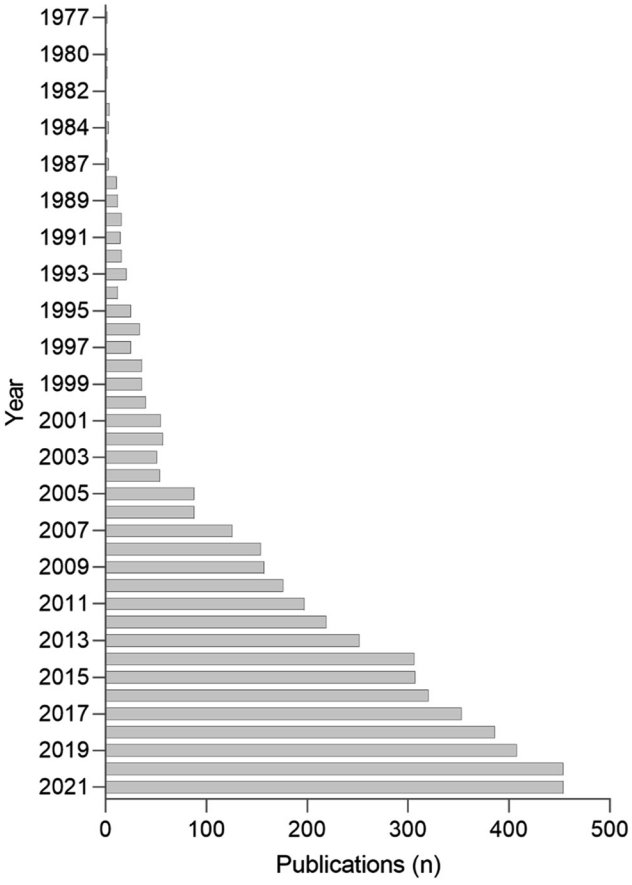

Figure 2: Number of publications dealing with preanalytical phase over time.

Table 1: Types of preanalytical errors.

Inappropriate test request	Inappropriate tests ordered with respect to the clinical question (Overuse)
	Incorrect tests ordered with respect to the clinical question (Underuse)
Sample misidentification	
Test request transcription error	
Unintelligible requests	
Incorrect sample type	Inappropriate matrix
	Inappropriate container
Incorrect filling level	Insufficient volume for testing
	Inappropriate sample/anticoagulant ratio
Inadequate transportation/storage	Sample not received
	Sample not stored correctly before transport/analysis
	Damaged sample
	Inappropriate transportation temperature
	Transportation time exceeds sample stability
Contaminated sample	Microbiological contamination
	Contaminated by treatment (e.g. i.v. fluids, i.v. medication)
Haemolysed sample	
Clotted sample	
Inappropriate sampling time	

Adapted from ref. [16].

analysis (Table 1). Among these errors, haemolysis may be considered as a category of its own, responsible for the majority of rejected samples [10], which is why most modern analyzers have built-in haemolysis detection functionalities. However, there is still no harmonisation regarding the measurement of free haemoglobin [11], the definition of test specific cut-off values [12] or on whether or not to report or to reject results from haemolysed samples [13, 14]. Circumstances causing haemolysis may originate from the patient (*in-vivo* haemolysis), incorrect phlebotomy techniques, inadequate specimen transport, incorrect intra laboratory processing or from inadequate specimen storage [15].

While haemolysis is detected and reacted to by the laboratory, other frequent preanalytical errors, such as patient misidentification, may go undetected. In consequence, these errors may severely jeopardize patient safety, due to incorrect treatment or missed/delayed diagnosis [17]. The latter is one of the major contributors to diagnostic error [18], which in turn is the third leading cause of death in the US, as Makary et al. found out [19].

Apart from affecting patient safety, preanalytical errors may cause serious financial impact. An OECD study found that 15% of hospital expenditure and activity in OECD

countries can be attributed to treating safety failures [18]. Studies, evaluating costs of haemolytic samples, although reaching different conclusions, depending on the local setting and the study design, calculated annual costs ranging from $100,000 to $1.2 million [20–23].

Based on all of these facts and the circumstances that the preanalytical phase obviously needed guidelines and recommendations in order to achieve normalisation, in 2011 the European Federation of clinical chemistry and laboratory medicine (EFLM) working group preanalytical phase (WG-PRE) was founded under the chair of Ana-Maria Simundic.

