Conversation with the doctor Caterina Congregati

Anna – Doctor, what is a genetic mutation?

Caterina – The term *genetic mutation* refers to an error affecting the DNA sequence. In reality, the term *mutation* indicates the event that causes this type of error; that is, a mutation is a change in the DNA sequence that can result in damage to the information derived from it. If we imagine a gene as if it were a chapter in a large book, which can be considered our instruction manual, if a letter changes, or a group of letters, or even the number of pages, the information that the cell subsequently reads also changes. However, the change caused by a mutation does not always result in damage to the information. So, in general, we speak of a mutation when a change occurs in the normal sequence of this hypothetical chapter of our DNA. In the past, when we used the term *mutation*, we were actually referring to what we now call *pathogenic variants*, that is, an alteration in the DNA sequence that does cause damage to the information the cell reads from this hypothetical chapter of our book. With regard to the BRCA1 and BRCA2 genes, under normal conditions these genes provide the cell with the information needed to produce a protein that must control cell replication and detect cells that make errors. If there is damage to this information, the cell produces a protein that is damaged—often missing a piece—so it performs its function less effectively and protects us less from the error mechanism that can normally occur during cell replication.

A – We are not born as blank sheets of paper; do we already carry a history in our genes?

C – I wouldn't say completely blank sheets. If you are referring to the idea that the environment can somehow modify the expression of the genetic information that each of us inherits from our parents, there is some truth to that, and it is an area studied by a discipline known as *epigenetics*. Going back to the "instruction manual" analogy: there are some chapters (genes) that are not always read, or rather, their information is read and used by the cell depending on a specific need and therefore on interaction with the environment.

A – I find it fascinating that science and genetic discoveries allow us to identify a genetic mutation. Is there a limit beyond which we cannot go in order to save our lives?

C – It is exciting rather than fascinating, and I must say even more so than when I graduated and completed my specialization. So yes, definitely—there is a limit. I believe that the limit, as in the rest of medicine, is dictated by common sense: not going beyond certain boundaries that may not actually bring health to people. Let me explain more clearly. If I look for alterations that explain what a disease is, or a predisposition to a disease, but I do not have a tool for defense, it becomes a sentence. I can tell a person, "You might develop this, this, this, and that," but I cannot tell them how they can protect themselves. At that point, we have to stop. In my opinion, the limit that we as doctors, as healthcare professionals, must set in this field is always to be very clear about what the clinical usefulness is for a person, as opposed to what is scientific research. Because research is fascinating, just like clinical practice itself, but we must be very clear about when something is not useful for the patient. It may intrigue you as a professional, but at that moment it is not helpful in clinical practice. And we also have to be very honest about this, in pointing it out. Because, unfortunately, we are also shaped by what we know.

A – In your opinion, is knowing that one is a carrier of a BRCA1 mutation a sentence or an opportunity?

C – An opportunity! Absolutely. Because while some knowledge we had until no more than ten years ago was mainly relevant in the field of research, it has now become useful in clinical practice. This allows us, especially in certain specific settings, to have clear and undeniable therapeutic opportunities. For example, in ovarian cancer where an alteration is found in one of the BRCA1 or BRCA2 genes, we can use drugs that exploit this defect. Mastectomy and oophorectomy are established procedures. They have now become part of diagnostic pathways and routine clinical practice.