Genomics-driven oncology

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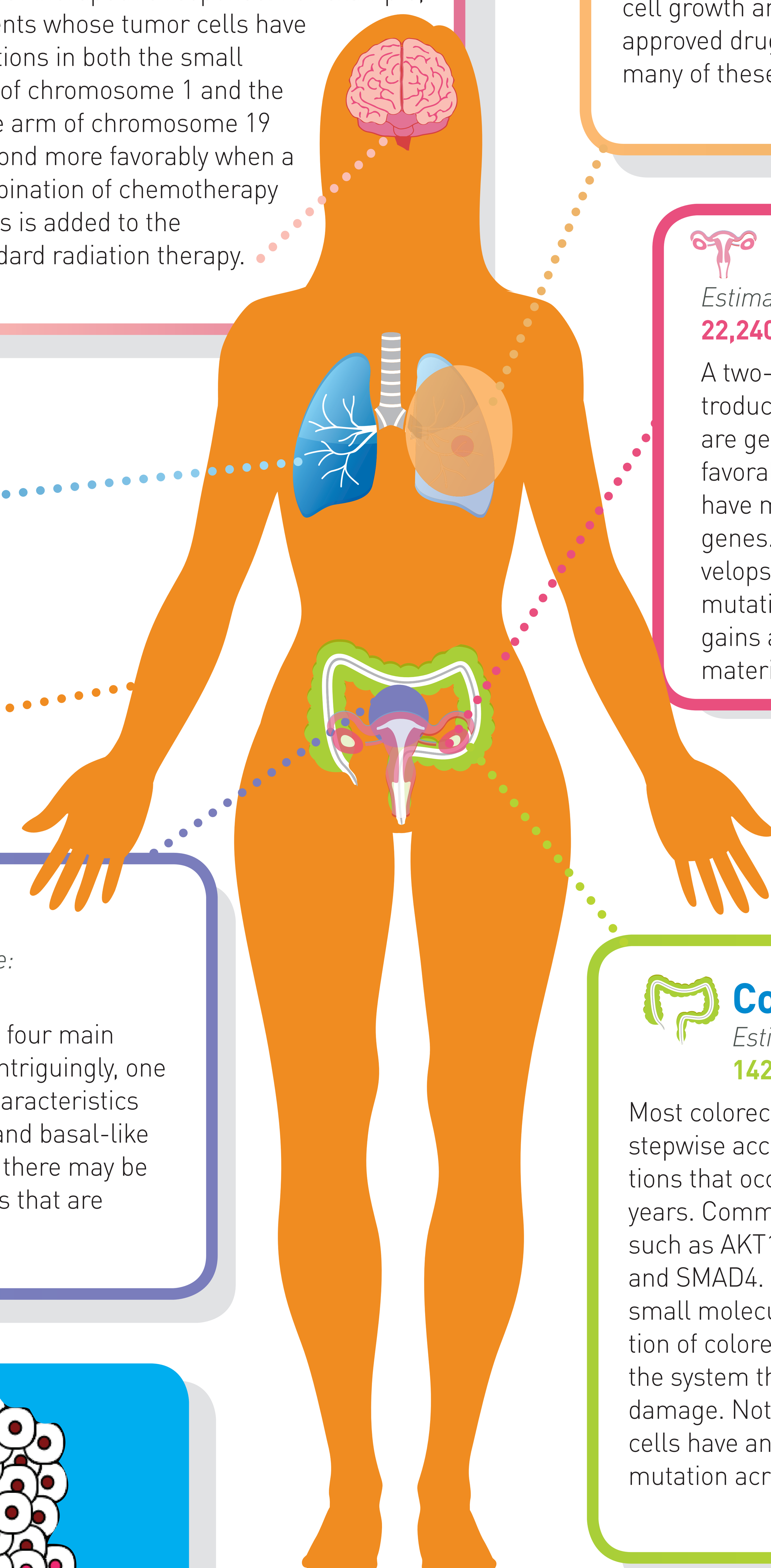
Nearly all cancers are caused by genetic changes that alter important biological pathways controlling cell growth and survival. Specific genetic changes influence the rate of cell growth, determine how aggressively the cancer will spread and control whether one drug will be more effective than another at killing the cancer cells.

