

## Opinion

**Will Genetic Testing be the Answer to the Definition of Treatments in the Era of Precision Therapies?**Joana Espiga de Macedo<sup>1</sup>, Manuela Machado<sup>2</sup>, Marta Diogo Pereira<sup>3</sup>, Francisco Viana Machado<sup>4</sup>, Matilde Amaral<sup>5</sup>

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**Abstract**

With the increasing and fast development of molecular medicine, we can aspire to carry out treatments directed to the sickness of each patient, and with this practice the idealized precision medicine. Its objectives are not only survival and response rates, but also best quality of life with lowest toxicity, with more cost-effective choices for each single patient. Defining the complete genomic picture of all cancerous lesions, in the near future, is a major goal in Oncology that will benefit everyone. The further and recent use of liquid biopsies, processed by next generation sequencing, as a method to determine specific genetic mutations, has obtained clinical utility and validity in the metastatic scenario, with a predictive value. Further clinical trials need to be performed in surgical cases, so that specific gene mutations can be used as biomarkers, to evaluate residual disease, stratify risk of relapse (prognostic value) and identify the patients that will need adjuvant treatment besides the classical staging system.

keywords: precision medicine, circulating tumor DNA, liquid biopsies, biomarkers

**Introduction**

In solid tumors, tissue biopsy has for long been the “gold standard” for histological diagnosis and immunohistochemical, genetic and molecular studies of the various neoplasms [1]. Traditionally, the anatomic, pathological and the imaging tools allowed, in combination, an evaluation of each solid tumor and its staging according to the clinical classification of Tumor, Nodule and Metastasis (TNM). To date most treatments in oncology are based on this staging and classification. Adding information obtained through molecular medicine is essential to optimize the therapy for each patient and each tumor.

In 1948, circulating tumor deoxyribonucleic acid (ctDNA) was first identified in human blood by Mandel and Metals [2]. The ctDNA is actually the DNA released by the primary or metastatic neoplastic cells, being released into the bloodstream and which can be isolated from a peripheral blood with a simple blood test. The discovery of tumor DNA in blood samples in what has been defined as “liquid biopsy” may be the key to avoiding or at least diminishing the need for some invasive procedures. This new technique may be the key, or at least a temporary solution to obtain a broader view of tumor heterogeneity and with this spectrum of the disease, allow the identification of different mechanisms of resistance to different drugs, in clinical practice to tailor each treatment to a patient / specific neoplasia. An even more ambitious goal for liquid biopsies in the near future is

the early detection of some neoplasms and thereby contribute to the overall reduction of cancer mortality.

**Technological Evolution**

One of the first challenges considered was how to discriminate the cDNA from DNA free from normal cells. It is now difficult to remember that, not yet for a long time, the biomarkers analysis was limited to 1-5 genes in the clinical routine. The sensitivity of the polymerase chain reaction (PCR) based on digital techniques has improved over time, however, with the increase in the number of biomarkers and the need for them to be analyzed simultaneously, several technical problems arise, as for example, the amount of sample required for DNA extraction.

The new next-generation sequencing technology (NGS), allows, in just 10ng of DNA, to determine the detection of mutations, translocations or variations of copies in a large number of genes simultaneously. This NGS technique allows to save material and obtain a fast response with acceptable sensitivities and specificities [3], assuming an essential role for the major objective that is the understanding of the complexity of the cancer through the analysis of the genome by sequencing of the exom or of the entire tumor genome.

At the American Society of Clinical Oncology (ASCO) in 2016, a study funded by Guardian Health Inc.

was presented, in which liquid biopsies of 15,000 cancer patients (37% lung cancer, 14% breast cancer, 10% colorectal cancer, and other cancers 38%) were analyzed; tumor biopsies were available from 386 of these patients. When comparing tissue samples with ctDNA, by the sequencing method, the results revealed an overall precision of 87% (336/386 patients) [4,5]. A correlation was also established between ctDNA quantification according to stage and tumor burden in colon, breast and lung cancer. It should also be emphasized that in some studies, the relationship between detection of tumor recurrence by circulating tumor DNA and resistance to target therapies has been demonstrated [6].

In May 2017, the College of American Pathologists, the Association of Molecular Pathology and the European Society of Pathology, validated the guidelines for the next generation sequencing (NGS) as the standard of understanding and validating this technique [7].

### Tumor Heterogeneity and Clinical Application ctDNA Detection

Cancer is a heterogeneous disease, involving different initial clones within the same tumor, one of them being the main motor of carcinogenesis at the beginning of the history of each neoplasia. Cancer is, in fact, a dynamic and heterogeneous disease, with multiple and complex genomic alterations, primary or acquired mutations, genetic rearrangements, among others. They occur from its origin and as time goes by, undergo changes due to the microenvironment and the aggressions to which they are subjected by different types of treatments (chemotherapy, immunotherapy, target therapies, radiotherapy). The major carcinogenesis pathways known nowadays are the "Driver" or Main pathways and the secondary ones are the "Passenger" pathways. When tumors are treated by many different options as already mentioned, they adapt themselves finding the alternative route to achieve the goal of carcinogenesis: proliferation, angiogenesis, migration, metastasis and survival of neoplastic cells.

The pharmacokinetics, or rather the better understanding of the cells biological activity associated with the evolution of the tumor and its genetic alterations, allowed to create the bridge between basic research and clinical investigation. This means to bridge knowledge from the basic biological concepts and its application in clinical practice. This is known as Translational Investigation, travelling from biology of the tumor cell to clinical and therapeutic intervention.

In 2017 Milholland et al. published a study which revealed that, on average, one mutation is expected per cell division [8]. However, in another study published in the Cell in 2012, in which the complete genome of a patient with breast cancer was sequenced, detected about 70,000 mutations, of which only five had an active role in carcinogenesis [9]; that is, all other mutations had no "driving force" to lead to tumor development. These are the so-called "Passenger mutations", which do not cause noise in the carcinogenic process. In contrast, the 5 most mutated mutations are "Driver mutations" and these lead the tumor cell to its objectives: proliferation, angiogenesis, migration, metastasis and survival. The authors concluded that tumors are explained by a limited number of mutations that change the behavior of the tumor, but their cellular complexity is much higher and depends on characteristics of the host, the microenvironment and the immunological profile.

### Future Perspectives

As a consequence of the many published studies and many others currently underway, there has recently been a need to standardized validation, and an OncoNetwork Global Consortium has been created: CANCER-ID 7, [10]. In this way everyone will use the same language and the same techniques to make translational research into a single language.

In the near future, in the era of Precision Medicine, the treatment of each of our patients will be based on an understandable genomic profile that detects the genomic alterations of solid tumors, namely microsatellite instability, tumor burden, among other biomarkers. All these joint efforts will certainly lead to greater knowledge of each tumor, which ultimately will translate into better treatment for each patient.

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