ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 3 Issue 1 January 2020

Short Communication

The Merry-Go-Round of Modern Diagnosis

Victor Lage de Araujo*

Laboratory Medicine, International Fellow, College of American Pathologist, Msc, Evidence-Based Healthcare (UCL), Brazil

***Corresponding Author:** Victor Lage de Araújo, Laboratory Medicine, International Fellow, College of American Pathologist, Msc, Evidence-Based Healthcare (UCL), Brazil.

DOI: 10.31080/ASMI.2020.03.0468

Received: November 27, 2019

Published: December 23, 2019

Introduction

Hermes trismegistus

Whom some authors consider an ancient Egyptian sage [1], wrote in the so-called Tabula Smaragdina [ARAS, 2019]:"What is below is like that which is above, and what is above is like that which is below, to accomplish the miracles of the one thing". In that document, purportedly written in one only emerald – thus named Emerald Table, he wrote the Principia to all things know about the World – Including Medicine and diagnostics. Hermes Trismegistus was namely the predecessor of all Alchemists, extending to the modern Clinical Pathologists. It seems that that single sentence is the summary of all diagnostic procedures, for each exam result shall be equivalent to a particular disease process, and be met with a precise diagnostic procedure, contributing to the greater good of the patient.

Hermes' writings have probably influenced Hippocrates, (born 460 BC, island of Cos, Greece - died 375 BC, Larissa, Thessaly) in his remedial actions and writings, of which a valued auxiliary was the art of Uroscopy. [Britannica, 2019]. Those were the times when a few drops of urine, plus regular medical examination – i.e., touching the patient, smelling him, perhaps weighing him or touching his skin – were the only means a doctor could use to diagnose his patients.

We are not living those times anymore; but then, diagnosis is still a necessity both for patients and of Doctors. Experts state that most Doctor's decisions and actions follow the requirement and evaluation of some laboratory or other complementary examinations. [Galoro, 2016]. Others debate their overuse [Sumita, 2017]. We must ponder that every day, for Medical Sciences have evolved exponentially after those mediaeval times, and we now have a myriad of complementary exams to choose.

To remember a few: There is not that much time since ultrasound examination has substituted traditional X-rays in some of its needs – with a significant advantage, and the science of Nuclear Magnetic Resonance was unknown but a few decades past. NMR suffered a rapid technological expansion, culminating in mighty magnets and the use of gadolinium-based contrasts, with unimaginable applications, that we nowadays witness.

Understanding laboratory exams

We have nowadays also a plethora of laboratory exams. Correspondingly, we must wisely consider their use, advantages and drawbacks.

On the laboratory's methodological side, we have three kinds of test:

1. The so-called invasive tests – such as Cerebrospinal Fluid and Synovial Fluid Analysis, that by their sampling methods may lead to significant infection.
2. The minimally invasive procedures, like most blood sampling techniques, that may result in nothing worse than a haematoma.
3. And the collection of faeces and urine, that are almost entirely harmless.

However, all complementary exams share a potential untoward effect about which health professionals do not often talk: those of misdiagnosis and mishandling – intended or not.

Fortunately, among all uses of complementary exams, we can analyse and classify most among a few categories.

1. Adult patients that are enjoying good health or feeling bad. They attend the doctor in search of a diagnosis of an existent or imaginary ailment. It will be necessary to distinguish those who are in good health from the ones who bear some disease or condition, and its severity.

- Patients willing to start on a healthy sports or diet.
- Patients who believe or fear they have some condition, even though they are asymptomatic.
- Patients who have contacted individuals attained with some disease, whose family presented some genetic condition, or who were victims of some exposure or accident.
- Patients who need to know if mild ailments are of immunological, viral, or bacterial origin, and therefore need adequate treatment.

- Patients severely ill.