The EFLM WG-PRE

Survey European laboratories on preanalytical sample handling, issuing best practice recommendations, promoting the importance of the preanalytical phase and organising conferences on preanalytical topics are among the aims of the WG-PRE. Originally, only the countries represented by the founding members were part of the WG-PRE (Ana-Maria Simundic – Croatia (Chair), Giuseppe Lippi (Italy), Mads Nybo (Denmark), Kjell Grankvist (Sweden), Michael Cornes (England), Mercedes Ibarz (Spain),), Zorica Šumarac (Serbia) and Svetlana Kovalevskaya (Russia). However, the group quickly expanded, currently representing 20 European countries, one representative from the Latin America Confederation of Clinical Biochemistry (COLABIOCLI), one representative from the US, two representatives from the European Organisation for external quality assurance providers in laboratory medicine (EQUALM), as well as consultants from 13 IVD companies.

After surveying laboratories on phlebotomy practices and preanalytical sample handling [12, 24–26], the WG-PRE has issued several recommendations and guidelines in the 11 years of its existence. Amongst others, the European consensus guideline on venous blood collection in co-operation with the COLABIOCLI [27], guidelines on fasting prior to blood collection [28] or on local blood collection tube validation [29] and the order of draw [30], recommendations on managing haemolysed samples in clinical chemistry testing [14], local quality assurance of haemolysis/icterus/lipaemia (HIL) indices [31], the CRESS checklist on how to report stability studies [32], the PREDICT checklist on how to avoid preanalytical bias in clinical studies [33] and a consensus document on how to meet the International Organization for Standardization (ISO) 15189: 2012 preanalytical requirements in clinical laboratories [34].

Current projects include recommendations on urine acidification for clinical chemistry testing, recommendations on how to perform and how to evaluate stability studies, as well as a free to use database of stability data for laboratory parameter's in different matrices.

Additionally, the WG-PRE has organised six preanalytical conferences throughout Europe, which attracted an increasing number of participants.

Recently, the WG-PRE has intensified the collaboration with the post analytical working group (WG-POST) of the EFLM, thereby being able to focus on topics spanning both pre and post analytical phase processes, such as demand management or laboratory diagnostic algorithms (these topics are discussed at the end of this manuscript).

Quality control in the preanalytical phase

The challenge of preanalytical QC, is that, in contrast to analytical QC, most process steps occur outside of the laboratory, being handled by a variety of professionals (clinicians, nurses, carriers, et cetera), without defined rules, guidelines, or standard operating procedures and with limited monitoring possibility for the laboratory [35]. However, there are several possibilities that should be implemented by every clinical laboratory, in order to maintain or improve high quality of the total testing process.

Quality indicators

In contrast to quality control in laboratory testing, preanalytical variables, potentially influencing test results, may be acquired and documented in form of key performance indicators (KPI), so-called quality indicators (QI) [36]. These QIs usually reflect preanalytical error rates, such as the amount of misidentified samples, the amount of clotted samples, the amount of haemolysed samples et cetera.

Similar to other KPIs, preanalytical QIs should be easy to retrieve in an automated fashion, should be of relevance to improve testing quality, should have defined acceptability criteria and defined actions upon the deviation from these criteria [37].

In the strive for standardisation, the EFLM working group of laboratory errors and patient safety (WG-LEPS) developed a model of quality indicators (MQI) for pre-analytical, intra-analytical and post-analytical processes, all categorized in distinct priority levels, including guidelines on how to measure them [16, 36, 38]. In addition the WG-LEPS provides a

free to use database for laboratories to input and document their QIs, making quality control over time as well as national and international benchmarking possible [39].

Apart from this International project, there are some other, similar preanalytical benchmarking projects and databases for QI input, either proactively (database input) or reactively (similar to external quality assessment), such as the German/Austrian RfB Preanalytical Benchmark Database [40], the Australasian QIs programme Key Incident Monitoring and Management System (KIMMS) [41], the Brazilian laboratory indicators benchmarking program [42], the external quality assurance preanalytical programme of the Spanish Society of Laboratory Medicine ($SEQC^{ML}$) [43] or the Nordic haemolysis project [44] amongst others.

