Opinion Paper

Giuseppe Lippi* and Giorgio Da Rin

Advantages and limitations of total laboratory automation: a personal overview

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Abstract: Automation is considered one of the most important breakthroughs in the recent history of laboratory diagnostics. In a model of total laboratory automation (TLA), many analyzers performing different types of tests on different sample matrices are physically integrated as modular systems or physically connected by assembly lines. The opportunity to integrate multiple diagnostic specialties to one single track seems effective to improve efficiency, organization, standardization, quality and safety of laboratory testing, whilst also providing a significant return of investment on the long-term and enabling staff requalification. On the other hand, developing a model of TLA also presents some potential problems, mainly represented by higher initial costs, enhanced expenditure for supplies, space requirements and infrastructure constraints, staff overcrowding, increased generation of noise and heat, higher risk of downtime, psychological dependence, critical issues for biospecimen management, disruption of staff trained in specific technologies, along with the risk of transition toward a manufacturer's-driven laboratory. As many ongoing technological innovations coupled with the current scenario, profoundly driven by cost-containment policies, will promote further diffusion of laboratory automation in the foreseeable future, here we provide a personal overview on some potential advantages and limitations of TLA.

Keywords: cost; diagnostic testing; effectiveness; laboratory automation.

***Corresponding author: Giuseppe Lippi,** Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37134 Verona, Italy, E-mail: giuseppe.lippi@univr.it.
https://orcid.org/0000-0001-9523-9054
Giorgio Da Rin: Laboratory Medicine, San Bassiano Hospital, Bassano del Grappa, Italy

Introduction

Automation has strongly contributed to revolutionizing many human activities, thus providing unquestionable benefits on system performance [1]. The abundant and multifaceted advancements of automation technologies have also generated a profound impact on the organization of clinical laboratories, where many manual tasks have now been partially or completely replaced by automated and labor-saving instrumentation [2, 3].

The impressive diffusion of laboratory automation has been strongly catalyzed by an ongoing process of reorganization of laboratory diagnostics according to the paradigmatic "hub-and-spoke" model, where laboratory facilities are increasingly organized within a network encompassing peripheral laboratories carrying out simple (i.e. first-line) testing and core facilities, where large volumes of samples are delivered for performing more specialized tests [4]. Albeit no single definition exists, laboratory automation is usually classified according to the complexity of instruments integration, ranging between no automation (all analyzers existing as stand-alone machines), partial laboratory automation (e.g. development of the so-called "automation islets", where laboratory analyzers are interconnected and partially integrated with preanalytical workstations such as in the serum work area, integrating clinical chemistry and immunochemistry testing), up to total laboratory automation (TLA), where most analyzers performing different types of tests (i.e. clinical chemistry, immunochemistry, hematology, hemostasis and so forth) on different sample matrices (e.g. whole blood, serum, heparinized or citrated plasma) are physically integrated as modular systems or connected by assembly lines (e.g. tracks, belts and other types of conveyers) (Figure 1) [5]. In the broader models of TLA, many preanalytical and postanalytical steps (e.g. sample input, check-in, sorting, decapping, centrifugation, separation, aliquoting, sealing and storage) are automatically performed in workstations physically connected with the analyzers and efficiently managed by software programs.

A recent survey carried out in Italy showed that the number of laboratories using partial or TLA approximates