2. Patients on chronic disease control or that use some particular medication. In this case, it is sought to determine:

- If the patient is using the medication regularly and according to the prescribed dosage.
- If any physiological or metabolic variable is altering the absorption and action of drugs.
- If there is a risk of drug intoxication.
- Patients with endocrine conditions, or to rule out such diagnosis.

Usually, in that situation, the doctor will order the blood dosage of some medication or substance (antimicrobial, anticonvulsant, hormone, or another). In other cases, such as diabetes, a physiologic test as HBA1c or Fructosamine may be asked [Horowitz, 2019].

3. Patients with a specific condition or disease under therapeutic follow-up. Usually, the doctor requests tests that assess the repercussion of diseases and medications on physiologically present chemical elements, such as:

- Sodium and Potassium, in patients under nutritional status assessment, hormonal disorders or chronic hypertension.
- Blood glucose, or Total Cholesterol and Fractions, for patients under evaluation for Metabolic Syndrome or Diabetes.
- Glucose, HBA1c or Fructosamine, and perhaps some other auxiliary test, for Diabetes.

4. As an initial or intermediate step in the diagnosis of certain diseases.

- For example: as evidence of inflammatory activity, such as Erythrocyte Sedimentation Rate and C Reactive Protein, in the evaluation of infectious, inflammatory or connective diseases.
- Complete Blood Count and kinetic tests of Iron, in initial or aetiological diagnosis of anaemias.
- Protein Electrophoresis for the diagnostic of a series of Inflammatory disease, or of Multiple Myeloma and related malignancies.

5. In the specific etiologic diagnosis of some diseases:

- Serum determination of antigens and antibodies in the evaluation of infectious diseases and to determine the stage of the diseases.
- Molecular tests for particular virus and microorganisms, the diagnosis of hereditary background diseases (genetic diseases) or in the detection of the genome of infectious agents (such as bacteria and viruses, multi-resistant organisms etc).
- Immunofluorescence exams for the characterization of auto-immune diseases, and also for some other specific conditions.

6. In the diagnosis and following of certain malignancies, and other specific diseases as Amyloidosis and other deposit diseases:

- Tissular biopsies in general, for the determination of malignancy, for future determination of surgical security margins.
- Liquid biopsy and similar procedures.
- Tumoral markers related to some disease, periodically, after or during the required surgeries or procedures.

7. What all those patients have in common is:

- They all need specific exams, accordingly to their disease or condition.
- They do not need unrelated exams to diagnose absent diseases or conditions, which will probably result either in economic burden for the patient or the health system – or worse: they may also result in some misdiagnosing, mistreating, or inadequate follow-up.

What the physician must consider here is that – since the times of Hippocrates, and probably before him – diagnosis is not merely the result of the interpretation of some exam (or collection of exams). Any diagnosis must start at the point where the physician hears the patient's complaints, then evaluates those, makes a complete physical examination, creates some diagnostic hypothesis, then order some exams. Those exams shall be able to either confirm or deny the original hypothesis. If there are more than a few possible hypotheses, we talk about differential diagnosis.

Some laboratory characteristics of exams

While asking for an exam, the Doctor must be aware of the Turnaround Time (i.e., the needful time until he will get a response) and costs of a given exam. He must, of course, be aware that in some cases, he needs to order the exam, instruct the patient accordingly, and promptly start the therapeutics, to be modified (if needed) after the results and in consequence of the clinical response. Also: each exam has its characteristics. The physician must be aware of those in order to interpret the results. Last but not least: all exams suffer three main phases in the Laboratory, which we must be aware of, consider and respected [Von Meyer, 2017]:

1. The Pre-analytical (i.e. from the medical requisition to the lab processing itself).
2. The Analytical (all analysis in themselves).

3. And the Post- analytical the actions of posterior Quality Management, Clinical Evaluation and Correlation, reservation of aliquots for possible future counter proof, and the release of the written (or informatic) report in itself.

