Review Article

Are we getting better at the preanalytical phase or just better at measuring it?

Giuseppe Lippi[1], Camilla Mattiuzzi[2], Chiara Bovo[3]

[1]Section of Clinical Biochemistry, University of Verona, Verona, Italy; [2]Service of Clinical Governance, Agency for Sanitary Service, Trento, Italy; [3]Medical Direction, University Hospital of Verona, Verona, Italy

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Correspondence to: Prof. Giuseppe Lippi. Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37100 Verona, Italy. Email: giuseppe.lippi@univr.it.

Abstract: There is now consolidated evidence that the vast majority of laboratory errors occur in the extra-analytical phases of the total testing process, and especially in the preanalytical phase. Although development and dissemination of best practice recommendations for this crucial area of diagnostic testing have greatly contributed to reinforce error identification and reporting strategies, it is also undeniable that the combination of greater consciousness about preanalytical issues and technological advancements have helped decreasing the inherent vulnerability of many preanalytical activities, thus finally making the preanalytical phase less vulnerable to errors, slips and lapses. Many potential strategies can be adopted for reducing preanalytical errors, including education and training of healthcare staff on phlebotomy practice and preanalytical errors, greater observance of available phlebotomy guidelines, dissemination of specimen collection modules or phlebotomist check-lists, certification of phlebotomists, transmission of periodic preanalytical quality reports to phlebotomists, establishment of direct feed-back between laboratory professionals and phlebotomists, use of quality and validated blood collection systems for drawing blood, along with introduction of harmonized means for recording preanalytical errors.

Keywords: Quality; errors; phlebotomy; laboratory medicine

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The total testing process

The total testing process can be conventionally split into five principal areas, only one of which is directly related to analytical testing. Briefly, the testing process begins with the pre-preanalytical phase (mainly related to diagnostic tests ordering), then continues with the preanalytical phase (involving patient preparation before testing along with collection, handling, transportation and storage of biological specimens), the analytical phase (i.e., sample analysis), the post-analytical phase (test results reporting), and finally ends with the post-postanalytical phase (pertaining result interpretation and the ensuing clinical decisions) (*Figure 1*) (1). Notably, the first and clear division of the total testing process in 3 to 5 phases, as currently accepted, can be dated back to 1981, when Gorge D. Lundberg, the former editor of the *Journal of American Medical Association (JAMA)*, coined the term "*brain-to-brain turnaround loop*" (2). Since then, this brilliant representation has been widely used to illustrate the inherent complexity of the testing process, which is no longer uniquely identified with the analytical phase (3).

The concept of preanalytical errors

In English dictionaries, laboratory error is defined as "*an error made by the personnel in a clinical laboratory in*

