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NOVEL OPPORTUNITIES FOR IMPROVING THE QUALITY OF PREANALYTICAL PHASE. A GLIMPSE TO THE FUTURE?

NOVE MOGUĆNOSTI ZA UNAPREĐENJE PREANALITIČKE FAZE. POGLED U BUDUĆNOST?

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Summary

The preanalytical phase is crucial for assuring the quality of in vitro diagnostics. The leading aspects which contribute to enhance the vulnerability of this part of the total testing process include the lack of standardization of different practices for collecting, managing, transporting and processing biological specimens, the insufficient compliance with available guidelines and the still considerable number of preventable human errors. As in heavy industry, road traffic and aeronautics, technological advancement holds great promise for decreasing the risk of medical and diagnostic errors, thus including those occurring in the extra-analytical phases of the total testing process. The aim of this article is to discuss some potentially useful technological advances, which are not yet routine practice, but may be especially suited for improving the quality of the preanalytical phase in the future. These are mainly represented by introduction of needle-wielding robotic phlebotomy devices, active blood tubes, drones for biological samples transportation, innovative approaches for detecting spurious hemolysis and preanalytical errors recording software products.

Keywords: errors; patient safety; quality; technology

Kratak sadržaj

Preanalitička faza je od presudnog značaja za kvalitet *in vitro* dijagnostike. Vodeći aspekti koji doprinose štetnosti ovog dela u odnosu na ukupni proces ispitivanja su nedostatak standardizacije različitih postupaka sakupljanja, rukovanja, transportovanja i obrade bioloških uzoraka, a u nedostatku odgovarajućih preporuka i brojnih ljudskih grešaka. Kao i u teškoj industriji, saobraćaju i aeronautici, tehnološko unapređenje obećava da će dovesti do umanjenja medicinskih i dijagnostičkih grešaka, kao i onih koje se javljaju u ekstra-analitičkoj fazi u odnosu na celokupni proces ispitivanja. Svrha ovog članka je da razjasni potencijalnu korisnost tehnoloških unapređenja, koja još uvek nisu u rutinskoj primeni, a mogu doprineti kvalitetu preanalitiče faze u budućnosti. Ovo se uglavnom odnosi na primenu naprava za robotičko vađenje krvi, aktivne epruvete za krv, dronove za transport bioloških uzoraka, inovativni pristup za detekciju sumnjivih hemoliza i preanalitičkih grešaka koje mogu da budu otkrivene pomoću odgovarajućeg softvera.

Ključne reči: greške, sigurnost pacijenta, kvalitet, tehnologija

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Introduction

The preanalytical phase, encompassing appropriate test selection along with all those activities needed for collection and preparation of biological samples before testing, is a crucial aspect for assuring the quality of in vitro diagnostics (1). It is now clear that preanalytical errors not only have a considerable impact on the reliability of tests results, but also represent the most important sources of diagnostic problems, so having more of an impact on the patients pathway than analytical and postanalytical mistakes. The leading aspects contributing to enhance the overall vulnerability of the preanalytical phase include the lack of standardization of different practices for collecting, managing, transporting and processing specimens, the still insufficient compliance with available preanalytical guidelines or recommendations, along with a considerable number of (preventable) human errors (2, 3). As in heavy industry, road traffic and aeronautics (4), technological advancement holds great promise for lowering the risk of medical and diagnostic errors (5, 6). This aspect is especially magnified in those processes importantly relying on human involvement, such as the many manually-intensive activities of the preanalytical phase (7, 8). A reliable approach for overcoming preanalytical problems is hence based on the introduction of lean management (i.e., six sigma or the value chain principle) or technological innovations, some of which borrowed from other human activities (9, 10). Therefore, the aim of this article is to discuss some innovative tools which may be especially suited for improving the quality of the preanalytical phase, especially those which are not yet ready for prime time, but may be seen as valuable opportunities for the future.