Inside the laboratory, each of those three phases have their subdivisions, according to methodologic considerations. Those are all necessary to guarantee error-free and precise results, which is why any laboratory exam takes longer than the simple theoretical time taken from the collection of a sample and its direct insertion into a quick mechanical analyser [Von Meyer, 2017].

For the right decisions to occur, good knowledge about the exams, as well as their Reference Values (RV), are necessary. Although the approximate RF values for all patients are, in some cases, almost universal, providing reliable reference intervals is one of the essential tasks of the clinical laboratory and diagnostic industry. For all cases, the existence of well-defined VR increases the accuracy and safety of diagnostics. One must estimate Reference values as a function of the values obtained for given analytes in healthy populations [2-4]. In order to meet all those requirements, the exams must also present.

1. Analytical efficiency, defined by statistical and analytical properties, such as Sensitivity, Specificity, Accuracy, Analytical efficiency.
2. A minimum of possibilities of error or failure in its execution phases: (pre-analytical, analytical, post-analytical)
3. A criterion capable of clearly distinguishing the normal, abnormal, pathological, physiological or pathophysiological states that are desired to determine (according to the specific case). This criterion is provided lately by VR.

Exams as markers of diseases and conditions

If we are to consider any exam as a reasonable predictor of some disease, an association with the condition must be present. For causality criteria, we generally use Bradford-Hill's criteria. [Statsdirect, 2019]. If no causal relationship can be determined, there must be at least some strong statistical association.

To allow the wise use of a laboratory exam, we must have some information about it. Only in consideration of those we can understand the true meaning that an exam is to purport us.

We show some possibilities on figure 1. Some exam must enable us to foresee what will happen in point B (i.e., fully developed disease) while we are still we are at point A (Asymptomatic or not sick). Furthermore, the earlier we get that information, and the higher the precision of the exam, the better. That is what allows efficacy in an early intervention.

Figure 2 shows evidence of the fact that one must have a clear notion of both the tests qualities and the stage of the disease when diagnosing some infectious diseases.

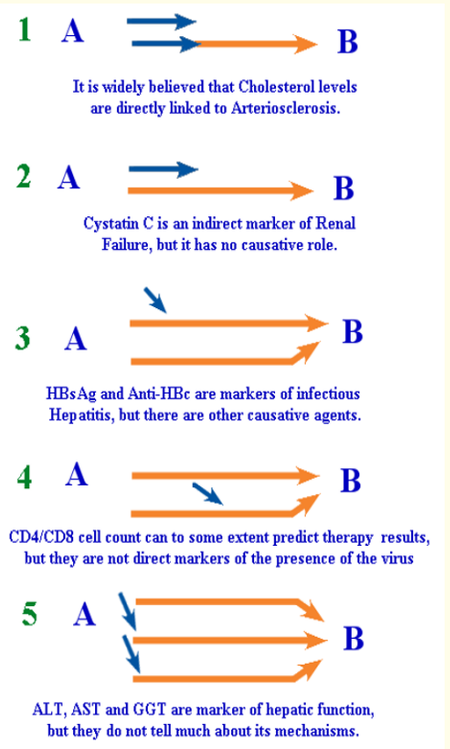

Figure 1: Some possibilities for diagnostic tests. A: point of start of the disease; B: point of full disease. Adapted from Twaddell, 2009.

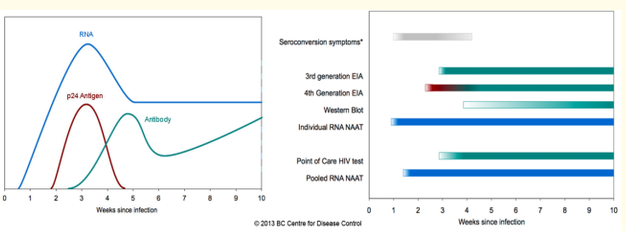

Figure 2: Extract from https://smartsexresource.com/topics/hiv-window-periods. It is essential to know both the phase of the disease and the tests employed when diagnosing HIV infections.