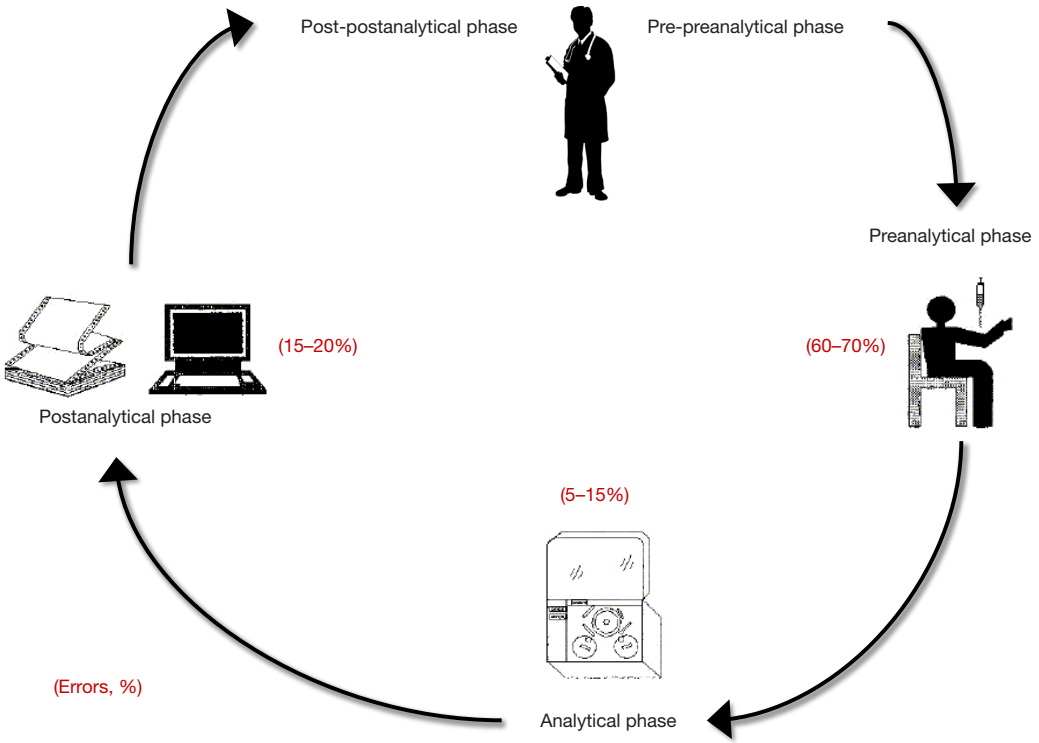

Figure 1 The risk of errors throughout the total testing process.

performing a test, *interpreting data*, *or reporting or recording the results*" (4). According to the ISO Technical Report 22367, the same concept is reported as "*a defect occurring in any part of the laboratory cycle*, *from ordering tests to reporting results and appropriately interpreting and reacting in these*" (5). These two definitions, which appear substantially identical, both emphasize that a laboratory error can be seen as any type of mistake occurring throughout the total testing process, i.e., from the pre-preanalytical to the post-postanalytical phase, so dispelling a widespread clinicians' perception that diagnostic errors are essentially or exclusively "analytical" (6).

As for many other human activities, the possibility that an error may occur throughout the total testing process is not irrelevant. Reliable studies attest that the overall frequency of laboratory errors can be as high as 0.31% of all tests performed (7). It is worthwhile mentioning here, however, that the burden of human errors is directly related to error probability per opportunity and to the number of opportunities for an error to be made (8). Therefore, although it is not difficult to believe that clinical laboratories may actually make 10- to 100-fold more errors than radiologists, the overall number of tests performed by a clinical laboratory is 100- to 1,000-fold higher than those performed by the radiology. When these two estimates are combined [i.e., (number of errors)/(number of tests)], it can be clearly concluded that errors in laboratory medicine have a frequency approximately 10 times lower than in radiology (9). It can hence be concluded that, indeed, "Houston, we have a (preanalytical) problem", but it is undeniable that other diagnostic areas actually have even bigger problems than laboratory medicine.

When the total number of errors is classified according to the different phases of the total testing process, it is now undoubtable that the vast majority of these (i.e., up to two-third) tend to occur in the preanalytical phase (7). Basically, a preanalytical error can hence be regarded as any error occurring from test ordering to physical performance of the test, a process including a kaleidoscope of manually-intensive activities that are still needed to collect reliable biological materials for testing (*Figure 1*).

Apparently, the research into the preanalytical phase and its related problems can be seen as a quite long journey, which has started more than 40 years ago. If one enters the search term "preanalytical" in PubMed, the first item that can be retrieved is a review article published by Statland

