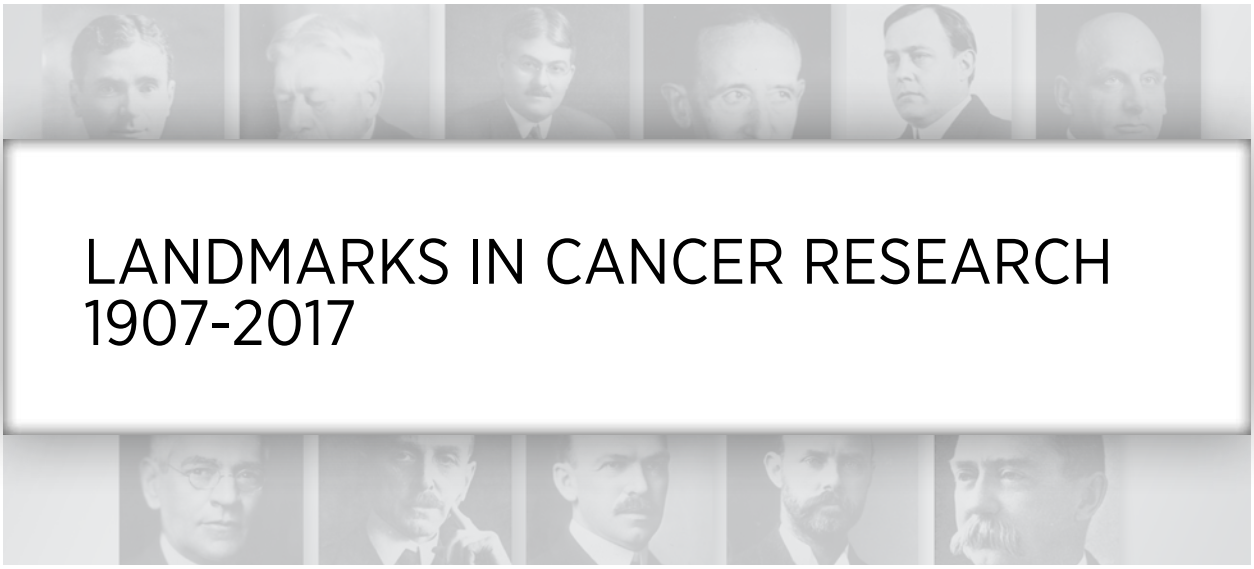
AACR
American Association for Cancer Research

1907 • YEARS • 2017



LANDMARKS IN CANCER RESEARCH 1907-2017

Ten years ago, the American Association for Cancer Research (AACR) marked its 100th anniversary with *Landmarks in Cancer Research 1907 – 2007,* a historical timeline of the seminal discoveries and events that took place in the AACR's first century.

The ensuing decade has brought a rapid escalation in the pace of progress against cancer. New drugs made it possible to treat cancer with more targeted strategies; data-sharing efforts opened doors to improved collaboration; and the nation's leaders took aim at cancer, pledging to support innovative programs and increased funding to accelerate progress against cancer.

This second edition of *Landmarks in Cancer Research,* therefore, stands as a tribute to the AACR's first century and a celebration of the remarkable decade of progress that followed.

We defined a Landmark as an event or discovery that has had a profound effect on advancing our knowledge of the causes, detection, diagnosis, treatment, or prevention of cancer. To develop our timeline, we convened a committee that included some of the world's leading cancer researchers and advocates. Our final selections are based on research, historical analysis, active discussion, and rigorous scientific review, and as we pointed out 10 years ago, this list is inherently incomplete.

The Landmark yet to be discovered may change a patient's life tomorrow. The scientific community is relentless in its quest to prevent and cure all cancers, and each Landmark is the culmination of years of hard work, often by teams of researchers, physician-scientists, policy makers, and advocates. Because of the complexities of attribution, we made the decision not to name the people behind these Landmarks, yet we owe them our gratitude.

Landmarks in Cancer Research is a living testament to those who strive to understand and eliminate the more than 200 diseases collectively known as cancer. The pioneering scientists who produced the first wave of discoveries in the early 1900s could not have imagined the breakthroughs of the past decade, but surely would be in awe of today's progress. Because of the stunning advances made over the last decade, we are filled with enormous hope for the lifesaving breakthroughs that will unfold in the near future. Our list offers a tribute to the past, and a challenge and inspiration for the future.