Over the past decade, advances in genomic technologies, tumor analysis and drug development have changed the landscape of cancer diagnosis and treatment.

In the laboratory, genomic information obtained from cancer cells has reshaped understanding of how cancer forms. In the clinic, this same information is beginning to guide therapeutic decisions, improving outcomes for patients with cancer.



Glioblastoma

Estimated U.S. annual incidence:
9,500 new cases

A series of genetic changes has been identified that classifies glioblastoma into subtypes. Some subgroups preferentially respond to certain medications, meaning these genetic markers can be used to predict therapeutic response. For example, patients whose tumor cells have deletions in both the small arm of chromosome 1 and the large arm of chromosome 19 respond more favorably when a combination of chemotherapy drugs is added to the standard radiation therapy.

Breast

Estimated U.S. annual incidence:
234,580 new cases

A majority of breast tumors contains mutations in a category of genes that regulate when cells divide. This includes the genes CCND1, ERBB2, FGFR1 and PIK3CA. The mutations often result in proteins that continually signal for cell growth and division. Fortunately, approved drugs now exist that target many of these genetic mutations.

Lung adenocarcinoma

Estimated U.S. annual incidence: **77,585 new cases**

Lung adenocarcinoma is the most common form of lung cancer. At least 60 percent of patients has identifiable genetic mutations that impact the rate of cell division. Approved or experimental anti-cancer drugs target more than half of these mutations. For example, tumors with activating mutations in the EGFR gene can be successfully treated with the drugs getfitinib and erlotinib, which bind to and silence the mutated EGFR protein. However, this therapy is completely ineffective if mutations are also present in a separate gene known as KRAS — a striking example of the complex genetic nature of cancer.

Ovarian

Estimated U.S. annual incidence:
22,240 new cases

A two-tier classification system was recently introduced for ovarian cancer. Low grade tumors are generally slow-growing and have a more favorable outcome. Approximately two-thirds have mutations in the BRAF, ERBB2 or KRAS genes. In contrast, high-grade ovarian cancer develops rapidly and nearly all cases have mutations not only in the TP53 gene, but show gains and losses in large chunks of genetic material throughout the genome.

Melanoma

Estimated U.S. annual incidence: **76,690 new cases**

Nearly 50 percent of melanomas have mutations in a gene called BRAF and the U.S. Food and Drug Administration has approved two drugs that target BRAF as part of a treatment plan. Melanoma has also been linked to mutations in the TERT gene, which encodes a component of telomerase. This protein regulates the length of telomeres – those repeating DNA sequences found at the ends of chromosomes. The cancer-associated mutations are believed to increase the level of telomerase, which allows cells to divide for a longer period of time. Found in over 70% of analyzed melanomas, this may be one of the most common drivers of cancer growth.