Needle-wielding robotic phlebotomy devices

Venipuncture is one of the most frequently performed medical procedures in healthcare (11, 12). Although a large heterogeneity exists around the professional figure of the phlebotomist worldwide (i.e., blood drawing can be performed by certified phlebotomists, nurses, physicians and even by the administrative staff in different countries) (13), this activity remains virtually unavoidable for obtaining whole blood, serum or plasma specimens needed for performing laboratory testing, and still necessitates to be manually performed by the healthcare operators. Several lines of evidence attest that blood collection remains one of the leading sources of preanalytical problems (11,12), which may often translate into tangible risks for specimen quality and patient safety. The main drawbacks making venipuncture a high-risk procedure for the quality of blood samples are insufficient training of phlebotomists, poor compliance with available guidelines and lack of standardization of this practice (14). Although some recommendations have been made available about the best procedure to be followed for drawing blood (8), the activity itself remains extremely operator-dependent, since each single phlebotomist has developed a subjective practice about the use of blood collection device (i.e., straight needles or winged blood collection sets), cleansing the venipuncture site, where (and how) puncturing the vein, inclination of the needle (or even bending it), the way to place the hand on patient's arm and managing the needle holder, the timepoint of tourniquet release, the use of cotton or gauge pads over the venipuncture site when the needle is still inserted into the vein, as well as accurate filling of blood tubes. Due to these many poorly standardized activities, educational programs and technological tools replacing phlebotomist's activity should be regarded as an intriguing opportunity (15), which may also be effective to abate the risk of needlestick injuries. Interestingly, some appealing solutions are being developed. One of this entails the use of needle-wielding robotic phlebotomy devices. The development of multi-axis arms industry has allowed to manufacture specific robots aimed to partially replace phlebotomist activity, more or less like surgical robots have partially relieved surgeons' activity (16). The Veebot System (Veebot LLC, Mountain View, CA, USA), one of these new portable devices, actually resembles a modified version of Epson's standard manipulator arms. Briefly, the vein to be punctured is selected by combining near-infrared illumination with computer vision software. According to manufacturer's claims, melanin concentration and skin tones do not influence the capability of detecting the vein. The use of an inflatable cuff allows arresting venous blood flow and pumping the vein, while the ultrasonic Doppler imaging permits to monitor the blood flow. The selected vessel is then immobilized by the device and a robotically driven needle is inserted into the target vein, driven by ultrasound imaging. The success rate of the Veebot System has reported to be around 80%, although no data have been published to confirm this claim. Moreover, no commercialization of this system is expected unless the rate of successful venipuncture will get over 90%. An alternative device has then been proposed by Chen et al. (17). The concept is basically the same, wherein this device also combines near-infrared imaging, computer vision and robotically guided needle (coupling a 2 degree-of-freedom [DOF] gantry system with a 3 DOF injection arm) within a portable case. Once the target vein has been visualized by imaging and real-time 3D mapping, the vessel is punctured, the needle is disengaged and the healthcare operator performs the remaining part of blood collection (i.e., drawing blood into collection vials). A touchscreen interface permits to strictly monitoring the entire process and intervention in cases of failure or emergency. Most importantly, the performance of the device in automatically puncturing the vein was evaluated in 270 repetitions using a dark-skinned phlebotomy training model, and yielded a first

insertion attempt success rate of 100%. Overall, the mean distance between the needle and the center of the vessel was found to be 0.43±0.21 mm (17). The interesting results of this prototype device were then replicated by the same team of authors in ensuing publications, with refined instrumentation based on 6 DOF, 7 DOF and 9 DOF image-guided venipuncture robots (18–20). The performance and applicability of these devices are actually very similar to those described for the former prototype.

Despite this technology holds great promise for improving standardization and, consequently, the overall quality of venous blood collection practice, some drawbacks need to be highlighted. First, the cost of these devices is still unpredictable, and it remains to be defined whether or not the expenditure may be sustainable by the healthcare system. Notably, some of these systems still need manual intervention for placing blood collection tubes into the robot and/or aspirating blood from the vessels. Therefore, the potential impact on personnel saving remains unclear. As phlebotomy is a common physician-patient or nurse-patient interaction, doubts remain as to whether human replacement with robotic devices will be serenely accepted by the patients. Last but not least, no clinical validation data (i.e., in animals or humans) has been published as yet, so that the potential clinical, economical and clinical advantages need to be fully defined.