We look forward to the next chapter of leading discoveries, targeting cures, and saving lives.

1907 Sunlight exposure is linked to skin cancer.
The first epidemiologic study of sunlight and skin cancer was reported; earlier observations had linked chronic skin conditions common in sailors to exposure to the radiation effects of the sun. Later work in animal models confirmed that skin cancer could be induced by ultraviolet light and sunlight. (1)

1907 American Association for Cancer Research is founded by four surgeons, five pathologists, and two biochemists on May 7 in Washington, DC.

1907 Japanese cancer journal, *Gann: Japanese Journal of Cancer Research* (now titled *Cancer Science*), is first published.

1907 Nine research papers are presented at the first Annual Meeting of the AACR in New York City.

1908 Cell-free extracts transmit cancer from one animal to another.
Cell-free agents were shown to transmit leukosis, a form of leukemia and lymphoma, and sarcomas in chickens. This finding would later be verified as evidence for viral initiation of cancer. (2)

1908 Martha Tracy, from Women's Medical College in Philadelphia (later dean of that college), becomes the AACR's first woman member.

1909 AACR writes President William H. Taft advocating funding for cancer research.

1910 Procedures for in vitro tissue culture are developed.
The fundamental culture techniques, now ubiquitous in the laboratory, allowed researchers to study the evolution of tumor tissue under known conditions and to observe living cancer cells at every stage of growth. (3)

1911 French journal, *Bulletin de l'Association Française pour l'Étude du Cancer*, and the Italian journal, *Tumori*, are first published.

1913 AACR member Thomas S. Cullen, MD, presents "Education of the People as to What Can Be Done in Early Cases of Cancer" at the Annual Meeting. This appeal for public education led the *Ladies' Home Journal* to publish "What Can We Do About Cancer," the first consumer-oriented article about cancer.

1913 A group of volunteers—including AACR founding member and past president James Ewing—establishes the American Society for the Control of Cancer, precursor to the American Cancer Society.

1914 Alterations in chromosomes are postulated to cause tumor growth.
From earlier work on sea urchin eggs and association of inappropriate segregation of chromosomes and changes in cell growth characteristics came the hypothesis that cancer was caused by abnormal chromosomes. (4)

1915 The first experimental animal model of chemically induced cancer is developed.
Repeated tarring of rabbit skin caused tumors. The discovery added to early evidence for the theory of chemical carcinogenesis, building upon the observation in 1775 of scrotal cancer in chimney sweeps. Later work published in the AACR's *The Journal of Cancer Research* would isolate and identify the specific components of coal tar responsible. (5)

1916 AACR begins publishing *The Journal of Cancer Research*, the first English-language cancer journal.

1916 Oophorectomy decreases breast cancer in mice.
Removal of the ovaries from female mice of a strain with a high incidence of spontaneous breast cancer resulted in a decrease in tumors. Later work published in *The Journal of Cancer Research* involving transplantation of ovaries into male mice showed an induction of mammary tumors, supporting the suggestion that hormones from the ovary could promote breast tumors. (6)

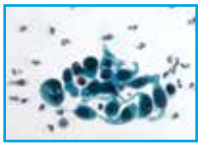
1921 American Society for the Control of Cancer creates the first National Cancer Week as an extensive public education campaign.

1922 U.S. Public Health Service opens Office of Cancer Investigations at Harvard Medical School.

1924 Metabolic studies show that tumors exhibit anaerobic respiration.
Whereas normal tissues use oxygen to break down nutrients for growth as their primary mode of respiration, it was observed that within tumors, cells respire anaerobically, fermenting sugars without oxygen. It will take several decades before hypoxia is revisited as a marker for tumors. (7)

1927 Cancer is named one of the top three causes of death in America by U.S. Census Bureau.

1928 Genetic mutation is proposed as the origin of cancer.



As an alternative to the infection theory of cancer, popular at the time because of the expansion of microbiology as a field of study, came the proposal that somatic mutation was the cause of cancer. As Mendel's works were rediscovered in 1928, the field of genetics grew. The term "somatic mutation" had been coined in 1916. (8)