Uterine

Estimated U.S. annual incidence:
49,560 new cases

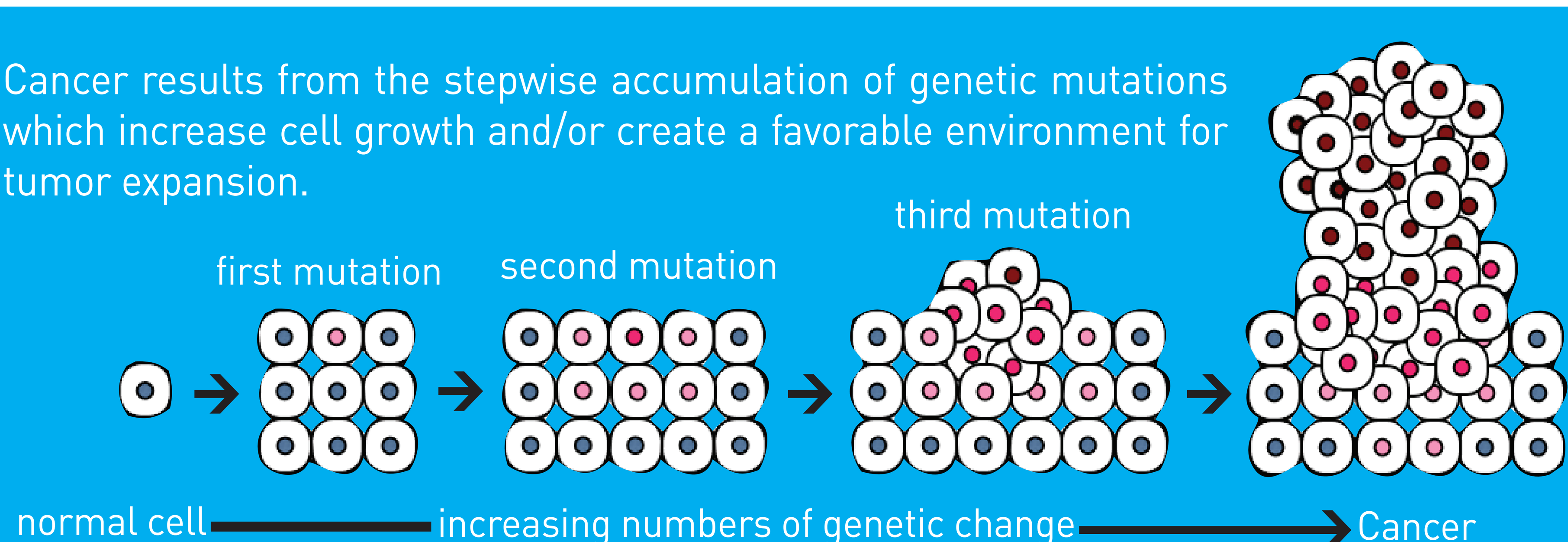
Genetic analysis has identified four main subgroups of uterine cancer. Intriguingly, one type shares several genetic characteristics with both high-grade ovarian and basal-like breast cancers. This suggests there may be common drug-based therapies that are effective for all three cancers.

Colorectal

Estimated U.S. annual incidence:
142,820 new cases

Most colorectal cancers arise through a stepwise accumulation of genetic mutations that occur over the span of many years. Commonly, mutations arise in genes such as AKT1, BRAF, KRAS, PIK3CA, PTEN and SMAD4. Many of these are targets for small molecule drugs. A significant fraction of colorectal cancers have mutations in the system that monitors and repairs DNA damage. Not surprisingly, these cancer cells have an unusually high frequency of mutation across their genome.

Cancer results from the stepwise accumulation of genetic mutations which increase cell growth and/or create a favorable environment for tumor expansion.



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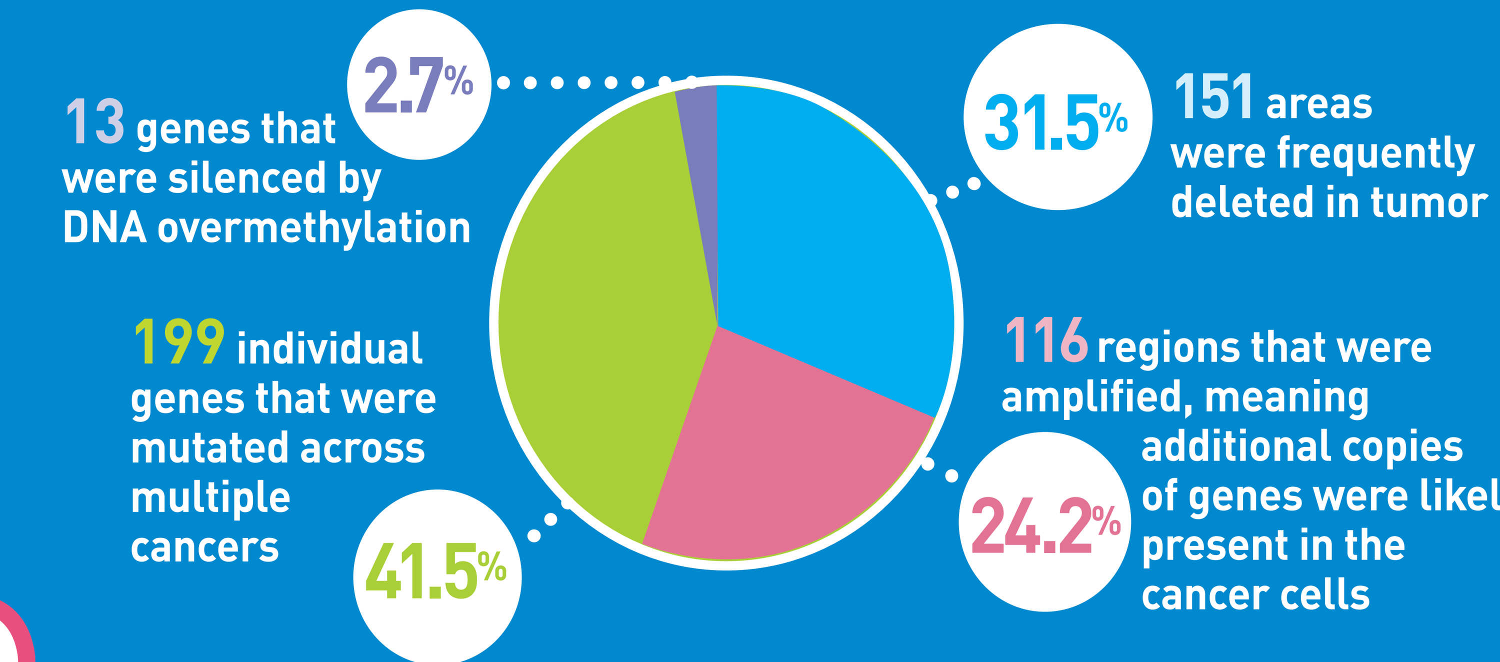
Annual incidences based on estimates from Cancer: facts and figures, 2013, American Cancer Society, and Ostrom, Q.T. et al. Neuro-Oncology 15 (supplement 2): ii1-ii56 (2013).