Active blood tubes

The intrinsic characteristics of the blood collection tubes are essential determinants for obtaining reliable results of in vitro diagnostic testing. The major aspects influencing the quality of a blood tube are the physical characteristics of the tube itself, of the additives and the plasma/serum separators (when these are present), along with high quality manufacturing and high standardization of batches of products (21). Due to their obvious function, the blood tubes should have such a high degree of quality that what will be contained within (i.e., the blood) maintains its chemical and biological characteristics for the longest time possible before testing. Another critical element is that the blood tubes should unequivocally match patient identity, thus preventing the risk of incurring in identification errors (22). This is typically achieved by placing a barcoded label on the tube, which is supposed to contain all the essential information needed for being used with the modern laboratory instrumentation (i.e., patient identity, type of tubes, filling volume, date of blood collection, type of tests ordered), which has bidirectional connection with the laboratory information system (LIS). Although the application of blood tube labels represents now the one and only approach for storage of essential data, and is hence virtually unreplaceable, some interesting approaches are underway. A silicon valley-based company has recently developed a 2-mm, ultra-wideband (UWB) passive radio-frequency identification (RFID) chip, which can be applied to conventional blood collection tubes (23). The 128 bits read-only memory of the chip allows the storage of a huge amount of data, much higher than that usually contained in a barcoded label. According to the manufacturer, additional advantages of this solution are the efficient locating capability, which allows to precisely know the location of the tube within a 20 m distance, as well as the possibility to transfer the information stored into the chip directly to the LIS, with no need of barcode reading by the analyzer, and so completely overcoming the well-known shortcomings of traditional labels (i.e., label detachment, illegible label, impossibility to trace time of collection and length of transportation, no information about phlebotomist). Although the marketing of this intriguing innovation has not been started as yet, there are great expectations that RFID chips on blood tubes may substantially contribute to enhance efficiency of laboratory organization and increase patient safety.

Microelectromechanical applications represent another possible breakthrough in manufacturing of blood collection tubes. The lab-on-a-chip technology has made enormous progresses in the past decade. Beginning with microscopic sensors system for continuous blood glucose (24) and potassium (25) measurements, the new generation of microelectromechanical devices has the capability of measuring a vast array of biochemical analytes (26). Therefore, one can truthfully imagine the tremendous advantages of placing microscopic sensors for continuous monitoring of glucose and potassium into a blood tube. The continuous monitoring of the concentration of these two analytes may allow to obtain extremely precise information about what has happened inside the tube, from collection to arrival to the laboratory. In fact, a gradually decreasing glucose concentration reflects blood cell metabolism during transportation, whereas increasing potassium values from tube collection to its arrival in the laboratory reliably mirror ongoing hemolysis or blood cells activation (27), thus providing much more reliable information about the conditions of sample shipment than using conventional data loggers inserted into transport boxes (28). Despite the cost of these microchips has been traditionally seen as a major hurdle for routine application, the new generation of biochips encompasses reusable devices, which may cost a few cents of an Euro (29).

Sample transportation by drones

The transportation of biological samples is a big issue in pathology and laboratory diagnostics. The ongoing revolution in the organization of laboratory medicine services worldwide, which is mainly driven by consolidation of tests within larger facilities according to the so-called »hub-and-spoke« paradigm, has contributed to generate enormous challenges related

to the optimal conditions of sample transportation, in terms of both length and conditions of conveyance (30). The increasing deliverance of biological samples to reference (i.e., »hub«) centers, or even from the wards to the laboratory in large healthcare facilities, is conventionally made by the healthcare personnel, or using motor vehicles such as bicycles, motorcycles, cars, vans or tracks.