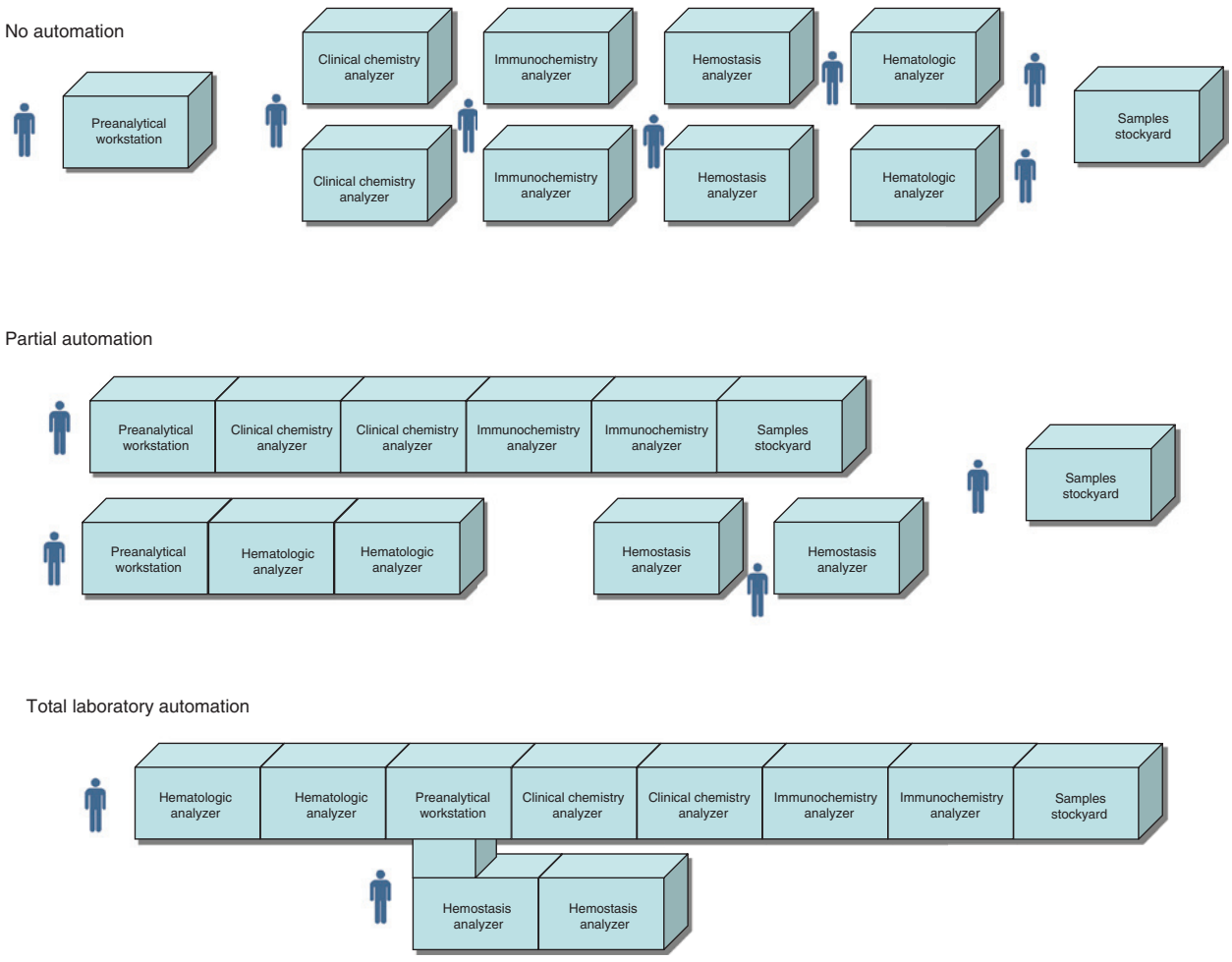

Figure 1: Different potential models of laboratory automation.

50% [6], whilst another questionnaire disseminated in the US showed that nearly 70% of laboratory directors have implemented, or are planning to introduce, large models of automation in their facilities [7]. As it is hence predictable that ongoing technological innovations, coupled with an economic scenario profoundly driven by cost-containment policies, will promote further diffusion of laboratory automation in the foreseeable future, here we provide a personal overview on some potential advantages and limitations of TLA.

Potential advantages of TLA

Lower costs on the long term

Several lines of evidence now attest that an efficient model of TLA can successfully lower the costs of laboratory diagnostics [8–10]. The net benefit (i.e. the return of investment) is indeed more appreciable on the long term, after reaching the so-called break-even point, when the higher initial costs (discussed in a following section of this article) will be offset [9]. Basically, the major economic revenue of TLA, resulting from merging many diagnostic platforms within a consolidated system, not only encompasses a reduction of manual workforce (especially auxiliary and technical staff) needed for managing high-volume testing [10], but is also attributable to lower pre-analytical and postanalytical expenditures. For example, consolidation of the so-called serum working area would actually need collecting a minor number of blood tubes for performing different analyses and will also require smaller storage units (i.e. stockyards) for storing a lower number of specimens after the tests have been completed. However, the economic saving is variable, depending on the final solution of automation adopted and on the relative volume of tests locally performed, as the larger is the

number of tests, the bigger is the consequent economic revenue of automating many steps of the total testing process [10]. This aspect may then allow suggesting or justifying the adoption of different model of automation based on local volume and complexity of testing.