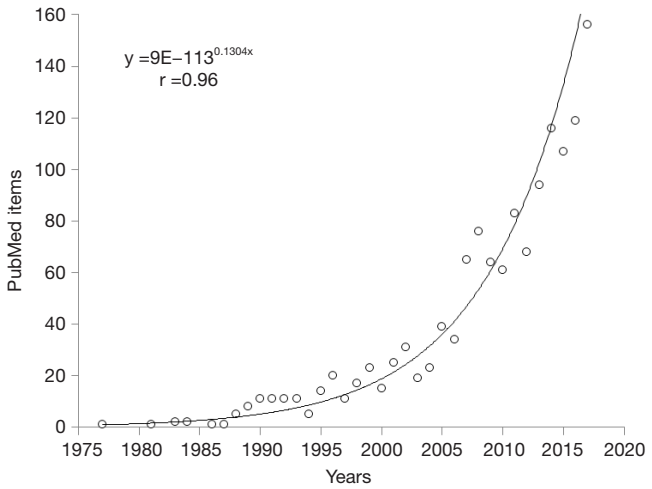

Figure 2 PubMed items retrieved using the keyword "preanalytical".

and Winkel in 1977, dealing with within-subject variability of laboratory tests performed in healthy individuals (10), Nevertheless, if one performs a similar digital search using the key word "laboratory error", the oldest article appearing in PubMed has been published (in Italian) by Mariani in 1954, and actually deals with erroneous data of erythrocytes sedimentation rate (ESR) attributable to problems occurring during collection and preservation of blood (11). Therefore, although the term "preanalytical" has only been officially endorsed in the late 1970s, the issue of the potential impact of preanalytical activities on quality of test results and patient safety is much older. Interestingly, the number of PubMed items retrieved using the keyword "preanalytical" is also shown in *Figure 2*, and the trend is very closely described by an exponential line, characterized by an extraordinary correlation coefficient (r=0.96; P<0.001). This hence mirrors the exponentially increasing interest in science and medicine for the preanalytical phase and in for its related vulnerability.

The nature of preanalytical errors

Although a thoughtful description of the main sources of preanalytical errors is beside the scope of this article, it is worthwhile giving some hints concerning their relative frequency. Overall, the vast majority of preanalytical errors occur during venipuncture, and are mostly attributable to negligence, suboptimal phlebotomy practice, ignorance of basic preanalytical principles (i.e., inappropriate filling or mixing of blood tubes), contamination with exogenous fluids (12). All these factors then contribute to generate a kaleidoscope of preanalytical problems such as (in decreasing order of frequency) hemolyzed samples, blood collected in wrong tubes, underfilled blood tubes, clotted or misidentified specimens (12,13).

Are we getting better at the preanalytical phase or just better at measuring it?

The answer to this question is quite challenging, if not impossible. It is clear to everybody that whenever certain systems or complex organizations are more strictly observed and monitored, the frequency of failures increases in parallel just because slips, lapses and even errors are more precisely identified and then recorded. This holds true for whatever human activity including industry, finance, information technology (IT) as well as healthcare and (laboratory) medicine (14). The answer to this question gets even more problematic because the number of studies which have systematically monitored (for a sufficiently long period of time) the frequency of errors within the same environment remains limited. One of the best publications that has addressed this issue has been published by Carraro and Plebani, who monitored the type and frequency of laboratory errors, in the same clinical laboratory and using the same monitoring system, over a 10-year period. In the first part of this investigation, published in 1997, the authors reported 0.47% frequency of laboratory errors (15), which had however decreased to 0.31% 10-year afterwards (7). In another study Giménez-Marín *et al.* performed a prospective study aimed to monitor preanalytical errors in a Spanish clinical laboratory (13), and concluded that the error rate had decreased by approximately 20% over a 5-year period (i.e., between the years 2007 and 2011).