The term drone, conventionally used for defining Unmanned Aerial Vehicles (UAVs) or Unmanned Aerial Systems (UASs), refers to aircrafts without a human pilot aboard, which have been originally developed nearly 30 years ago for military purposes. A typical civil drone is a device with a cost comprised between 5000 to 20000 Euros, which can fly with a few hours autonomy at a speed usually comprised between 60–100 km/h, conveying 5–10 kg payload, over a distance of 30–100 km depending on the model (31). Shortly after their introduction for military purposes (i.e., intelligence service, acquiring targets, delivering missiles and bombs), the potential advantages of flying these devices for civilian purposes have emerged, thus including policing and surveillance, deliveries of goods, aerial photography and agricultural services. More recently, the reliable use of these devices for humanitarian response and disaster relief has also considerably increased (32), along with their potential employment for transportation of biological specimens. In an interesting study, Amukele et al. (33) flew a set of blood samples with a small fixed-wing aircraft, for a period comprised between 6 to 38 min. Interestingly, the comparison of test results of as many as 33 laboratory parameters obtained in blood samples transported by the drone or held stationary displayed a very modest variation, with a mean difference always <1%, except for glucose (i.e., bias, 3.2%). In a subsequent study, the experiment was repeated by using the drone for transporting 6 leuko-reduced red blood cells (RBCs) and 6 apheresis platelet units (34). This study also showed no evidence of hemolysis and no significant change of platelet count, pH or mean platelet volume. Although this experimental data seemingly suggests that biological sample transportation by drones may be regarded as a feasible and viable perspective for the future, some important issues need to be addressed. The internet resources Drone Crash Database lists all military drone crashes since January 1, 2007 up to the last update (March 18, 2016) (35). Overall, 267 accidents have been recorded in 10 years of experience flying military drones. As regards civil or domestic usage, and beside events with broad media coverage such as the drone nearly hitting the six-time Alpine sky World champion Marcel Hirscher in December 2015, the US Federal Aviation Administration (FAA) has recorded nearly 600 drone incidents in six months (i.e., from August 2015 through January 2016) (36). Most of the drone accidents are actually attributable to loss of control in-flight, unpredictable events during takeoff and in cruise, or to equipment problems. Overall, technical failure of aircraft components were implicated in nearly two-third of the accidents, with human errors representing the remaining part (37). This important evidence leads to the conclusion that flying drones for shipping biological samples is indeed a valuable perspective for the future, but many doubts remain as to whether the advantages of widely using these devices for healthcare purposes may overwhelm the tangible perils at present.

Innovative approaches for detecting spurious hemolysis

Hemolysis is conventionally defined as injury or complete breakdown of RBCs in blood, a phenomenon that often reflects a more generalized issue of all corpuscular blood elements damage (i.e., erythrocytes, leukocytes and platelets). This pathological process is conventionally classified in two main categories, that is »in vivo« hemolysis (also known as hemolytic anemia), when RBC are damaged into the circulation due to presence of hemolytic diseases, or »in vitro« hemolysis (i.e., spurious hemolysis), when the erythrocytes are injured at any stage from blood collection to analysis. It is now undeniable that spuriously hemolyzed specimens are the main preanalytical problem in laboratory diagnostics, since the release of hemoglobin and other intracellular compound in serum or plasma may seriously jeopardize the quality of testing, but also carries substantial impact on healthcare budget and organization (38). Although there is still controversy on how the laboratory should deal with hemolyzed samples (39, 40), their systematic and automatic identification by using the hemolysis index (HIL) is now commonplace (41). The superiority of this approach over traditional visual inspection of centrifuged samples has been clearly demonstrated (42). Nonetheless, some problems remain for accurate detection of sample hemolysis, especially when processing whole blood specimens, or when the modern instrumentation equipped with the serum indices is unavailable such as outside the conventional laboratory environment or in low income countries.

The issue of identifying spurious hemolysis in whole blood specimens is especially concerning, considering that the hemolysis rate can be as high as 4% in whole blood samples collected for blood gas analysis (43). These unsuitable samples may remain virtually undetected because physical separation of plasma or serum from blood cells is not necessary using whole blood analyzers. To overcome this issue, some interesting opportunities are emerging (*Table I*). Based on the original study of Kobos et al. (44), a first patent has been granted to the company Instrumentation Laboratory (Boston, MA, USA; inventors: Balasubramanian S. and D'Orazio P.) for the use of whole blood hemolysis sensors (45). As for specific details available in the patent application, this reagent-free invention is based on an electrochemical hemolysis sensor with an external membrane for

Table I Innovative technologies for detecting hemolysis in whole blood.