Decreased congestion in the laboratory

Directly linked to the previous point, the decrease of personnel needed for performing identical volumes of tests after implementing TLA would also produce lower staff congestion within the laboratory [10]. An optimized layout of integrated workstations would in fact prevent technicians moving back and forth many times from one analyzer to another, thus minimizing the distance covered by the personnel for performing multiple analyses on different instrumentation.

Improved efficiency

Beside cost-containment benefits, which are especially cherished by policymakers and healthcare administrators [11], TLA provides some other advantages within the laboratory environment, most of which are attributable to using customizable assembly lines, which can be organized to meet specific requirements and layouts of different laboratories. Several lines of evidence now demonstrate that an efficiently designed TLA may be variably effective to reduce turnaround time (TAT) and concomitantly increase laboratory productivity (i.e. throughput) [12–17]. Notably, modern assembly lines can transport a huge number of blood tubes or secondary aliquots at high speed (i.e. between 3000 and 10,000 tubes per hour at a speed of 20–100 m/s) [18], thus considerably offsetting manual transportation. One valuable example is that recently published by Yeo and Ng [19], who showed that the workload of a laboratory service can be substantially increased after implementing TLA, and that such an increased volume of tests may also be accompanied by a notable expansion of the test repertoire. These valuable goals could be essentially achieved by workflow optimization, automatically encompassing diversion or prioritization of samples among the different analyzers, especially when an analyzer is full or has some technical failures. Very understandably, however, the adoption of a model of TLA incorporating several diagnostic lines (e.g. clinical chemistry, immunochemistry, hematology, coagulation and even microbiology) has an impact on personnel expertise, that will be more comprehensively discussed in a following section of this article.

Alongside this line, TLA offers the additional advantage of allowing a combination of modern preanalytical workstations with analytical platforms [20]. The former instrumentation now enables check-in, sorting, decapping, centrifugation and fully-automated liquid aliquoting of different tubes types and sizes, followed by circulation of automatically labeled secondary aliquots into TLA, thus overcoming the challenge of adapting different analyzers to different types of tubes.

Even here, however, a preliminary analysis of the workflow within the laboratory and a constant monitoring of TAT over time seem critical for implementing the most efficient solution and eventually correcting system flaws. This would enable identifying *ex ante*, or adjusting *ex post*, some critical steps of sample management within the system, ultimately optimizing its performance in terms of managing high volumes and complexity. Notably, some models of TLA are now equipped with input stations (e.g. bulk modules) where blood tubes can be randomly entered by hand or, more efficiently, that can be physically connected with pneumatic tube systems (where available). Except for pre-centrifuged blood tubes (i.e. the quality of some gel separators may be unsuitable to prevent leakage of molecules from blood elements underneath the gel barrier) [21], bulk input modules reduce manual sorting and save time. Finally, optimization of workflow and shorter TAT would also permit to more timely report data to the requesting physicians, thus reducing the need for priority urgent testing.

Improved sample management (e.g. rerun, reflex and add-on testing) and traceability

Information technology (IT) has profoundly contributed to improving medical laboratory work and organization. Query-host communication has virtually eradicated some high-risk activity connected to manual transcribing data and has also enabled reducing the TAT [22]. The modern generation of laboratory instrumentation is also equipped with advanced software programs, allowing better sample management. Setting decision rules based on predefined criteria now permits autoverification of data, automatic re-analysis of samples with highly abnormal or suspect results, as well as triggering reflex (reflective) and add-on testing, thus ultimately contributing to enhance the quality and safety of diagnostic testing [23, 24]. The efficiency of performing these important activities is enormously magnified in laboratories using TLA, where sample management within the system is more efficient (i.e. all samples can be stored within on-line stockyards and automatically