Reliable evidence that the risk of making preanalytical errors can be actually reduced is also supported by a series of interesting interventional studies. As previously discussed, the vast majority of preanalytical errors are attributable to sample collection and, most precisely, to inaccuracies in phlebotomy practice or blood collection systems (12). In a series of interventional studies aimed to optimize the use of blood collection devices in the emergency department we previously showed that both manual aspirations of blood using closed systems (16), as well as specifically-designed blood tube holders (17), can be effective to substantially decrease the rate of spuriously hemolyzed specimens when blood is collected from intravenous catheters. Similar results were obtained by other groups by using low vacuum tubes

Table 1 Potential strategies for reducing preanalytical errors

Education and training of phlebotomists about phlebotomy practice and preanalytical errors
Observance of available phlebotomy guidelines
Dissemination of specimen collection modules or phlebotomist check-list
Certification of phlebotomists
Transmission of periodic preanalytical quality reports to phlebotomists
Establishment of direct feed-back between laboratory professionals and phlebotomists
Use of quality and validated blood collection systems for drawing blood
Use harmonized means for recording preanalytical errors

in association in indwelling catheters (18,19). Regarding blood collection practice, which widely differs among different phlebotomists (20,21), Lillo *et al.* showed that an educational program targeted for healthcare personnel can substantially reduce the number of sample errors and generate significant improvements of sample quality (22). Similar improvements were recorded by Bölenius *et al.* after establishing educational intervention programs for phlebotomists (23), and by Ying *et al.* who applied a training system aimed to improve quality awareness about the preanalytical phase and behaviors of medical staff (24). A higher degree of sample quality could also be ensured by instructing phlebotomists to avoid collecting blood from small and fragile veins (25), by transmission of periodic preanalytical quality reports to phlebotomists and establishment of direct feed-back between laboratory professionals and phlebotomists (26), by strict observance of available blood collection guidelines (27), by design and dissemination of specimen collection modules (28), or by implementation of phlebotomy check-lists (29).

Taken together, these proof-of-evidence studies clearly attest that the correct answer to the crucial question as to whether we are getting better at the preanalytical phase or we are simply systematically and more accurately identifying and monitoring errors, is… both. Indeed, the dissemination of recommendations and guidelines on the best practices for the preanalytical phase, along with the establishment of many international and national working groups on this topic [e.g., the European Federation for Clinical Chemistry and Laboratory Medicine (EFLM) Working Group for Preanalytical Phase (WG-PRE) or the International Federation of Clinical Chemistry and Laboratory Medicine Working Group on Laboratory Errors and Patient Safety (WG-LEPS)] (30-32), have greatly contributed to enhance the awareness about the importance of reducing laboratory errors and improving the quality of the preanalytical phase. On the other hand, the increased consciousness on these crucial topics has promoted the development and implementation of a number of quality indicators throughout the total testing process, thus including the preanalytical phases, which are increasingly used by clinical laboratories for monitoring local performance and benchmarking with others (33). Since error recording policies are many and multifaceted (e.g., audit, manual recording processes, incident reporting, laboratory information systems or specific software) (34,35), this process shall entail the development of harmonized means for recording errors and other non-conformities.

Conclusions

The management thinker Peter Drucker, the man who conceived modern business management, is often quoted as saying that "*you cannot manage what you cannot measure*". The Italian natural philosopher Galileo Galilei is also quoted as saying that "*you should measure what can be measured, and make measurable what cannot be measured*". If we combine these two foremost quotes and translate them into the field of laboratory medicine, what can be concluded is that we should place more efforts for increasing measurement of preanalytical quality indicators and then intervene upstream to correct areas of the total testing process with greater vulnerability. Although we cannot deny that the interest in identifying and recording preanalytical errors has notably increased over time (36), it is also clear that the combination of a greater consciousness about preanalytical issues and technological advancements for assessing sample quality (i.e., automatic measurement of serum indices) and for decreasing the risk of making errors (i.e., specimen labeling devices), have helped decreasing the inherent vulnerability of many preanalytical activities (*Table 1*) (37). Many other valuable opportunities are in development, including robotic phlebotomy devices and active blood tubes (38).

With diagnostic testing increasingly committed to the cutting-edge personalized medicine (39), but still plagued

by many questionable "political" issues (40), best quality throughout the total testing will become even more critical for supporting clinical decision making and safeguarding patient safety.

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Footnote

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