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Short Communication

Revolution of Oncology 2020. Targeted Therapies based on the Genomics of Each Patient

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Introduction

We know that cancer is not a disease, but more than 200 different types of tumours, and that its diversity is not depleted in the type of tumour. Thus, three people with lung cancer, for example, will benefit from three different treatments. And one with gastric cancer can respond to a medication used in breast cancer (Figure 1).

Figure 1: Her2neu in gastric cancer.

One of the biggest challenges facing doctors and health systems today is being able to know in advance what therapies will work for each patient and which will not. And for that you need to obtain and understand a huge flow of information inscribed in the genome of the tumours.

The promise of precision medicine is to match patients with targeted therapies using genomics. The ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) Project consortium, which this week published in the journal Nature sequencing results of 2,658 tumours corresponding to 38 types of cancer in 20 open access articles.

Cancer is a disease caused by mutations in key genes. What the Pan-Cancer Project achieved is to establish a comprehensive narrative, the most detailed so far, of the biological changes that determine the beginning of each tumour, which paves the way for future treatments and early diagnostic methods.

Although it has no specific therapeutic application in the short term, its theoretical teachings are numerous: better knowledge of the genetic mutations that cause the multiplication of cancer cells, sometimes surprising similarities between different types of cancer or extreme variety of tumours of an individual to the knowledge accumulated on the origin and evolution of tumours could allow developing new tools to detect cancers earlier, as well as (develop) more personalized therapies, to treat patients more effectively, says Dr. Lincoln Stein, one of the scientists who commanded the project, in a statement from the Ontario Institute for Cancer Research (Canada).

Unveil the secrets of the genome of cancerous tumours to improve their understanding and thus be able to combat them: that is the titanic project that more than a thousand scientists went to for several years, hoping to achieve one day personalized and effective treatments.

The results of this research program called Pan-Cancer Project were detailed in about 20 articles published in the specialized journal Nature and other medical journals of the same group (Figure 2).

Figure 2: Cell (https://www.cell.com/cell/newarticles).

Each of the mutations can be a possible target for the development of new medicines, there are working and joining efforts 1,300 scientists from 37 countries.

It is an extremely important work because it opens doors to continue advancing in the identification of new biomarkers and in the development of drugs that inhibit them.

The results also certify that the future of cancer treatment will go through the deepening of personalized and precision medicine.

The patient (presumably healthy) will go to a doctor's office, they will draw blood, have a liquid biopsy and from that we will have the "Identity Document" of the tumour, which will contain its genetic sequencing and so we will know how to treat it, regardless of what be in the breast, in the lung or in the brain.

We will know how it is biologically and the treatment will come out by virtue of the rapidity with which the advances occur, that could be a reality towards the end of this decade.

In the coming years, data from genomic studies will provide information with an impact on relevant parameters, such as survival, quality of life and costs associated with the use of techniques and treatments. In addition, scientific advances will open additional therapeutic options.

Actual state

Currently, precision medicine is used in breast and lung cancer. It is that they have been able to establish a handful of biomarkers - a protein or gene - that, if expressed in the tumour, make it susceptible to being treated with drugs that are already available. These biomarkers help select the treatment and have changed the prognosis of these types of cancer.

We are going towards an oncology that is going to focus more on genomic sequencing than on the type of tumour.

If I have an X biomarker and a drug that inhibits it, it doesn't matter if it's a breast, lung or bladder cancer.

An example: 20% of cases of stomach cancer express HER2neu, one of the best-known biomarkers in breast cancer, so both can benefit from the same treatment (Figure 3).

In the United States, due to cost reduction, a genomic sequencing costs almost the same as measuring biomarkers separately. At some point it will be more convenient to sequence the genome than to measure specific points separately. That still does not happen in practice. There is a big gap between research and practice.

Impossible not to also take into account the access gaps that widen along with the advances, we are talking about genomic sequencing, when in Argentina there are large disparities, to the point that there are people who do not access a tomography.