retrieved and re-analyzed hours or days after initial testing). Moreover, the integration of different instrumentation enables automatically performing many different types of tests, planning automatic reflex or add-one testing, using different sample matrices. For example, consolidation of hematologic analyzers within the serum working area may allow setting automatic rules for troubleshooting anemia (e.g. generating ferritin, transferrin, folic acid, vitamin B, creatinine and other clinical chemistry tests when hemoglobin values are below the reference range), and thus providing more thorough and timely laboratory data for diagnosis and treatment [25]. Last but not least, specimen traceability is consistently enhanced by maintaining all routine and stat samples within a unique environment, enabling digital traceability of all the processes a tube has been subjected to, from time of delivery to the laboratory, up to storage once testing has been completed.

Enhanced standardization for accreditation/certification

Keeping all the different phases of the total testing process under control, thus including extra-analytical activities, is a mainstay of total quality in laboratory diagnostics [26], which has also become a mandatory requirements of International Standards Organization (ISO) 15189:2012 accreditation [27]. It is now undeniable that consolidating different diagnostic areas within the same workspace would require less administrative efforts to develop and update standard operating procedures (SOPs), wherein multiple procedures for preanalytical and postanalytical sample management can be merged when many analyzers are integrated within the same model of TLA. Notably, TLA also seems profitable for many aspects related to the analytical quality, such as quality specifications of the assays, traceability of calibrators, improved quality and stability of reagents, along with some other aspects that laboratory professionals should evaluate in addition to technical planning before the adoption of a specific solution of TLA.

The increased accuracy and repeatability throughout the total testing process enabled by automating operations would also grant paramount benefits in terms of standardization, thus simplifying certification and accreditation procedures.

Improved quality of testing

Standardization and harmonization are two crucial issues in laboratory diagnostics. Most efforts made over the past decades have been essentially focused on the analytical part of the total testing process [28], whilst major attention has only recently been given to preanalytical [29] and postanalytical [30] activities. Conventionally, automation allows taking over the bulk of many manual ordinary activities (i.e. specimens sorting, loading, centrifugation, decapping, aliquoting, sealing) from humans, thus enabling to alleviate substantial differences among persons and from sample to sample [12]. Such improved process standardization will yield tangible benefits on the quality of the total testing process, thus lowering the risk of diagnostic errors, especially those emerging from the manually-intensive activities of the preanalytical phase [19]. A paradigmatic example has been published by Hawker et al., who showed that implementation of a major automation system in a medical laboratory was effective to decrease the number of lost specimens by over 50% [9]. However, the analytical process can also be carried out more safely and efficiently using TLA, as several activities such as dilution of samples with results lying outside the range of linearity, or sample resting when results are alerted, can be both automatically performed, by more efficiently retrieving specimens from the storage unit, without manual intervention. Notably, some integrated preanalytical workstations can also automatically perform quality assessment for monitoring specimen integrity (i.e. sample volume, presence of clots or bubbles, serum/plasma indices and so forth).

Lower sample volume

Containment of unnecessary diagnostic-related blood loss and prevention of blood drawing-related anemia are especially important in subjects such as neonates, anemic patients or those needing repeated laboratory testing for critical illnesses [31]. The use of lower blood volumes may also be a viable option in patients with difficult veins, for whom drawing multiple blood tubes may be unfeasible [32]. One of the previously mentioned advantages of TLA is the opportunity to reduce the number of blood tubes needed for testing. The so-called serum working area is a paradigmatic example, wherein the same serum (or lithium-heparin plasma) tube can be used for multiple clinical chemistry and immunochemistry tests [33], thus allowing to consistently reduce the total volume of blood needed for testing. Importantly, a reduced sample volume will also generate a lower impact on biological waste disposal, thus producing an additional economic saving.

More efficient integration of tests results

The consolidation of many diagnostic areas with the same space (e.g. the so-called "core-lab") has additional organization and technical benefits. The considerable advancements of IT now allow laboratory staff to navigate and manage data flow of delivery, analytical and archival systems [19]. The middleware of most models of TLA enables integrating a vast array of test results produced by different analyzers, even before data are transferred to the LIS. This not only would permit to define larger, more complex and accurate auto-validation criteria, but would also allow the laboratory personnel to have a broader picture of patient's results, thus more efficiently detecting potential errors or identifying critical situations needing timely communication to the clinicians [19].