1928 Cervical cancer cells are visible in smears of exfoliated vaginal cells.
Findings of cervical cancer cells in smears were met with skepticism, and it would take until the 1960s before the "Pap" smear would become widely accepted as an effective method of screening and cancer prevention. (9)

1928 X-rays are shown to be mutagenic.
X-rays were shown to be mutagenic in the common fruit fly. This discovery formed the basis for thinking about how carcinogens participate in tumorigenesis. (10)

1930 The first pure carcinogen, benzopyrene, is isolated from coal tar.
The known cancer-causing environmental substance, coal tar, was fractionated into components and assayed in mouse models to identify the individual chemicals responsible for carcinogenesis. (11)

1930 The Ransdell Act establishes the National Institute of Health.

1931 *The American Journal of Cancer* replaces *The Journal of Cancer Research* as the official AACR publication.

1932 Injected synthetic hormones induce breast cancer in mice.

Building on work on endogenous hormones, it was demonstrated that addition of synthetic exogenous hormones such as folliculin (and in 1952, diethylstilbestrol) can induce cancer. (12)

1932 Electron microscope is invented.

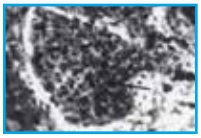
The electron microscope permitted the visualization of minute subcellular structures, allowing observation of detailed differences between malignant and normal tissues. (13)

1937 The National Cancer Institute Act establishes the National Cancer Institute (NCI) as an independent research institution.

1937 Transplantation of a single leukemic cell transmits leukemia in mice.
Studies published in AACR's *The American Journal of Cancer* showed that not all cancer cells behaved in an identical manner; some were uniquely capable of initiating and maintaining a tumor. This work laid the foundation for the later search for a cancer stem cell. (14)

1938 Telomeres are identified.
The ends of chromosomes were shown to be protected by a structure that prevented their fusion. Later, it was shown that telomeres are repeated simple sequence elements that are added by an enzyme, telomerase, which is not normally expressed in somatic cells. In each cell division, telomeres shorten. When they become sufficiently truncated they cause the cells to enter into senescence and die, limiting the number of divisions a cell can undergo and suppressing tumor development. (15)

1938 The discovery of antigens explains why tumors can be transplanted within inbred strains.
Previous work to transplant tumors had been successful in some instances but failed in others. The discovery of



major histocompatibility antigens later led to an immunologic explanation that applied to grafts of normal tissue as well as to malignant tissue. (16)

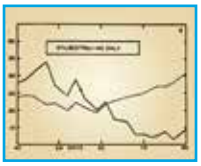
1938 Chemicals induce cancer in two distinct steps of initiation and promotion.
Tumorigenesis was identified as a multistage disease, and it was shown that chemicals induce cancer in two distinct steps of initiation and promotion. A nonspecific irritant (wounding) was shown to promote tumorigenesis after initiation with a suboptimal dose of carcinogen (tarring or application of Shope papillomavirus to rabbit ears). Further study of the significance of cocarcinogenic action was later published in *Cancer Research*. (17)

1939 Transplanted animal tumors are shown to grow blood vessels.
Tumors transplanted into the ears of rabbits elicited a vascular network. This was early evidence of the phenomenon of angiogenesis, or new blood vessel growth, which would later become a target for antiangiogenesis cancer therapies. (18)

1940 Caloric restriction reduces tumors in mice.
Studies published in *The American Journal of Cancer* and later in *Cancer Research* showed that caloric intake was proportional to the incidence of tumors of several kinds, including spontaneous mammary carcinomas and hepatomas in susceptible mouse strains and benzopyrene-induced skin tumors. Only recently, with the increasing prevalence of overweight and obesity in the global population, have the implications of the work been revisited. (19)

1941 *Cancer Research* replaces *The American Journal of Cancer* as AACR's official journal.