Definition of reference range or reference value (VR)

Many laboratory exams usually go beyond binary results (i.e., Positive/Negative). For those, we require some anchor that points us the meaning of the results.

We generally define VR as an interval between two limits (or alternatively either below or above a given limit), which is estimated for a percentage of values (usually 95% of reference or healthy individuals), as indicative of a given condition, disease or serum concentration of substance relevant chemistry for the population of individuals under study.

In other words: each exam (in our case, laboratory medicine test) can be considered as a substitute or surrogate marker and may have some characteristics [De Gruttola, 2001].

As elements of biochemical analysis, they correlate to one or more pathophysiological events or pharmacological processes. That in its turn results from a process of health, disease or treatment. (in short: we can state that for any examination there is a Gold Standard).

At the time of the Uroscopies, people used to let the urine dry and attract insects – or even taste it, in more urgent cases – to determine if a given patient had either Diabetes insipidus or Diabetes mellitus. At such times, it could one could say that the golden Standard was "Sweet" versus "insipid" urine.

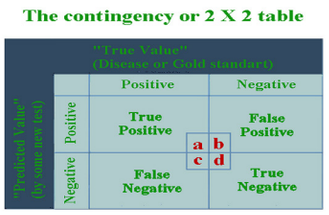

Figure 3: Created by the author with the use of free clip art.

Fortunately, science has evolved well enough that we now have better standards and earlier markers, so that we can diagnose both diseases at an earlier stage with sound methods. However, nowadays we need some comparator or standard for every laboratory standard. That has been termed the golden standard in comparison to the history of Economy. Just like the hypothetical gold stores on Fort Knox, the golden standard is what is considered the best diagnostic means. At mediaeval times It might be a sick person or the disease itself – or, in the case of the Uroscopies, the taste of urine. However, this standard often has some inconvenient characteristics (no one wishes to taste urine), so we use some comparator (i.e., the most commonly used exam or surrogate). Nevertheless, we can easily compare a given exam to its Golden Standard by building a Contingency table with accurate data, that will allow us to calculate the relevant statistic characteristics of our exam.

Figure 3 By knowing the comparable results, and applying a simple 2X2 table, we can have better knowledge about our exam. The industry applies this kind of statistics when determining the sensibility of a new exam; Physicians should use it to calculate the Positive or Negative Predictive Values for their specific epidemiology.

The fabricant of the tests generally calculates Specificity, Sensibility and Accuracy (those are the so-called stable proprieties) of a test [Zhu, 2010]. While the most desirable characteristics are the highest value (i.e., nearly 100% specificity and sensibility), one may understand certain caveats:

1. The newest tests (e.g. those that are in the process of research, or that diagnose an emerging illness).
2. Even for the most developed and better tests, there is always a trade-off between sensibility and specificity, so that fabricator and physician must decide whether they wish to use the more sensitive test (risking to have some false positives), the reverse, or a combination of both.
3. Those data are calculated in trial scenarios, and do not represent usual epidemiologic situations.
4. They may get better, as some industry improve their tests or some laboratories acquire tests of higher standards.
5. If not locally obligatory, it is customary for the best laboratories to mention those data in their reports.

Doctors can calculate Positive and Negative Predictive values can from the same table [MEDCALC, 2019]. Here, he may use the values of Sensibility and Specificity offered by the fabricator, applying those to the Prevalence in his population. Because Prevalence vary from place to place, those are the so-called unstable properties of a given exam. They are the best way to preview if a given patient is sick (or not sick) when evaluating all data collected during the Interview and Clinical Examination, Plus the local epidemiology and the characteristics of the tests.

Good Laboratory Practice determines that each exam laboratory validates new exams through studies in real individuals in real situations. Alternatively, the fabricator must offer the relevant data, and that will allow suitable verifications through practice and statistic essays.

