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Review Article

Analytical Variables in the Clinical Laboratory

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Abstract

All patients go to the doctors to assess their health status, and there is seldom a medical appointment in which the doctors do not order a laboratory exam – from the very common urinalysis, stool examination, and Complete Blood Count to some very specific and sometimes intricate exams. Yet most doctors and patients are unaware of some needful procedures that must occur before a result is reported [1, 5, 6]. Not all people are aware of the requisitions of reproducibility, precision and accuracy any lab exam must have if it is going to be useful for their needs: most people still treat laboratory exams as some kind of magic where the report will intrinsically lead to the best judgment by the clinician.

If that is to change, both patients and Doctors must know what the best practical procedures are, and how each of the involved people can collaborate. While demonstrating why some errors and inadequacies as to Laboratory exams and their use can sometimes happen, this article focus on the fact that any laboratory must be treated as a highly precise industry [38] – with correspondingly complex and complete procedures – if they intend their reports to be suitable for daily clinical use and comparable from past, present and future results – of any given Laboratory.

Keywords: Analytical; Clinical

Introduction

Laboratory exams are part of our lives. At any time, we go to the doctor – either because we are or feel ill, have had some accident, or wish to prevent a given condition or disease; or else, because we wish to establish healthy activities and dietary acts, and to practice preventive Medicine [1]. To that effect, most medical appointments eventually result in the ordering of at least a few laboratory exams. We trust those to help the Doctors manage our health and disease status. At a next appointment, the doctor will read the report with some alphanumerical information, and reach some decision (even if it is the decision to do nothing), hopefully after a thorough evaluation of said exams and discussion of outcomes with the patient. Nevertheless, how does that work, for the Laboratory? Moreover, what if we need to repeat those exams again on another Laboratory, or travel to a distant country?

Figure 1: A Real Clinical Laboratory is far too complicated to be considered child´s play. Adapted using free clipart from http://clipart-library.com/science-safety-pictures.html.

What that is all about

If Laboratory results are to be adequate indicators of clinical outcomes (either of health or disease), those must display high precision [1]. That means much more than collecting some samples, identifying those accurately, making sure they are ready to analysis and free of (known) interferences, preserving them intact until the moment of analysis. It does also go beyond the analysis itself: plainly, putting each sample into some automated equipment (or performing some reaction sequences and measuring some results as coagulation speed, particle aggregation, or some colour change). If not properly installed, even a computer monitor can cause a flickering and stroboscopic effect that is undesirable to proper operation. Those can be strong enough to induce a neurological effect on some susceptible individuals [25].

Most modern Laboratories are almost entirely automated [47]. That does not turn any Automator or machine into a black box into which one pushes samples, then waits and watches, unaware of the machine's operation and, finally, observes and transmits the results into a Patient's [electronic or paper-based] records. Any health professional should neither take those lightly nor trustingly evaluate those at face value.

Trusting even the better machines will do all work in an invariable and always safe way equals being bound to suffer eventual misleading [15,17,21,24]. Even more important, the reasons for failure are not always readily apparent or logic.

I have been the testimony of a perfectly functional Blood Analyser, that started to consistently present unreliable platelet analysis, despite a thorough mechanic and electronic review, in a laboratory where the electrical current had been carefully measured and found out to be suitably stable. Upon putting a dedicated no-break directly in front of said Automator – to the despondence of the Electric Engineer that granted every reasonable measure had been taken – the machine promptly gave the customary, perfect, and trustable results.

At another opportunity, an Immunology Automator demonstrated perfect results under a given operator – who disliked the Lab's illumination as excessive, and usually turned off some lights – and then produced randomly erroneous results under another operator – who was fond of a brighter room. As usual, every mechanical and electronic parameter appeared to be in order. When we finally reviewed the electronic hardware of the fluorescent lamps above the said machine – it now operated fully well, under both operators!

ARTEL (2019) [2, 3, 4] has demonstrated that – even under the best operation circumstances, Immunology plates and other equipment can present minute variations that potentially interfere with the results of Enzyme-Linked Immuno-Fluorescent Assay (ELFA) and other essays.