Lower biological risk for operators

Worker safety is one of the most important advantages of automating industrial operations. Automated systems not only remove operators from the workplace, but also safeguard them against the risks of performing biologically hazardous operations and handling biohazardous materials [34].

Staff requalification and job satisfaction

The minimization of manually-intensive labor is one of the major advantages of TLA, which would then translate into a net saving of staff (both technical and auxiliary) needed for managing laboratory workflow [9]. Hence, this would enable to requalify the personnel, eliminating manpower and redefining job roles towards value-added tasks such as quality assessment or implementation of new tests (e.g. genomics, proteomics, theranostics), thus ultimately leading the way towards personalized (laboratory) medicine [35]. It is also worthwhile mentioning here that personnel requalification can be intellectually satisfying, thus enhancing the morale and productivity of the staff.

Potential limitations of TLA

Higher costs on the short term

The investment for implementation of TLA is inevitably associated with an initial escalation of costs for accommodating the project (i.e. environmental modifications, powerful air conditioners, soundproofing), for system installation and for the new hardware (e.g. enhanced expenditure for preanalytical platforms and assembly lines used for connecting separate analyzers). This may be an issue in some facilities, where the budget allocated to the laboratory by the hospital administrations for a new tender remains unvaried or is even lower than for former tenders [10]. Hence, a negotiation with the hospital administration would be necessary, to clearly illustrate the possible return of investment achievable by shifting toward TLA, accompanied by a reliable financial planning accountable for expenses and projections of revenues [36].

Increased costs for supplies (i.e. maintenance, energy and supplies)

The implementation of new hardware, essentially represented by preanalytical workstations, assembly lines and sample storage units, carries subsidiary costs for running the system (i.e. energy and water) and for supplies (e.g. tips for aliquotters and caps for sealers). A large model of TLA would also require a higher level of maintenance than for manually-operated instrumentation [36].

Space requirement and infrastructure constraints

Space requirements and infrastructure constraints are major issues for implementing TLA. Accommodating multiple analyzers and new hardware into a preexisting environment may be a challenge, especially when the building is not purpose-built or fit for this scope. It is understandably easier to create a new space than renovating an existing one especially when the infrastructure of the building is old [37]. In the latter scenario, when renewing possibilities are limited, the configuration of the system should be necessarily designed around the local environment, so that analyzers orientation and access for maintenance or repair may be acceptable. Flexible models of TLA may be preferable when the environment does not allow developing an ideal solution.

Overcrowding of personnel

One unquestionable benefit of implementing TLA is that the staff no longer need to move many times from one

analyzer to another. On the other hand, consolidation of many different analyzers within the same area may consistently increase the risk of generating overcrowded work environments, with many technicians occupying the same space at the same time [34]. Therefore, an efficient plan, aimed at identifying a lean laboratory layout concept, should be elaborated.

Increased generation of noise, heat and vibrations

The consolidation of many analyzers in the same area (e.g. in the "core lab") will concentrate noise, heat and vibrations in a narrow environment. Hence, this may be perceived as excessive warming and increased exposure to acoustical or electrical noise in the workplace [37].

Increased risk of downtime

The higher is the complexity of the system, the greater is the risk that a system failure would generate serious consequences on laboratory functioning. This concept especially applies to laboratories using vast TLA models, where many analyzers are physically connected by assembly lines. Critical system failures, especially involving the assembly lines, would require restoring manual procedures for managing samples (i.e. manual sorting, centrifugation, decapping, aliquoting, loading and unloading), thus producing variably protracted downtimes, delaying analysis of specimens and prolonging the TAT [36]. These unfavourable consequences are magnified by a consistent decrease of manual workforce and understaffing, as is commonly achievable with TLA. To overcome this problem, a back-up power supply, hardware, software, emergent procedures or even implementing back-up point of care testing (POCT) analyzers should be seen as suitable alternatives for limiting downtime. The possibility of manual sample loading into the analyzers during emergency situations should always be preserved [36].