Comparing mutation patterns across cancer

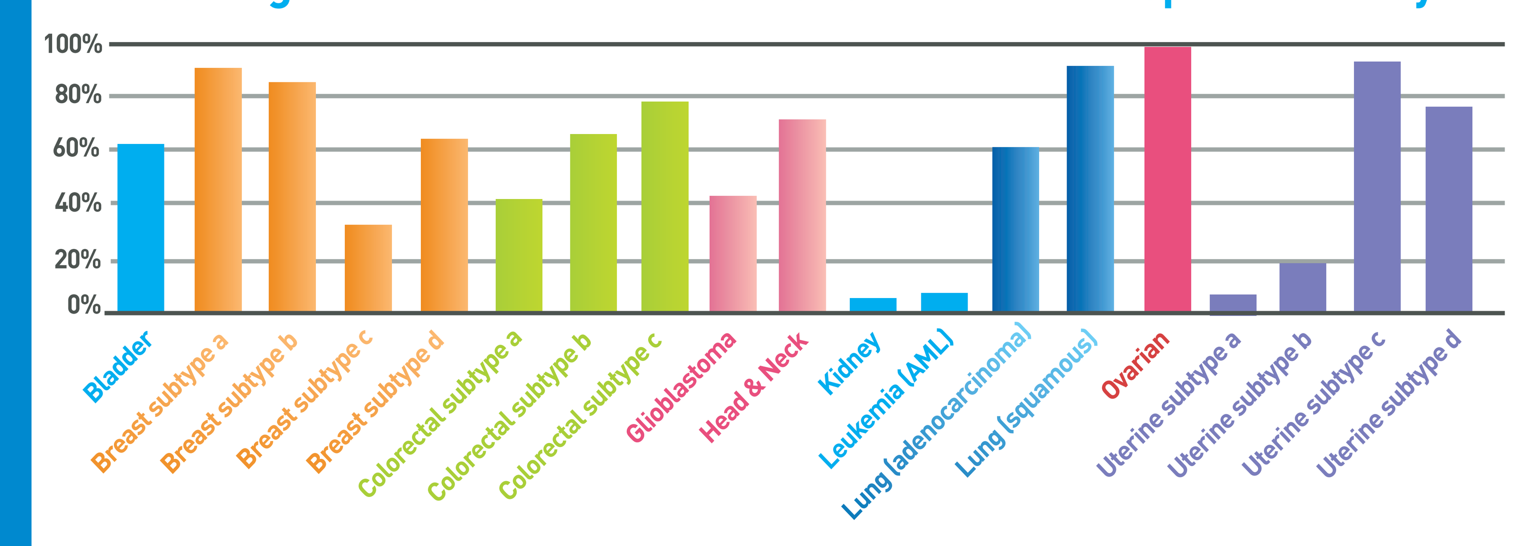
A recent study by The Cancer Genome Atlas analyzed the genetic changes present in over 3,000 tumors from 12 different cancer types. Alterations were consistently identified in over **479 regions** of the genome.