We are not talking about some Conspiracy Theory [https://www.imdb.com/title/tt0118883/], where all Labs join to master the unwitting humanity. Nevertheless, if all the participants (patients, Healthcare professionals and Laboratory people) do not pay close attention to the analytic processes, something is bound to go wrong at one time or another.

Perfect imperfection?

All citizens were living the so-called cold war back in the 1980's when – under the Presidency of, Mikhail Sergeyevich Gorbachev (Michael Gorbachev, 1931) [11,12,28] – the Government of the USSR started a process that would be known as Restructuring (Perestroika, or Reformulation) [12,22,46]. Its main characteristic was the so-called Publicity (Glasnost – openness, candour or enlightenment) displayed to their citizens and the world about what was happening in the USSR. To be sure, Perestroika and Glasnost were later questioned by numerous modern historians as having led to the fall of the former USSR Empire (arbitrarily dated stated at December 25, 1991, the day when the Soviet flag appeared over the Kremlin for the last time) [34]. Some of the notorious consequences were the independence of several smaller Baltic countries from the former USSR and the disclosure of deep corruption across governments. However, we can consider Russia nowadays (and the remaining Baltic countries) as an evolving from an Anocracy towards a Democracy [16]: Citizens now can elect their presidents, even though some characteristics of the previous Regime remain. Eventually, the apex of that reforming process hit Germany, and the fall of the Berlin Wall influenced a starting globalisation process throughout all countries [8,52].

We must not forget the realisations of the past, however. At the year of 1961, Yuri Alekseyevich Gagarin (Yuri Gagarin, 1934 - 1968), thrilled the world when he said that "the Earth is blue". [18,39] – a significant victory of the former USSR. Does it mean that all those

countries will eventually understand each other, and come again to terms? While we currently experience a fierce process of globalisation, nobody knows. The fact is, Reformulating and Exposing the facts in candour undoubtedly resulted in a better world; the same would happen for the Clinical Laboratories.

Glasnost, perestroika and the laboratory

We could say about the life of Clinical Laboratories: We are all the same, but not the same. We perform the same analysis in different processes and vice-versa. In a globalising world, where people travel around at jet-speed, and multiple citizens migrate from country to country, the best usage of laboratory exams and information requires that all labs seek for the most suitable processes that best serve each and all of their clients. We need our own Perestroika, with as much Glasnost as possible. It is imperative to treat all data with the utmost Clarity – and we must know how each process results in the required data; with what degree of accuracy and reliability, and – most of all – how the results of a lab can compare, or correlate, to those of other labs, either local, national or international.

Figure 2: Glasnost in the lab: We need to know that what is in the tubes are real people's sample, and people come in various shapes and sizes. Adapted from clipart extracted from https://pbs.twimg.com/media/DvBcxmKW0AETHTb.jpg and http://clipart-library.com.

It is not as if a Lab Glasnost would be unable to disclose its share of deceit. As an instance, medical costs were in the high by the 1970s, and a crisis in Lab's fees burst. The facts are, while Medicine is a need to which many citizens and organisations fail to put a desirable limiting cost, the increasing complexities of the technology mean all Industries shall have some gain. That enhances the importance of a thorough administration and choice of the test menu of a laboratory. [BERGER, 1999]. The needs of practical education of patients and physicians did nothing to make a lousy crisis better. As a result, the interdisciplinary movement of Choosing Wisely (https://www.choosingwisely.org/) has been started (2012), with the explicit intentions to obviate, declare and discuss – with Doctors and patients – when not to ask for a given exam or intervention. The movement is growing, with promising results.

Error and its treatment

Everything in Lab analysis is about procedures – if not manual, then semi-automatic or else automated. Moreover, all procedures require clear objectives, exact measurements and reproductive performance. That is why every laboratory procedure needs adequate documentation. Ordinarily, we can make it through a laboratory-specific Standard Operator Procedure (SOP) [48]. The main executors shall write SOP's of the activities, and accordingly consult all other executors; the most qualified (Biochemist, Biologist, Pathologist or other) professional who is deemed responsible for that must overlook ad supervise the results. One suggests that an SOP must suffer annual or at least biannual review and revision. These are the documents that must testify and ground for the training of new professionals, and they must be freely available to any auditing professional. SOP's consist of the written evidence about the execution and techniques of processes, and also the first document to be reviewed in case of major failures or updated of the procedures. They are the ultimate key to the best quality of procedures.