Internal quality control (IQC)

Haemolysis, icterus and lipaemia (HIL) are preanalytical biasing variables, measured in a similar fashion to other clinical chemistry testing parameters and can therefore be monitored by using quality control material. According to the answers of 1,405 laboratories to the WG-PRE survey on preanalytical sample handling, assessment and management of haemolytic, icteric or lipaemic samples is highly heterogeneous across Europe [12]. However, given the frequency of haemolysis and the fact that it is one of the major contributors to preanalytical error and simple rejection, the level of free haemoglobin should be measured in every sample entering the laboratory in addition to the ordered tests. Upon exceeding defined thresholds, the laboratory should then act in a standardized manner. As mentioned above, the WG-PRE provides recommendations on the selection, preparation, storage, use and the assessment of in-house haemolysis quality control material, including recommendations on where to set the performance goals and how to manage unacceptable IQC data as well as recommendations on the practical management of commercial HIL IQC materials [31].

An issue still not resolved, is the need for harmonization of HIL measurements. While quantitative measurement seems preferable, several analytical instruments from a variety of IVD manufacturers are currently reporting haemolysis levels in semi-quantitative categories, reducing the granularity of possibilities to react to haemolytic samples [11]. Additionally, benchmarking haemolysis levels as overall sample quality predictor is made near to impossible.

External quality assessment (EQA)

In addition to daily internal quality control, correctness of HIL results need to be controlled using external quality control. The above mentioned quality indicator bench marking systems could be considered as such. Additionally, over the past years most EQA providers have incorporated some kind of preanalytical scheme, either as an online survey on preanalytical questions and hypothetical situations or by distributing preanalytical altered samples.

Current standards and regulations

International regulations

Since the preanalytical phase was neglected for some time, laboratory regulations incorporated according paragraphs only in recent years/decades. The accreditation standard ISO15189 added regulations on the preanalytical phase in the 2012 update, requiring documentation, definition of thresholds and criteria or improvement actions in preanalytical quality management, blood collection, sample transport, reception and acceptance [45]. This document is also referred to from other ISO standards, focusing on laboratory diagnostics, like the ISO 22870 standard for point-of-care testing [46]. A detailed list of these requirements as well as recommendations for clinical laboratories on how to comply with these, was published by the WG-PRE in 2021 [34].

Other standards from the ISO or the European Committee for Standardization (CEN) focus specifically on laboratory sub-disciplines, like the ISO-20184/-20166/20186 or CEN/TS-16835/-16945, regulating molecular *in vitro* diagnostic examinations, including its preanalytical requirements [47].

National guidelines

In addition, several national standards have been issued, referring to preanalytical requirements, like those from the Clinical & Laboratory Standards Institute (CLSI) [48–52] or the German "Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen" [53]. In 2013, the WG-PRE therefore surveyed 28 European countries on phlebotomy guidelines, education and training and found that 7 of these countries have a national guideline [25]. Additionally, the results from the survey

showed a large heterogeneity among the professions of the phlebotomists (nurses, laboratory technicians, clinicians, and even administrative staff, among others), as well as the educational level specific to phlebotomy.

Phlebotomy guidelines

Based on these findings and the fact that several different phlebotomy guidelines with partially contradicting statements exist [27, 52, 54], the WG-PRE decided to issue a European consensus guideline for venous blood collection, which, in contrast to existing guidelines, would provide more in-depth explanations, including grades of recommendation, as well as free-to-use educative supplemental material (PowerPoint presentation, printable posters, instructional videos) [27]. This guideline was developed in collaboration with the COLABIOCLI and approved by the national members of EFLM and COLABIOCLI.

In-vitro Diagnostic Medical Device Regulation

With the transition of the *In vitro* Diagnostic Medical Devices Directive (IVD-D 98/79/EC) to the *In-vitro* Diagnostic Medical Device Regulation (IVDR 2017/746), medical laboratories and IVD manufacturers are required to certify their existing diagnostic tests, providing information on the scientific validity as well as the analytical and clinical performance of the test [55]. The regulation entered into force on 26th May 2017 with a 5-year transition period, so the date of conversion was the 26th May 2022. However, due to implementation challenges, the IVD-R was partially delayed, depending on the classification of the test, but until 26th May 2027 the latest. After this date most CE-marked IVDs can only continue to be marketed if they comply with the IVD-R. This regulation applies also to long since established CE marked tests. The certification or validation of diagnostic tests also include possible influences due to preanalytical factors. Therefore, the IVDR explicitly requests information related to the sample quality in the context of product verification that relates to assay performance (IVDR Annex II: 6.1.1), including preanalytical variables, such as sample types, sample stability (including time and temperature limits) and effects of freeze/thaw cycles [47].