Sequencing the genome of a tumour has a cost of $ 4,000 to $ 5,000. A tumour of any type can be studied. The patient can pay for that money and this study of his tumour genome may prove useful, or that no drug is yet available and he will not benefit from anything.

Figure 2: Inmunohistochemistry according to the magnification rule.https://www.nature.com/articles/modpathol2011198#Fig1.

As the implementation of precision medicine progresses, on the one hand with better genomic tests, and on the other because of the reduction in the costs of such tests, all this will contribute to better and more accessible cancer diagnoses, specific for each patient and best treatments tailored to each one.

The future of the Pan-Cancer project

The increasingly growing matcheo among patients and targeted therapies is an aspiration of the Pan-Cancer Project.

However, project leaders point out that an important barrier to this is the "daunting heterogeneity" of cancer "from tumour type to tumour type, from patient to patient, from clone to clone and from cell to cell".

What it is about is finding recurring patterns among such diversity. The construction of significant clinical predictors from genomic data is possible, they say, but it will require knowledge banks that comprise tens of thousands of patients with a complete clinical characterization, something that is impossible without international collaboration and data exchange.

The next phase of the project, advance its leaders, will bring the cancer genomics community together with health care providers, pharmaceutical companies, data science and clinical trial groups to create complete knowledge banks of clinical outcomes and treatment data for patients with a wide variety of cancers, along with a detailed molecular profile.

a, Top, putative driver mutations in PCAWG, represented as a circos plot. Each sector represents a tumour in the cohort. From the periphery to the centre of the plot the concentric rings represent: (1) the total number of driver alterations; (2) the presence of whole-genome (WG) duplication; (3) the tumour type; (4) the number of driver CNAs; (5) the number of driver genomic rearrangements; (6) driver coding point mutations; (7) driver non-coding point mutations; and (8) pathogenic germline variants. Bottom, snapshots of the panorama of driver mutations. The horizontal bar plot (left) represents the proportion of patients with different types of drivers. The dot plot (right) represents the mean number of each type of driver mutation across tumours with at least one event (the square dot) and the standard deviation (grey whiskers), based on $n = 2,583$ patients. **b**, Genomic elements targeted by different types of mutations in the cohort altered in more than 65 tumours. Both germline and somatic variants are included. Left, the heat map shows the recurrence of alterations across cancer types. The colour indicates the proportion of mutated tumours and the number indicates the absolute count of mutated tumours. Right, the proportion of each type of alteration that affects each genomic element. **c**, Tumour-suppressor genes with biallelic inactivation in 10 or more patients. The values included under the gene labels represent the proportions of patients who have biallelic mutations in the gene out of all patients with a somatic mutation in that gene. GR, genomic rearrangement; SCNA, somatic copy-number alteration; SGR, somatic genome rearrangement; TSG, tumour suppressor gene; UTR, untranslated region.

Figure 3

The Pan-Cancer Project is focused on the study of oncogenesis mechanisms, but does not seek to describe them, but its objective is the development of a "robust and reliable tool" for diagnosis of clinical use (Figure 4).

Figure 4

Project in Argentina

The project in Argentina is based on the study of ancestry, which will allow us to know whether or not there are regional differences in our population with respect to world reference genomes. The initial stage, which consisted of evaluating and validating a panel of genetic biomarkers in 52 genes associated with the development of different types of cancer, has already concluded.

As a long-term objective, the project aims to forge a map of tumour genomic actionability in Argentina, generating for the first time frequency data with this relevance at the local level, which will be made available to the medical and scientific community of all the country through online database.

The use in clinical oncology of this tool will allow the rational application of cancer drugs, say those who make up the working group.

The multidisciplinary team concludes that in order for personalized and precision medicine to cease to be a promise and become an extended reality, strategic plans at the national level are required in order to establish research projects, quality indicators, electronic medical records that Integrate patient data and allow to share the information generated, within a regulatory framework that ensures the treatment of the data and the confidentiality of the information [1-5].

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