We often talk about human error in the Laboratory [38]. In the same way, some error may result in the fall of a plane, and a human error may result in a catastrophic mishandling of laboratory data and results and untoward effect to patients. Automation is one of the keys to tackling that question [47]. It offers essential improvements in patient's and operator's safety; the possibilities of a by-directional working interface; more accessible computing and analysis of data; the promise of Artificial Intelligence and Systems integration [33].

Minimising manual procedures is vital to reduce error [17, 27]. However, on the other side, machines' working – as well as the attending humans – are all influenced by multiple interferences. Analytical errors – including equipment malfunction as well as other, preventable causes – can reach up to 15% of all laboratory errors; Those can also include the (deliberate or not) use of expired or inadequate reagents; and undetected failure in quality control [47].

The possibility of cascading error (what has been termed "the Swiss cheese" theory, when all factors concurrently determine a common failure) is ever-present [38]. All processes must, therefore, be continually overseen by personnel in order to assure the best results. The practice of simplification, wherever possible, will be an improvement. Laboratories, more than ever, must recognise themselves as high reliability and complex organisations, that must practice a continuous sharpening towards error handling and prevention [38].

Automation or semi-automation do have a significant advantage over simple human, or manual procedures: its results tend to be more reliable, reproductive and precise. Over the time – and History – of Laboratory Medicine [9,29,53], that has allowed the continuous improvement of quality of the chemical procedures, methods and determinations producing much more accurate results of chemical analysis. Furthermore, new methods and improvements result in breakthroughs once considered impossible. That results in a growing menu of available exams – that must be proven adequate to a variety of different outcomes. Meanwhile, people live in different countries, with different socioeconomic status, political regimens, ethnology and kinds of the environment – from the Arctic Igloos to the Scorching savannahs of Sahara. What may be adequate, or economically possible, to a given population may be utterly different from the solutions adopted in a different community. The ideal of laboratories is to adapt and accommodate to such differences.

As to the analytic measurements themselves, we can classify biochemistry procedures in three basic types: automated, where a machine or device performs the whole process; semi-automated, where some beforehand preparation of the sample is needful; and manual, where humans manually perform all or most chemical reactions. Error rates as reasonable as 1 in 1,000 are a standard for manual procedures, while for automation, those can reach the number of 1 in 10,000 with due administrative measures [17].

Liquid handling is critical In all procedures. For all manual pipetting procedures, the instrumental pipets that must be periodically calibrated, to guarantee that the adequate delivery of liquids (either sample, diluting water, or reagent chemicals). Semi-automatic pipettes must also be thoroughly checked and cared for before and after each use. For semi-automated systems, any semi-automated pipetting used for liquid handling and pipetting must also be optimal and its quality, guaranteed. Periodic calibration of all pipettor systems is paramount [2,3,4].

Pipetting errors constitute a significant source of inaccuracy, also in many automated systems. Multiple factors and mechanisms –often unnoticed – tend to cause such errors, risking compromising the accuracy of results [2,3,4]. Thus, the performance of any liquid handlers, including automated pipettors inside immunology analysers. Also, more complex Automator's must be regularly assessed. Even immunology plates of reaction, industrially produced through highly reliable automated systems, can suffer dilation and form change in consequence to thermal effects or positioning of the plate in the Immunology analyser. Those can produce a minimal but significant error, even if the pipettors of the Immunology analysers are suitably calibrated. The control and obviation of such effects may require sophisticated techniques and procedures of periodic verification. That may call for a variety of techniques, including gravimetry; absorbance; fluorescence; Dual-dye Photometry; or combined methods.

Administrative measures are also paramount in every Laboratory: at the same time that automation and semi-automatic seek to minimise manual procedures progressively, one must obviate, standardise and establish straightforward flux and geographic standards for each remaining manual step of the procedures [6]. Laboratories are prompted to organise an individual quality plan, addressing Lab and staff obligations, operational procedures, and including its own Code of Conduct; a regulating committee; regular and documented educational procedures; effective communication; discipline and adhesion of all participants; auditing; and protocols for prompt correction of present errors and prevention of future ones [44]. Other measures may be necessary.

