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# Metrological Aspects to Identify and Quantify Cancer Malignancies

**Esther Castro Galván*, Mauricio Maldonado and Melina Pérez Urquiza**

*Department of Materials Metrology, Centro Nacional de Metrología, Mexico*

***Corresponding author:** Esther Castro Galván, Department of Materials Metrology, Centro Nacional de Metrología, Queretaro, Mexico.

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**Abstract**

Cancer research is currently one of the most challenging topics in the health area, notwithstanding the implementation of Network research groups, like PAN-Cancer and Cancer Core Europe, that provide a powerful knowledge base. Cancer marker information made available by these networks is making it possible to develop "macro visions" that will enable the achievement of better prognoses. The availability of big data produced by sequencing techniques requires new kinds of infrastructures in the field of bioinformatics, which are being used by these networks to manage information produced around the World. Acute Myeloid Leukemia (AML), affects children and adult individuals, with a higher mortality rate among members of the adult group. Several research teams are working on AML and, according to some researchers, the effectiveness of medical treatments is still poor. Some National Metrology Institutes (NMI) are working on the development and certification of Reference Materials in order to provide a practical quality assurance tool for diagnostic analysis, specifically for laboratories that use PCR and sequencing techniques. Metrology is the science of measurements in all fields of physics, chemistry and biology. The combination of interdisciplinary efforts from oncologists, geneticists, biomedical researchers and metrologists, among others, is necessary to solve a problem as complex as cancer. Metrology can provide an alternative point of view, considering the problem as a measurement task that needs to be improved.

**Keywords:** Cancer; Prognosis; Metrology; Leukemia; Sequencing

## Introduction

Sustainable innovation in cancer detection is a 21st century challenge. Possibly, one of the main problems in cancer diagnosis and reliable prognosis is the identification and quantification of all mutated genes that could be responsible for the malignancy, in a phase when the detection allows the application of an effective treatment. For example, leukemia is a group of hematological malignancies that could undergo around 23 mutations [1,2]. This diversity of mutations makes diagnosis more difficult because it is still unknown if the emergence of each mutation is activated at different times. Sometimes, cancer detection is made in a step when the mutations are few and the analysis techniques cannot detect a specific cancer marker.

## Networking

The International Cancer Genome Consortium and The Cancer Genome Atlas (ICGC/TCGA) are leading a Pan-Cancer Analysis of Whole Genome Consortium (2020). The main objective of the project is to sequence the whole genome in all possible kinds of cancer. Massively parallel sequencing techniques are providing a powerful tool to identify mutations in the entire genome [3]. Additionally, it is important to mention the Cancer Core Europe network, which brings together six of the best European cancer research centers, with the main objective of optimizing research results and avoiding duplication [4]. In the end, all these research efforts on cancer malignancies should be decisive to improve prognosis and treatment.

Cancer research by sequencing techniques is producing an immense amount of data in those networks. Big data analysis is one of the major hurdles that researchers have faced in cancer determination, considering their work in bioinformatics and the treatment of genomic and molecular data. On the other hand, the use of super-fast computers, cloud computing, etc., allow researchers to share information in a network of centers. Access to this information allows the possibility to produce "macro visions" and conceivably reach better conclusions that benefit the patients directly. One successful example is the recent complete molecular classification

of colon cancer. It had not been possible until researchers were able to add up large amounts of data and identified the subtypes that will eventually enable the production of personalized drugs for colon cancer [3]. There are other efforts like the RELA from International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) that have a program Eqa-somatic-tumor-mutation-v5-2019, external quality assessment-proficiency testing in molecular diagnostics including a list of assays for different somatic tumor mutation.

In regard to the Acute Myeloid Leukemia (AML), it is important to say that this cancer disease affects a great number of children and is currently studied in several laboratories around the World [5-7]. The disease is affecting also older individuals with a high mortality [7]. According to Shaheedul et al., 2020 [5], the effectiveness of medical treatments is still poor and, consequently, so is the prognosis. Reviews about AML recent treatments are being published by several authors on a yearly basis [8-11].

## Clinical trials

The attraction of talent and clinical trials with experimental drugs that are still in the early stages not only offers advantages to patients, but also produces savings for the healthcare system [1,12]. Josep Tabernero in the Instituto de Oncología del Vall d'Hebron de Barcelona [12], studied nearly 1,500 samples from patients who were tested molecularly with a complete genomic and proteomic characterization of their tumors. Treatments with innovative medicines under study that are not yet marketed, increased 25-30% its effectiveness in patients who need some form of medical treatment. Additionally, it was reported that this approach saved more than eleven million euros per year to the health system, compared to traditional approaches.