Diagnostic tests undergo both validations from an analytical point of view and a biological point of view. So, given a specific exam, the Reference Value is the one associated with the situation one needs to diagnose. For some – such as qualitative exams showing the presence or absence of antibodies or microorganisms – it will suffice to state a binary result ("positive" or "negative"). The reference will state to each condition (i.e., either the absence or presence of a given antigen or antibody) corresponds a presumed state of health. For the quantitative exams, a more sophisticated analysis may be necessary.

The values of any chemical analyte, such as Urea, Creatinine, Glycaemia, Sodium, Potassium are intended to distinguish healthy and disease states. Thus, it makes sense, when releasing results of a laboratory test, also release the RV or Reference Intervals most relevant to this examination.

Definition of reference values

The main instrument available for the definition of VR is a statistical evaluation of populations. This type of evaluation must have been carried out before the execution and release of the results,

preferably in studies of large populations relevant to the laboratory analysis in question. However, several factors can lead to a review of VR. That is how, for example, around the year 2,000, the diagnostic criteria for Diabetes Mellitus were revised worldwide. This review followed an extensive study on blood glucose and blood glucose states, which modified previous conclusions; gradually, the new values had become accepted worldwide.

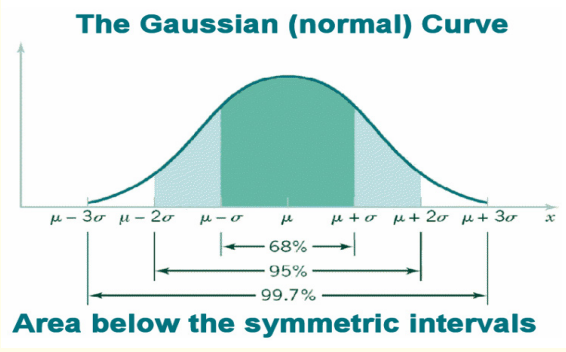

Figure 4: The Gauss curve. Free clipart.

For the statistical evaluation of VR, considering studies in large populations, values of individuals are taken after clinical evaluation regarding the condition under study, and the results are evaluated according to a statistical study of the results. Values such as mean, standard deviation, and coefficient of variation are generally used. This kind of study is generally named "parametric statistics". For this analysis, we need to review the properties of the so-called "Normal Distribution", or "Gauss Curve" [5-13].

- Look at gauss curve. The mean range +/- 2 Standard Deviation (σ) establishes 95% of the sample.
- It is worth saying that, according to the above definition, 95% of the values observed in healthy patients should fall into this range.
- That is, if we studied a sufficiently large population of healthy individuals, 95% of these presented values within the interval thus defined.

However, some facts are indispensable for this analysis to be performed according to this type of statistic:

1. A previous calculation of the sample number (i.e., the number of individuals whose data will be evaluated, or reference individuals) is needful in such a way that the analysis has adequate statistical power.
2. All reference subjects must suffer previous evaluation by well-defined criteria (e.g. criteria that ensure that these individuals are not sick)
3. It is necessary to prove that the phenomenon under analysis follows a proven Gaussian distribution, or that methodological conversion to such a reduction is possible (e.g., by applying logarithm on values).

For some analytes, a difference between lower and upper values matters; for some others, one uses either a "higher" or "lower" value as standard. One must understand that some values are considered of universal used because they come from extensive population studies [such as glucose and cholesterol]. Nevertheless, many others require specific consideration, in that they may be specific to a population, sex, or age gender. We must also consider that, in modern society, gender identity means the often consideration of the individual choices of the patient, since gender surgery and use of synthetic hormones influence in several biologic characteristics. While they must be not judgemental, both physicians and the Laboratory must be aware of that [Treadwell 2016].