Any automated equipment must have its standards verified before the Lab places it in a daily routine [49,50,51]; suffer regular surveillance and preventive maintenance (besides, of course, the needful corrective ones); and operate under strict conditions (set-up and bench stability, electric current, and any other specifically required).

From the middle ages to nowadays – How much perfect is perfect?

Clinic Laboratories may have started at the time of the Uroscopists – Old Wise men or Alchemists and relied mostly on their

senses and on primitive ways to help diagnose human ailments [9]. However, in due time, the religious notions that pointed out diseases as God's punishments and established that Odours or Miasmas were the sole causes of diseases, gave way to microscopy and the Germ Theory, and subsequently to chemical knowledge and progressive instrumentation. From the first ways to estimate Haemoglobin (1892) to Blood counting, culturing and Urinalysis (1914) [9], throughout the slow emergence and progression of semi-quantitative and quantitative methods all Labs, the development of clinical Biochemistry was initially constructed with what we now consider rudimentary semi-automated machines such as spectrophotometers [13,14,20]. The term Clinical Pathology, created in In 1890, means the examination of biological fluids and their chemical components [40]. At first, it relied at the very best in semi-automated procedures; as precision needs became necessary for the best care of the patients, that technology improved and in the explicit need of Quality Control became apparent. The Quality movement for Hospitals and Laboratories probably started in America in 1918, when the College of Surgeons started making inspections [9]. After that, progressive measures requiring certification of personnel and methods evolved, and in 1922 the College of American Pathologists [http://www.cap.org] started its activities. While international organisations are also available [https://www.ifcc.org/about/history-of-ifcc-members-societies/list/], the CAP is still very significant as a normalising international institution, along with the International Federation for Chemical Chemistry IFCC [https://www.ifcc.org/].

As the designation itself suggests, Quality Control is a set of processes and measures designed to detect analytical errors within the Lab and guarantee both the reliability and accuracy of test results. Its main objective is to make sure to provide the best possible care to the patients. Another objective is to manage costs, results and schedules effectively. Internal and external auditing is necessary to enhance safety and assurance. Statistical tools are indispensable [7,10,26].

Some needful modern procedures in modern laboratories are Internal Quality Control (including the processes of validation and determination of error and bias) [30,31,36], External Quality Control **(**critic to the best results) and Accreditation [35,36,57]. (necessary for purposes of Benchmarking and external recognising of the quality of a given Laboratory) Those should be daily activities, carried out transparently and continuously, in any modern laboratory.

No matter what the fabricant of a given Laboratory Chemistry Kit or Automator says about its quality, clinical and Laboratory practice must be able to verify that [7,10]. A high number of variables interfere in chemical reaction – e. g, temperature, air humidity, time, exposure, stability of the reagents – and in the functioning of automation – electricity, stability of electric current, mechanical pieces and their harmonic work, capacity of aspirating air for pipetting of samples and reagents, imperviously of internal fluid ducts among others. It would be too simple to admit that each analyser or system has the same quality and regularity profile.

That is why each system must suffer some statistical analysis, even before the active operation. This procedure is widely known as validation [7,32,43]. To validate a given system, a statistical evaluation of the so-called linearity (i.e. the regularity and width of variation the process suffers in response to the concentration of the analytes) is necessary. Let us say; the more glucose is present in a blood sample, the more intense a colour that reagent will develop; and that intensity must keep some grade of proportionality between glucose concentration and developed colour. If the exam is to be useful, the system must reliably measure glucose concentration in all clinically relevant possible values. Otherwise, the system must be reconstructed or substituted. One must also evaluate accuracy, imprecision and bias of each determination. Those must be compatible with biological variations and clinical meaning if a given exam is to be considered useful. [http://www.westgard.com].

Internal Quality Management is possible through processing samples of a known result, sequentially, along with the regular patient samples. Following the same procedure, it is possible to estimate if a given laboratory determination is under control, i.e., if the results are following a regular pattern and we – therefore – have a reasonable guarantee that a repeated dosage on any patient's sample – say, of glucose – will produce a result that is acceptably close to the previous result [21,23,42].