1. Hemolysis sensors
2. Integrated systems of plasma separation followed by optical hemoglobin assessment
   a. Velocity gradient plasma separation using non-positive blood pumps
   b. High velocity plasma separation within a reagent disc
   c. Microfluidic-based plasma separation
   d. Gravity separation of plasma
   e. Capillary separation of plasma coupled with smartphone camera-based assessment
3. Equations based on routine hematological parameters

increasing the efflux of hydrogen peroxide (H_2O_2) combined with another membrane containing a H_2O_2-triggering oxidoreductase enzyme (e.g., glucose oxidase or lactate oxidase) and a flow chamber close to the external membrane enabling direct contact with blood. The addiction of a whole blood hemolyzed specimen within the electrochemical sensor triggers an electrochemical reaction with generation of H_2O_2 in the presence of free-hemoglobin (Fe^{2+}). The registration of a decreased electrical current between 4–50% compared to a non-hemolyzed whole blood specimen is then suggestive for the presence of hemolysis in blood. The major advantage of this technique is that whole blood specimens do not need to be centrifuged before being introduced in the system. Despite no analytical evaluation has been published so far, the performance of the original sensor developed by Kobos et al. (44) was proven to be excellent, displaying 97% agreement with the reference cyanmethemoglobin assay. Notably, an alternative approach has been published nearly 30 years ago by Ito et al. (46), which was based a compact hemolysis sensor where plasma is continuously separated from blood cells by velocity gradient (i.e., using a non-positive blood pump) within a disk installed on a housing wall. The change of hemoglobin concentration is detected as variation of plasma absorbance through an optical monitor unit consisting of a LED (λmax, 560 nm), an interference filter (λ, 540 nm) and a photodiode. The device has been originally developed for continuously monitoring the changes of free hemoglobin concentration in blood during extracorporeal circulation, but its potential application for detecting spurious sample hemolysis are noteworthy.

These solutions are intriguing, but have remained mostly speculative so far since no commercial application has appeared. However, an alternative solution is already available in the market. The compact analyzer Abaxis Piccolo Xpress (Union City, CA, USA) is a point of care instrumentation designed for the measurement of a large number of clinical chemistry analytes (47). According to the claim of the manufacturer, the instrument performs automatic detection of physical interferents such as hemolysis, lipemia and icterus, which should hence eliminate the need for visual inspection of the samples. Briefly, heparinized blood is introduced into a reagent disc containing a diluent and test-specific reagent beads. The disc is then placed into the analyzer, and is spun at high velocity for separating plasma from blood cells. The presence of hemolysis, lipemia, and icterus is then assessed by means of absorbance readings at 340 nm, 405 nm and 467 nm, respectively. A semi-quantitative measure of sample indices is finally reported along with each test result, without excessive delay in turnaround time or additional sample volume needed for testing. The principle of microfluidic-based plasma separation has been used by Son et al. (48) to develop a simple and robust on-chip blood plasma separation device, in which a membrane filter has been positioned on the top of a vertical up-flow channel. This system allows obtaining a highly efficient plasma separation (e.g., containing ~90% of protein and ~100% of nucleic acids of original blood). The separated plasma can then be visually inspected to identify the presence of cell-free hemoglobin. A similar solution for non-invasive detection of cell-free hemoglobin in blood bags has been proposed by Netz et al. (49). The optical device consists of a hemoglobin sensor which assesses cell-free hemoglobin in a flexible tube connected to the bag, after separation of plasma from blood cells by means of gravity sedimentation. The hemoglobin detection limit was found to be 0.02 g/L, with a 2.4% imprecision at hemoglobin concentration of 10 g/L. Notably, the use of point of care devices with integrated means of hemolysis detection seems more practical for routine use than other devices needing separate sample analysis.

Archibong et al. (50) recently developed a point-of-care mobile phone-based system capable to rapidly detect the level of hemolysis in plasma. The software has been adapted to be used with a vast array of commercial mobile phones and is coupled with a 3D printed sample holder that can be attached to the smartphone. Briefly, a microtube or a ~1 mm diameter capillary tube are placed into the holder, the blood is inserted into the capillary and then subjected to gravitational sedimentation for 5 to 10 min. After this period, the plasma at the top of the tube is photographed and the software immediately translates plasma hue into a semiquantitative scale of hemolysis (i.e., cell-free hemoglobin ≤0.05 g/L, 0.05–0.30 g/L, 0.30–0.60 g/L, 0.6–3.0 g/L or ≥3.0 g/L). This device has originally been developed for screening preeclampsia and HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome, but its potential application for monitoring spurious hemolysis in whole blood samples is rather obvious. Although the accuracy of cell-free hemoglobin assessment with this system has been claimed to be as high as 90% compared to a standard photometer measurement (50), no external validation has been carried out so far and no indications can be found on how (or where) the software and the hardware can be purchased.