The development of molecular techniques for the identification of translocated genes provides a very effective tool for researchers that are looking for better treatments. Yilmaz and Daver [1], report the results for AML in the Cancer Genome Atlas study, in which 23 mutated genes are more common and were found in patients. Presently, "genomic medicine" is based on sequencing techniques, in order to identify mutated genes in a specific and more accurate way.

The main target is alternative and target-specific drugs to improve the survival rate. Molecular genetic alterations underlie the core of AML pathogenesis and disease progression. Hence, understanding these processes is vital to develop more disease-specific therapies [5].

## Metrology

Even with all the advances and efforts in the identification and diagnosis of cancer, the complexity of the problem is daunting and treatments are far from reaching a satisfactory level. Fortunately, recent progress in sequencing and bioinformatics allow researchers to obtain more information and in the near future the prognosis and treatment will be more focused and effective. Nevertheless, there is still a need to assure a better quality in the measurement process. In other words, it is necessary to assure that the equipment performs according to the manufacturer's specifications and with the required precision, that measurements between laboratories are comparable and, in general, the measurement process needs to be improved. Laboratories who routinely analyze samples to identify cancer markers with techniques such as Polymerase Chain Reaction (PCR), flow cytometry etc., need to maintain and improve their core capabilities. This means constant evaluations of the entire measurement process and analysts' capabilities. It is necessary to make sure that quality measurement tools like the use of reference materials, instrument calibration, control charts, traceability and proficiency tests are present in the process [13]. PCR can identify and quantify a target gene, a cancer marker for instance, but needs a validated methodology from the sample extraction to the analysis of results. Therefore, it is important to introduce Metrology, in particular reference materials, to underpin the massive amounts of raw data produced by the new molecular techniques [14].

Metrology, in general terms, is the science of measurements. Measurements are made in every field of the exact sciences, such as chemistry, physics and biology. The main objective of metrology is to understand each part of the measurement process, and to determine how each part affects the final result. If a researcher can understand the entire measurement process and all the uncertainty sources, it will possible for her to improve it. To do this, metrologists need reliable references and standards. In general, metrology science is developed in National Metrology Institutes (NMI) in every country, NMIs establish and maintain National Measurement Standards for all the base and derived units in the International System of units (SI), of interest for that country. The SI base units are the kelvin, the mole, the candela, the meter, the kilogram, the second and the ampere [15]. Given the notable increase in genetics and biotechnology, NMIs have developed mechanisms to support measurements related with the identification and quantification of genes, genomes, and in general DNA and RNA. The 9th edition of the SI brochure issued by the Bureau International des Poids et Mesures (BIPM), (2019), mentions for the first time the measurement of a number of cellular or biomolecular entities (for example copies of a particular nucleic acid sequence), as counting quantities associated with the unit **one**. "The unit one is the neutral element of any system of units" [15], and when a measurement results from a counting process traceability can be established by appropriate and validated procedures. This formalization of counting in the SI confirms how measurements of biomolecular entities are as much a part of metrology as measuring meters or kilograms. According to the International vocabulary of metrology (VIM), a reference material is a : "material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in the examination of nominal properties" (JCGM, 200:2012) [16].

For example, the Certified Reference Material (CRM) for BCR-ABL 1 transcripts was developed and certified by a NMI for calibration of qPCR assays quantifying the BCR-ABL 1 b3a2 transcript [17]. Another example are PCR-based DNA Profiling Standard Reference Materials (SRMs) for the forensic community, for calibration and validation of currently used methods for quality assurance purposes.

## Conclusion

Improvement of treatments and prognoses of cancer malignancies need better understanding and knowledge of the diverse mutations, more practical sample preparation, powerful instruments and networking collaboration. Sequencing techniques and bioinformatics are providing extraordinary support for cancer research. Projects such as PAN-cancer are multiplying international efforts to obtain a complete map of cancer mutations. Advances in prognosis have had very promising results, but it is necessary to maintain reliability and comparability (i.e. "quality") in biomolecular measurements. NMIs are working to develop practical tools such as reference materials in this field. While interdisciplinary efforts will bring about major breakthroughs for improved treatments of cancer malignancies, more efforts around the development and certification of reference materials are needed to satisfy the quality needs of all the laboratories.

## Conflict of Interest

The authors have identified no potential conflict of interests.

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