mutations may cause alterations in the amino acid composition of the gene product, and they have been observed in many tumors. A well-known example of such a modification is the exchange of amino acid 12 from glycine to valine in the Ras gene product. The mutation may be more extensive, leading to the absence of part of the protein (deletion). Repeated copying of a normal oncogene can lead to its amplification in the chromosome and consequently to increased amounts of the oncogene product. The same effect can be seen when there is a reciprocal exchange of segments between chromosomes (translocation). Thus, the normal *myc* gene on chromosome 8 has been translocated to chromosome 14 in many patients with Burkitt's lymphoma, a form of non-Hodgkin's lymphoma in which cancer starts in the B cells of the immune system. Chromosome translocations occur in many different tumors.

Mutated genes that encode protein components of signal transduction pathways enable external signals such as growth and survival factors to move from the cell surface receptors to key promoter–enhancer regions along the 24 human chromosomes, where they turn up the expression of genes needed for cell growth and division and evasion of programmed cell death (apoptosis). The latter event is very important and underlies the ever-growing resistance of late-stage aggressive cancer cells to radio- and chemotherapeutic therapies. Among the multiple molecular pathways that bring about cell growth and proliferation, each with their own specific surface receptors, cytoplasmic transducers and promoters as well as enhancers of gene expression, exists much potential cross talk, which allows new DNA mutations to create new pathways to cancer when preexisting ones are blocked by a given treatment.

In 1984, Mak, a pioneer in developing genetically engineered mice known as "knockout mice" because one or more of their genes have been inactivated, demonstrated the inhibitory effect on T cells of a protein called cytotoxic T-lymphocyte antigen 4 (CTLA-4), also known as CD152 (cluster of differentiation 152). This protein is an inhibitory co-receptor that interferes with T-cell activation and proliferation.[10] This landmark discovery was an important breakthrough in understanding the human immune system, pioneering further work in the genetics of immunology that has had a direct impact on the development of personalized cancer medicine. In recent years, clinical researchers have developed techniques for re-engineering the T-cell receptor gene to target certain cancers. Such treatments, although still in the experimental stage, have yielded dramatic results in some patients, especially those with leukemia and melanoma, in part because T cells are capable of being better targeted than surgery, radiation, chemotherapy, or hormonal therapy. Those findings led to the development of ipilimumab (Yervoy®), which blocks CTLA-4 and enables T cells to proliferate and destroy certain cancer cells.[11] The editors of the journal *Science* chose cancer immunotherapy, a strategy that harnesses the body's immune system to combat tumors, as the scientific breakthrough of the year for 2013.[12]

Pharmacogenomic studies first focused on inherited genetic variants of the germline DNA, but they have been extended to somatic alterations of DNA in a tumor. These studies allow the establishment of a relationship between a drug response and the patient's genetic alterations, maximizing the chance of treatment success and minimizing the risk of toxicity. Genomic markers may be predictive, identifying whether a patient will respond or not to a drug, or prognostic, predicting the clinical course of a given cancer irrespective of treatment. Because cancer is a disease of the genome, each cancer cell may harbor many genomic alterations that differ in different tumor types, even within the same tumor in the same patient.

The impact of variations in the human genome depends on their nature and on their location. These variations may be single nucleotide polymorphisms (SNPs), variations in copy numbers, and chromosomal rearrangements (inversions and translocations). The function of proteins is altered most when nucleotide mutation alters their amino acid sequence as a consequence of nonsynonymous variations