This control calls for the use of a specific graphic [7], i.e., one sequentially compares the results of the so-called control(s) over time using Gaussian analysis and the so-called Levey-Jennings graphic; Traditionally, those the Westergard Rejection rules will be necessary to determine the stability of the results. [https://www.westgard.com/] If the known sample strays too much from the desired values, or presents any tendency (bias), the system is considered not to be under control. Then, some intervention is needed.

That intervention may mean the recalibration of the system, some mechanical or maintenance, or eventually a complete substitution of the system.

External Quality Control [23,42] is compulsory for all Laboratories in most countries nowadays. In that case, Labs regularly receive samples from a given Proficiency provider of analysis and then perform the routine determinations, unknowingly of the results. After an appropriate time, al laboratories return results to the central provider Lab for Proficiency Testing. While that central Laboratory often uses the same Automator Brand that some of the participants use, there is no guarantee that those results represent the correct value. However, what follows in the most times is that the central Proficiency testing Laboratory can now statistically evaluate the results of each and all participants. The more participants, the better the result – as the sample of participants is more prominent, and the power of the statistics of the evaluation results are robust. All participants are granted anonymity and discretion. Results can be evaluated per Laboratory, per analytical system, per group – whatever proves more useful from the statistical and economic point of view. Whatever Laboratory falls without the statistical pattern of its peers, becomes a suitable warning showing their processes might be out of control, and the Proficiency tester an also help the Laboratory to diagnose the problem and evaluate the results.

External control also means most results of a given laboratory are comparable to those of its peers – either locally, nationally or across the world [23,23,37].

All laboratories must perform according to a set of routine procedures, generally termed good laboratory practices. [45,49,50,51,57] But then, who does it? Well, a laboratory may voluntarily adhere to an Accreditation contract. Accreditation institutions may be general Hospital or specific Laboratory accreditors. The way it works is that the accrediting institution must be knowledgeable of Laboratory works. It must know the main characteristics of labs, and even work as an advisor for the client Laboratory, before their auditing process begins.

Accrediting Facilities [19,64, 66] have a set of ideal standards, whereby they indicate the Lab to submit to those and agree that it will be verified. After that introducing period, the accrediting institution can visit any of their clients anytime, for a verifying audit of the correct procedures Elsewhere, there are two possibilities: either the Lab is reproved, or it is approved but pending to a future audition.

While centred on procedures rather than standards, Accreditation is also a way to tackle with inter-laboratory differences. Since their processes are supported, standardised and verified by third parties, with specific expertise and experience, grants itself an extra layer of safety, and inter-comparability with Labs that share the same system.

The bottom line is, no machine or procedure should ever be a so-called black box where some people or machines execute a sequentially unknown procedure then output some result that must be read and considered as unquestionable and whose determinants are unknown. For the Laboratory to be useful, it must present transparent procedures, where all results are potentially reproducible and whenever possible comparable to national and international results. The modern technology that allows it is the simple "PDCA" process – which must be thoroughly observed by all participants, from Doctors to the Lab, and never excluding the patient.

Figure 3: Setting goals towards better lab results. Adapted from http://www.artel.com.

Conclusion

Doctors and patients must be aware that granting the excellent quality of Laboratory results is no easy, straightforward task. In this

short review, we have just scratched the surface of the complexity of Analytical Quality. Besides the need for precision diagnosis, Labs face the challenges of Reproducibly and intra-comparability of results; inter-comparability with local or national results; and international standardisation. We must not let ourselves deceive by the apparent simplicity of the execution of some procedures. Laboratories are not anymore the hermetic and Alchemic sceneries of mediaeval times, where induction and intuition were the masters instead of scientific and deductive processes.

Even though it may not be apparent, the concepts of current administration re essential to all Labs, lean principles must be applied to the Lab for the minimisation of all errors [17].

As for the doctors and patients, they must be always aware that, even if the industry produces fast and convenient diagnosis system, they must evaluate and consider each exam as to its power, convenience of use, and the manifold analytical variables – Not to mention the pre- and post-analytical ones, which we did not account for in this review. As clients, both of them shall seek to be aware of the variables involved in their choices among the best laboratories.

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