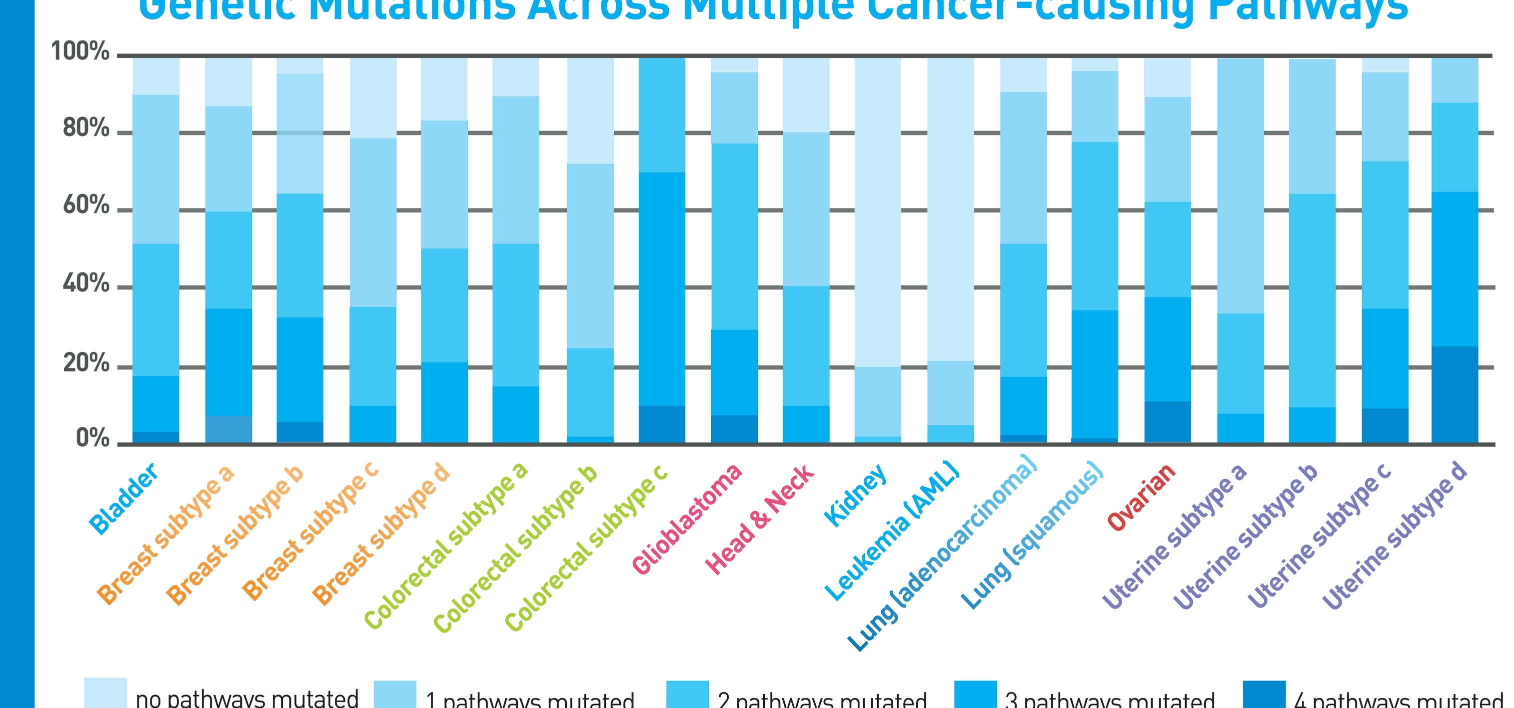
Classification of genetic alterations

The various mutations and alterations can be loosely grouped into one of four major biological pathways: two involved in receiving and transmitting "grow" signals from outside the cell, one that oversees DNA replication and cell division, and one that searches for and repairs DNA damage. Mutations within the same pathway are common to many tumor types. Additionally, most cancers have a combination of mutations that impacted multiple pathways.

Percentage of Tumors with Mutations in the DNA Repair Pathway



Genetic Mutations Across Multiple Cancer-causing Pathways



Tumors with mutations in the four pathways

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