Psychological dependence on automation

There has been a long debate regarding human psychological dependence on automation, nicely reviewed by Stanton and Young in the context of driving automation [38]. Basically, replacement of manual activities with automation has some major consequences, i.e. locus-of-control in the staff, rapid deterioration of skills and inefficient resuming of manual functioning when automation should fail. These last two aspects are especially important in clinical laboratories, as the transfer of technical skills to the operational environment would then make it challenging, both technically and psychologically, to resume manual abilities. It may even seem paradoxical but replacing many manual activities with automation would make the staff feel like being sent into the middle of nowhere when facing automation failures [39]. The human response to automation failure was shown to often be dramatic [40], and this might be attributable to – at least – two major causes. The first, discussed earlier, is the almost irreversible loss of confidence in manual skills, whilst the second, even more challenging, is the lack of manual power (consequent to staff reduction) needed for resuming all those activities that have been conveyed to automation (e.g. sorting, centrifugation, decapping, aliquoting or recapping, sample loading and unloading, and so forth). This challenge is magnified for young or new staff, who may have little experience with manual laboratory work, thus paralyzing the laboratory, being unable to provide data to the clinicians and ultimately jeopardizing patients' health. There is no easy way to come out of this situation other than by implementing an expensive back-up system, as previously discussed, or delivering samples to another neighboring laboratory. Additional staff-related problems can then be highlighted, including anxiety, uncertainty and even resistance to the changes. Hence, the laboratory management should be engaged in emphasizing the exciting aspects of the changes, highlighting the many possible favorable consequences and opportunities that may be generated by the new organization.

Differential requirements for sample management

The essential of TLA is that different types of samples, thus reflecting different biological matrices (i.e. whole blood, serum, heparinized or citrated plasma, among others) can be introduced almost simultaneously in the system. Albeit this really means that all samples may be managed in the same way along their path to the analyzers, it has been defined that the different biospecimens may need different preparation before being tested [41]. More specifically, EDTA-anticoagulated samples for hematologic testing do not need centrifugation; serum or lithium-heparin samples can be efficiently separated by combining short and high-speed centrifugation, whilst the current guidelines mandate that citrated samples for hemostasis testing should be centrifuged at $1500 \times g$ for 15 min [42].

Therefore, consolidating hemostasis testing within TLA remains a largely debated issue [43]. Unless stronger evidence is generated that hemostasis tests are not affected by shorter centrifugation times, higher centrifugation forces or centrifuge brake [44], criteria should be set that citrated samples would need to follow a specific path within the system, with dedicated centrifugation, or else that hemostasis analyzers should not be integrated within the TLA. Setting all centrifuges at $1500 \times g$ for 15 min does not seem a reliable solution, as this would probably impact the TAT of serum or lithium-heparin plasma samples. An additional concern is the stability of coagulation samples within TLA, as there is no stable separation after centrifugation (by gel or other physical barriers) between citrate plasma and the blood cells underneath. Therefore, the possibility that blood cells may contaminate plasma when samples travel at high speed, pass over switches and slots or collide with other tubes must be accurately prevented.

Generation of potential bottlenecks

The optimal management of stat (i.e. urgent) testing is another critical issue in laboratories using TLA. The larger the volume of routine testing, the higher the risk of creating bottlenecks, which may then reduce system productivity and TAT [45]. This circumstance may be especially concerning for stat testing, with the risk that urgent patient samples will wait for long before being centrifuged and analyzed. This would actually impose a detailed analysis of workflows within the system, with the development of rules and criteria enabling stat samples to by-pass routine specimens [46]. On the other hand, priority criteria will need to be accurately balanced, thus avoiding that routine samples will be subjected to interminable delays within a fully-integrated system prioritizing stat testing. In this scenario, the flexibility of the automation system is foremost, as it would enable the laboratory to introduce changes (i.e. external centrifugation, manual loading of stat samples) even once the system has already been implemented.