Overdiagnosis

We must always consider the real need for any exams we order. Excessive laboratory orders may result, not only in burdening of the health system and the patient but also in the undesired pursuit of expected or feared diagnosis. If we consider that any laboratory exam has the potential to give at least 0,5% to 1% of false-positive results, it is easy to conclude that an extensive list of exams will eventually produce a false positive even in the healthiest individual. The questioning about those may lead to even more significant problems. That and other related discussions have led to the Choosing Wisely movement (https://www.choosingwisely.org/)

Evidence-based healthcare

Another concept that must never be forgotten when ordering and interpreting medical tests is that of Evidence-Based Healthcare. Medical science and knowledge increase its corpus of knowledge by the minute, ad not every published science is reliable or applicable to a given doctor's practice. One must always be aware that any new exam, or even new appreciation of order exams, must be subject to the rigorous appreciation of science. However, no matter the Doctor's conclusions, the patient must not be considered as one more number, or one more spot in some flow chart: he is the voice that must be heard when reaching a final decision (Figure 5).

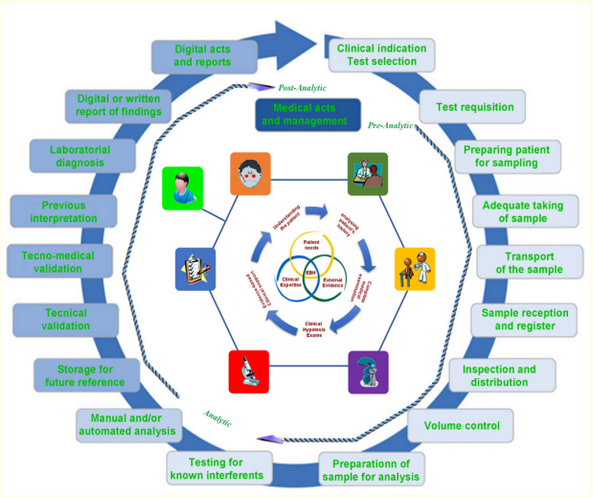

Figure 5: The Merry-go-round of diagnosis, from a demanding patient to a healthy one – considering the Analytical processes (external layer), the behaviour of the clinician (Middle Layer) and Evidence-Based Healthcare (core). Even though technology is paramount today, the time when humane management of the patient will be dispensable seems hopefully still very far away. Adapted from. Bhavani (2019, Eichler (2015) Von Meyer, 2019. With use of some free clipart from http://clipart-library.com/.

Bibliography

1. Ebeling F. "The Secret Historu of Hermes Trismegistus. Hermetism from Ancient to Modern Times". Translated from the German by David Lortonl Cornell University Press, Ithaca and London. Kindle Edition (2005).

2. Mendes ME. "Os Valores de Referência no Século XXI". 44th Brazilian Congress of Clinical Pathology". *Laboratory Medicine* (2010): 14-17.

3. Andriolo A. "How to define the Reference Values in my Laboratory? 48th Brazilian Congress of Clinical Pathology". *Laboratory Medicine* (2014): 9 -12.

4. Slhessareenko N. "Como Definir os Valores de Referência". 48th Brazilian Congress of Clinical Pathology". *Laboratory Medicine* (2014).

5. UFMG. Gaussian Distribution.Probabilistic Model for Continuous Variables (2013).

6. Ferreira CES. "Intervalos de referência no laboratório clínico". *Jornal Brasileiro de Patologia e Medicina Laboratorial* 44.1 (2008): 11-16.

7. FVBM. "VariaçãoBiológica na Interptretação dos Resultados Laboratoriais dos Paciemntes do IPEC Portadores de AIDS/HIV". *Disponível em* (2018).

8. SBPC. "Recomendações da Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial (SBPC/ML): Coleta e Preparo da Amostra Biológica". *Disponível em* (2013).

9. SOPERJ. "Sociedade de Pediatria do Rio de Janeiro". Converta-se. Disponível em (2018).

10. Bradford Hill. Hill's Criteria for Causality.

11. The pope die papstin imdb.

12. Enciclopaedia Britannica. Hippocrates.

13. Enciclopaedia Britannica. Uroscopy.