1941 Hormone dependence of prostate cancer is demonstrated.



In a study published in *Cancer Research*, the therapeutic use of physical castration or chemical castration by treatment with estrogens was shown to decrease disease burden in metastatic prostate cancer whereas injection of androgens increased metastases. (20)

1944 DNA is identified as the active material in the genes of bacteria.
It was not known whether the protein or DNA components of the chromosomes contained the information necessary for inheritance. This work showed that DNA contained the heritable information and set the stage for many important works and techniques. (21)

1944 The American Society for the Control of Cancer becomes the American Cancer Society.

1944 The Public Health Services Act designates NCI as a division of the National Institutes of Health.

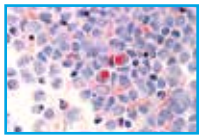
1945 The Atomic Bomb Casualty Commission is established to monitor the effects of radiation exposure.

1946 Nitrogen mustard is established as the first chemotherapeutic agent.
Observational reports that soldiers exposed to nitrogen mustard during wartime had low white blood cell counts led to testing of nitrogen mustard as chemotherapy for cancer. Intravenous nitrogen mustard was shown to slow the growth of lymphomas and leukemias in patients refractory to radiation therapy, and it achieved remissions of a few months. Nitrogen mustard was approved for cancer treatment in 1949. (22)

1947 The Nuremberg Code establishes the legal principle of voluntary consent for human subjects of research.

1947 At the 38th AACR Annual Meeting, May 16-17, a policy presentation titled, "On the Organization and Support of Cancer Research," concludes that the AACR should advocate for increased funding for cancer research.

1948 First successful chemotherapy for childhood leukemia is reported.

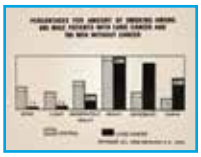


A synthetic folate antagonist achieved a 3-month remission in 10 of 16 children with leukemia. Although not successful by today's standards, this was an important result that would lead to further work on antimetabolites and the first generation of effective chemotherapeutic agents. (23)

1948 The United Nations establishes the World Health Organization.

1950 First rationally conceived nucleotide analog chemotherapeutic agents are developed.
Drug design had been primarily by trial and error. The design of molecules similar to the bases of DNA, but sufficiently different to prevent replication, proved an effective drug targeting approach that led to several chemotherapeutic drugs for cancer such as 6-mercaptopurine and 5-fluorouracil, which are still in use today. (24)

1950 Epidemiologic work links tobacco smoking to lung cancer.



A retrospective analysis of the smoking habits of patients with lung cancer showed an association with tobacco. This was followed by a prospective study of male doctors that showed a clear relationship between smoking and lung cancer deaths. Tobacco exposure is now a known risk factor for many cancer types, accounting for an estimated 30% of all cancer mortality. (25)

1951 Leukemia in mice is shown to be transmissible by a virus.
Leukemia had been considered an inherited disease before it was shown that it could be transmitted from one mouse strain to another by a virus and then passed from one generation to another via vertical transmission. These findings laid the groundwork for later research on other mouse tumor viruses and those in other species. (26)

1951 Cobalt-60 irradiator is developed.
Radiotherapy previously had been carried out using radium, which was in limited supply and needed to be used in close proximity to the tumor. Radioactive cobalt provided a continuous source with greater ability to treat internal tumors, with less damage to the intervening tissue. Clinical cobalt-60 is still used in much of the developing world. (27)

1951 Ultrasound imaging is developed for detecting tumors.
Although earlier studies had used ultrasound as a therapy and had examined its use as an imaging tool, research showed that ultrasound could detect differences in density between malignant and normal tissues. (28)

1953 AACR Annual Meeting abstracts are published for the first time as *Proceedings of the American Association for Cancer Research* (154 abstracts).