Disruption of staff trained in specific technologies

The development of the so-called "core lab", where a large part of laboratory staff will be committed, is an obvious consequence of consolidating many different diagnostic areas [47]. This would really mean that the specific background required to laboratory professionals for managing increasing complexity of tests should be considerably expanded. On the other hand, this will also pose some threats, as the larger the volume of knowledge required, the lower the competency on specific technologies. For example, consolidation of two rather different diagnostic areas such as laboratory hemostasis and clinical chemistry would necessitate that laboratory hemostasis technicians will need to acquire biological and technical background on clinical chemistry, whilst clinical chemistry technicians will need to acquire biological and technical background on hemostasis. Eventually, the enhancement of workforce flexibility may finally contribute to decrease competency and skills in specific tasks especially in laboratory services shifting toward a model of TLA which incorporates several different diagnostic lines (e.g. clinical chemistry, immunochemistry, hematology, coagulation and even virology and microbiology) [48]. Then, although it is undeniable that technology and automation have made life much easier, it turns out that some specific and practical skills may well be lost over time. Overall, automation tends to limit the experience that laboratory specialists harvest on a daily basis, thus potentially leading to decreased skills and expertise in analytical procedures, which may reduce the ability to apply pressure on companies for innovation.

Risk of transition toward a manufacturer's-driven laboratory

A highly automated clinical laboratory strongly depends on efficient software programs (including the LIS) and constructive partnership with manufacturers [36]. The establishment of a strategic relationship with suppliers is thus essential for achieving the goal of an efficient TLA. Importantly, the manufacturers of some laboratory automation systems can integrate analyzers from many different companies, whilst this option is still under development for other companies. This implies that tenders should be more accurately defined according to the expected laboratory layout. Full commitment to a single vendor may be an additional risk, as this may pave the way to a manufacturer's-driven laboratory. Hence, this may substantially limit, or even avert (in the worst scenario), laboratory professionals from organizing and managing their own laboratories.

Conclusions

Automation should be considered one of the most important breakthroughs that has occurred in laboratory

Table 1: Potential advantages and limitations of TLA.

Advantages	Limitations
– Lower costs in the long term	– Higher costs in the short term
– Reduction of manual workforce	– Project accommodation
– Lower number of blood tubes	– Installation
– Decreased congestion	– Larger equipment
– Improved efficiency	– Increased costs for supplies
– Shorter TAT	– Maintenance
– Higher throughput	– Energy
– Enhanced complexity	– Water
– Possibility to manage different tubes types and sizes	– Tips for aliquotters and caps for sealers
– Lower need of urgent testing	– Space requirement and infrastructure constraints
– Improved sample management	– Overcrowding of personnel
– More efficient management of rerun	– Increased generation of noise, heat and vibration
– More efficient management of reflex testing	– Higher risk of downtime
– Easier add-on	– Higher risk of system failures
– Enhanced traceability	– Shortage of personnel for response to emergency situations
– Improved process standardization for certification/accreditation	– Psychological dependence on automation
– Improved quality of testing	– Differential requirements for sample management
– Enhanced standardization	– Generation of potential bottlenecks
– Lower risk of errors	– Disruption of staff trained in specific technologies
– Lower sample volume	– Risk of transition toward a manufacturer's-driven laboratory
– More efficient integration of tests results	
– Lower biological risk for operators	
– Staff requalification and job satisfaction	

TAT, turnaround time; TLA, total laboratory automation.

diagnostics over the past decades [49]. Because the one-size-fits-all paradigm does not apply to laboratory automation, selecting the most suitable (often flexible) model of laboratory automation is a challenging and time-consuming enterprise, which is now an integral part of a laboratory director's duties [50]. The opportunity to connect multiple diagnostic specialties to one single track has been proven effective to improve efficiency, organization, standardization, quality and safety of laboratory testing, whilst also providing a significant return of investment on the long-term and enabling staff requalification (Table 1). On the other hand, developing a model of TLA presents some potential problems, mainly represented by higher costs on the short-term, enhanced expenditure for supplies, space requirement and infrastructure constraints, staff overcrowding, increased generation of noise and heat, higher risk of downtime, psychological dependence, critical issues for biospecimen management, disruption of staff trained in specific technologies, along with the risk of transition toward a manufacturer's-guided laboratory (Table 1). Hence, the accurate analysis of all these theoretical advantages and limitations should guide laboratory directors to configure a local solution suitable for meeting current testing needs and handling future demands.

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