One last approach, virtually the simplest and less expensive, has also been proposed for rapid estimating the risk of sample hemolysis in whole blood. This encompasses the use of a specific equation based on some routine hematological parameters such as hematocrit, hemoglobin and mean corpuscular volume (i.e., [hematocrit/hemoglobin] × [mean corpuscular volume]). In one preliminary study the use of this formula has allowed identifying the presence of hemolysis in whole blood specimens with over 99% accuracy (51). Nevertheless the widespread applicability of this approach still needs extensive validation in other centers, using different hematological analyzers.

Preanalytical errors recording software products

Systematic monitoring and recording of errors, either being near misses or adverse events, is one of the mainstays for reducing medical and diagnostic errors (52). Besides theoretical considerations, compliance with the accreditation criteria defined in the International Organization for Standardization (ISO) 15189: 2012 standard firmly demands implementation of an efficient procedure for errors identification and recording (53, 54). There are many potential ways the clinical laboratory can store preanalytical errors, but some of these carry important drawbacks. Although manual recording on paper forms is probably the oldest and the most widespread means to keep track of all preanalytical problems occurring in daily activity, this practice has a kaleidoscope of limitations such as the risk of accumulating a variety of unintelligible writings, unstandardized codification of errors, archiving of incomplete information and, especially, cumbersome calculation of statistics due to the need of re-entering data in a statistical software. Direct entry of preanalytical mistakes in the LIS overcomes most of these limitations, but the possibility to perform comprehensive statistic analyses is still extremely dependent upon the possibility of exporting data in a format compatible with the statistical software. The number of information about the specific event which can be stored in the LIS is also limited, so that important data such as the action undertaken to correct the error cannot always be recorded. A first step to harmonize data reporting in clinical laboratories is to find an agreement on a specific set of preanalytical quality indicators, which should be identical worldwide in order to compare the local situation with that of other laboratories, so allowing efficient benchmark. To overcome this issue, the Working Group on »Laboratory Errors and Patient Safety« (WG-LEPS) of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has recently defined a comprehensive list of Quality Indicators (QIs) (55), which also includes the most frequent types of preanalytical problems encountered in clinical laboratories. Since the routine application of these performance measures by recording errors with paper forms or entering data in the LIS may still be problematic, as earlier discussed, the WG-LEPS and the Working Group for the Preanalytical Phase (WG-PRE) of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) have jointly developed a preanalytical errors recording software for facilitating and harmonizing the activity of recording preanalytical errors (56). This program runs under Microsoft Access® (Microsoft, Redmond, WA, US), and allows recording the most important information relative to the single preanalytical mistakes, i.e., date, specimen number, patient name, healthcare setting where the sample has been collected, type of request (routine or stat), biological matrix, action undertaken, name of the laboratory professional who is recording the data and, especially, the type of errors codified according to the list of WG-LEPS QIs. The data recorded in the database can then be easily exported in various formats (e.g., »xls« or »xlsx« for being used with Microsoft Excel®), so allowing easy and efficient generation of statistics. Regardless of this software, more pressure should be placed on manufacturers of LISs to develop easy mechanisms to log and audit the data related to laboratory errors.

Conclusions

Despite many expectations were raised over the past decades, in vivo and non-invasive diagnostics remains an un met target (57, 58). With limited exceptions, such as in vivo continuous glucose monitoring (59), it is now undeniable that the blood sample collection will remain an essential part of the total testing process for long.

There is a common saying, that because you have always done something in one way, it does not mean that this way may be right. This actually reflects a human inclination to resist change, and contradicts the notorious concept that »intelligence is the ability to adapt to change« (Stephen Hawking; Oxford University graduation). Technology is taking over many human domains, including health care. It is hence rather obvious that the translation within the preanalytical phase of many promising technological innovations, such as those discussed in this article, holds great promise for decreasing the vulnerability of in vitro diagnostics and ultimately enhancing patient safety. So, the time has come to start thinking »out of the box«, or as George Bernard Shaw would put it »*The reasonable man adapts himself to the world: the unreasonable one persists in trying to adapt the world to himself. Therefore all progress depends on the unreasonable man*«.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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