Terminology standards

Apart from regulations on preanalytical sample handling, the need for a harmonized system for preanalytical error and quality indicator terminology has emerged, thereby being able to systematically document, monitor and benchmark respective numbers. Currently there are some models available, like the LOINC-, SNOMED or SPREC-Coding systems [56–58]. However, to date no real consensus exists about which system is to be applied in what way.

The pre–pre analytical phase

Historically, the preanalytical phase processes are spanning from sample collection to sample processing prior to analysis. However, technically speaking, the preanalytical process begins with the clinicians intent to order specific laboratory tests, selected on the basis of the medical condition of the patient. This phase has been called pre-preanalytical phase by some authors [59]. The patients safety risk that lies within the process of test selection by far exceeds the risk inherent in all other preanalytical process steps combined. The published numbers on the frequency of over- and underuse are diverging, depending on the local setting and the study design, ranging from 16 to 70% and from 40 to 44% for over- and underuse, respectively [6, 60–63].

These inappropriate laboratory test utilisation habits may result in severe patient harm by inadequate follow-up diagnostics or treatments or by missed or delayed diagnosis. Several studies have shown that diagnostic errors are one of the main contributors to overall patient safety risk [18, 19].

Inadequate test selection, either by ordering none needed tests (overuse) or by not ordering needed tests (underuse) may be caused by a variety of reasons [64], but the absence of laboratory specialists, aiding in this task may be the major contributor. This absence may obviously be caused by lacking medical information of the patient, accompanying the laboratory request. However, several methods, proven to be effective in overcoming over-/underuse may be applied, all of which subsumed under the umbrella term “demand management” strategies [65–68]. These strategies can be categorised into laboratory diagnostic algorithms, educational interventions, gate keeping

strategies, harmonisation of test panels and request for design and review of offered tests. All of these strategies may be implemented to overcome overuse, but only laboratory diagnostic algorithms are able to overcome underuse. However, such algorithms are very laborious, as they have to be based on current evidence and developed in collaboration with clinicians and updated regularly. Additionally, they have several limitations, such as the need for clear yes/no decisions and their ineffectiveness in multi-morbid patients [69].

The role of the *Clinical Chemistry and Laboratory Medicine* (*CCLM*) journal in understanding the preanalytical phase

Similarly to the preanalytical phase itself, scientific articles on this topic have been understated and trivialised over a long period of time. The *CCLM* journal was one of the first to take this topic seriously, publishing countless articles regarding preanalytical error rates, causes and consequences of preanalytical errors or strategies to overcome such issues. The Journal has published all of the above-mentioned manuscripts and recommendations/guidelines from the WG-PRE and many other stimulating and thought-provoking articles, which serve as the foundation of many inspiring follow-up studies. Without the *CCLM* journal, knowledge and awareness of errors during the preanalytical phase would not be as developed as they are today, which is why we, on behalf of the WG-PRE, all preanalytical enthusiasts and laboratory professionals around the world, want to thank the Journal for its support in the endeavour of understanding and improving the preanalytical processes for the benefit of laboratory quality and ultimately patient safety.

Congratulations to the Journal on its 60th anniversary and a well-deserved, ever-increasing impact factor.

Where are we now and what is coming next?

As previously mentioned, handling every individual laboratory order separately is unfeasible, given the low number of laboratory professionals in most healthcare settings. Therefore, the obvious solution is the development of artificial intelligence (AI) systems, supporting test selection and interpretation as well as the identification of preanalytical biased samples [70–72]. Currently, only few AI models have been implemented in laboratory medicine, while in other diagnostic disciplines such as radiology, they are far more frequent [73, 74]. The reason most probably lies in the fact that most of the diagnostic disciplines mainly depend on image recognition, a task for which already very refined models have been developed. In contrast, in laboratory medicine a far more complicated network of variables have to be considered, such as the patient's anamnesis, physical examination, medical preconditions, medication, current symptoms, current and previous test results et cetera. However, publications on AI models and laboratory medicine are exponentially increasing over the past years, giving hope for a soon to come disruption in laboratory medicine [75, 76].

The preanalytical phase has gained increasing recognition over the past years/decades, but there is still a long way to go in order to oversee all preanalytical process steps and minimise according errors. In recent years including test selection into the preanalytical phase, has led to a more medical approach of laboratory medicine, being able to provide the vast expertise of laboratory professionals to clinical care. Hopefully, in the near future AI systems will help us providing this expertise not only to selected but to all patients.

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