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Genomic Studies in Cancer: Ready for Use?

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Since the human genome was first entirely sequenced in the beginning of this century, huge research efforts have been made to translate these knowledge into clinical practice. In the cancer research field, the chance of identifying genetics factors- both in the patient and the tumor- that would influence the risk, prognosis, and therapeutical management of a particular cancer, brought the new world of the so-called personalized oncology. Thus, the prevention and treatment of cancer evolved from an indiscriminate, old fashioned strategy to a promise of individual and tailored cancer care [1].

The classic approach of identifying a candidate gene to answer a given question (risk, prognosis or treatment) has retrieved benefits for the clinical practice in a relatively small proportion of tumors. The description of specific somatic mutations, lead to the development of targeted therapies that improved the survival in tumors that were resistant to chemotherapy treatment. These are the examples of BRAF mutation in melanoma, EGFR mutation in lung cancer or BRC-ABL fusion gene in chronic myelogenous leukemia, as remarkable examples. On the other hand, the identification of high susceptibility germline mutations in genes like BRCA1-2 for breast and ovarian cancer, or mismatch-repair genes for colorectal cancer -just to mention a few- permits improving the outcome of patients and their at-risk relatives through the oncology genetic counseling process [2,3].

However, despite of these and other advances, the real individualization of cancer care is far from being a reality yet. Unfortunately, many tumors lack genetic alterations that can be considered treatable with drugs, leading many patients to be not candidates to targeted therapies. To make it more complicate, a high proportion of patients treated with targeted therapies relapse after a variable time, probably because alternative escape pathways are activated [1]. On the other hand, in the heredo-familial cancer field, many cases that compliance hereditary cancer criteria remain elusive, since in many of them it is not detected any mutation in the genes studied. Moreover, the cancer risk within one particular family carrying the same mutation in a given gene varies widely.

What is the reason for this failure? One explanation is that cancer, especially solid cancers, are diseases whose genetic complexity cannot be explained by a single mutation in a single gene, but by hundreds or thousands of them in multiple genes. Some of these mutations are the so called driver mutations, defined as those that confer a selective proliferation advantage to the cell. These are different from the passenger mutations, defined as those which do not alter the cell status but occurred in a cell with driver mutations. If these passengers are mere traits or confer changes in the effect of the driver mutations is still unclear. For example, high throughput strategies have shown that around 100 genes are mutated in each single colorectal or breast tumor analyzed, being at least 15-20 of them driver mutations [4]. In the germline DNA mutations linked to an inheritable risk to cancer, we could extrapolate it with rare mutations/drivers and common polymorphisms/passengers. Taking it all into account, the current clinical approach of determining a single mutation in a tumor and/or germline DNA of a patient seems to be obsolete. It would be like looking at a landscape through a very narrow hole instead of through a wide open window.

In the past years, it was impossible to have a wider view of the genomic landscape, because of technical limits. The sequencing techniques were very laborious and expensive to deal with multiple gene analyses. Now those days are the old days thanks to the next generation sequencing, which permits simultaneous analysis of wide genome areas, in a faster and more efficient way. There is an explosion of bio-tech enterprises that can sequence the whole genome or the exome of a given organism-including humans- in a record time and cheaper than ever. We have now the keys in these technical facilities to open a wide window to look at the landscape of cancer genetics. But there is a problem, which is the landscape itself.

At the present time we are used to make decision plans based on single gene alterations of the dichotomist type, such as "mutation present/absent". But if we move to a wide genomic approach, it is impossible to manage this information with this dichotomy. Thereby, the first problem is the way that we are going to analyze the big picture. Classic statistics cannot afford this, and thus bioinformatics may play a crucial role in the interpretation and correlation of this data with the epidemiology data, patient outcomes and treatment results. An effort must be made to compile data from multinational consortia for a useful correlation between the clinics and the genetics.

The second problem, even more delicate, refers to germline DNA analysis, which has important bio-ethical implications. In genetics, the pre-test counseling is capital. If we are looking for a specific gene, we can counsel our patient/proband for the consequences of harboring a mutation in this gene: For example, we can counsel about prophylactic surgery in BRCA1 or 2. But if we are going to analyze the whole genome/exome, we can find unexpected findings, such as another gene mutation that currently has not effective risk reducing strategies: to continue with the previous example, CHEK2 gene. Or, moreover, we can find mutations in genes that we were not investigating at all in our patient: For instance, Huntington disease gene, leading to a non-planed bioethical and, possibly, legal problem. One solution could be to pre-counsel about all the possible genetic alterations that could be found, leading to never-ending informed consents, or maybe to censor those results from which a patient does not want to be informed. But once the information is out there, it is difficult for both the patient and the oncologist to neglect it.

In conclusion, the genomic studies bring us an exciting scientific and clinical challenge in the cancer genetics. Although wide genomic studies are today technically and economically possible, a huge effort must be made by all the scientific community involved in the fight

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against cancer to correlate this information with the clinical data, in order to keep improving the patients care. Maybe we are not still ready for the genomic studies in cancer, but we should be willing.

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