1953 Structure of DNA is described.

Not only was the global structure of DNA identified, but how the bases pair and possible implications for methods of replication were also elucidated. (29)

1953 Human carcinoma cell line, HeLa, is established.
The HeLa epithelial cell line is readily grown in laboratories worldwide and has become a fundamental tool for studying many aspects of molecular biology. Stable cell lines such as HeLa allow researchers to use genetically identical cells for experiments over long-term courses of repeated culturing in a manner not possible with primary cells. (30)

1953 Medical linear accelerator is developed for radiotherapy.
Unlike early radiotherapy machines that used a

radioactive source to generate X-rays, the linear accelerator produces a beam of electrons. This eliminated the need to replace the radioactive source and is limited in power by the length of the accelerator tube. (31)

1955 Tumor clonogenic assay is developed.
Although human cells had been cultured before, these new methods allowed cultures to be propagated from single human cells, enabling the kind of detailed genetic studies previously only possible for bacterial cells. (32)

1955 U.S. Congress funds National Chemotherapy Program to test compounds that might be effective against cancer.

1956 First successful chemotherapy for solid tumors is reported.
Building on earlier work on folate and aminopterin, another antifolate, methotrexate, was developed. The drug was shown to be effective in a small group of three patients with metastatic choriocarcinoma and chorioadenoma. (33)

1957 Elizabeth C. Miller is the first woman elected to the AACR Board of Directors.

1958 The Association of American Cancer Institutes (AACI) is founded. Its mission is to reduce the burden of cancer by enhancing the impact of North America's leading academic cancer centers.

1958 Food Additives Amendment prohibits food additives shown to induce cancer in humans or animals.

1959 AACR membership passes 1,000.

1959 In vitro viral carcinogenesis is demonstrated.
Earlier work had shown that viruses could be used to transmit cancer from one organism to another. New studies showed that chick embryo cells infected with Rous sarcoma virus continued to grow in culture and produce more virus. The infected cells had changes in morphology and rapid, disordered growth characteristic of cancer cells. (34)

1959 DNA repair after radiation is demonstrated.
Chinese hamster ovary cells subjected to X-irradiation and surviving did not display heritable damage but repaired the damage prior to cell division. This finding confirmed the presence of DNA repair mechanisms, later shown to be defective in some cancers. (35)

1959 Dose-response relationship is shown in radiation-induced leukemia.
Radiation carcinogenesis was unequivocally established in human populations, and the nature of the dose-response relationship was described. (36)

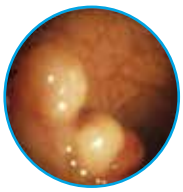
1959 Radioimmunoassay is developed.
The radioimmunoassay uses antibodies to detect the amounts of specific proteins in a solution. Originally developed to measure insulin levels in the blood of diabetics, this technique is now the basis for diagnostic tests to measure serum proteins and biomarkers, such as prostate-specific antigen, although now the detection mechanism often uses fluorescent rather than radioactive labeling. (37)

1960 American Cancer Society urges widespread use of Pap smear to detect cervical and uterine cancers.

1960 The Philadelphia chromosome is discovered.
An abnormally small chromosome was identified in the neoplastic cells of patients with chronic myelogenous leukemia. This small chromosome, later named the Philadelphia chromosome after the city in which it was discovered, was the first chromosomal abnormality found to be consistently associated with a specific human cancer. (38)

1960 Growth factors are purified and identified.
The fact that growth factors were necessary for cells to survive and replicate had long been known, but the individual components of serum responsible had not been identified. The purification of nerve-growth factor (NGF) led to the identification of other growth factors, their cognate receptors, and their complex signaling pathways. These pathways have emerged as novel targets for therapies such as those targeting the epidermal growth factor receptor. (39)

1960 Screening techniques for prevention of colon cancer are adopted.



The sigmoidoscope permitted early identification of colorectal cancer as well as precancerous polyps, leading to increased survival rates. Today, it is estimated that screening by sigmoidoscopy, colonoscopy, barium enema, or fecal occult blood testing may result in a 20% decrease in colorectal cancer mortality. (40)

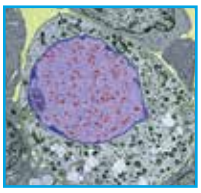
1961 The first AACR award, the G. H. A. Clowes Memorial Award, is presented to Renato Dulbecco for meritorious cancer research.

1961 Triplet code for amino acid translation is deciphered.
A synthetic RNA molecule consisting entirely of uracil was shown to produce a polypeptide of repeating phenylalanine amino acids. Researchers went on to show how triplets of DNA bases transcribed to RNA are then translated into the individual amino acids of peptides, with different triplets representing the different amino acids, providing the mechanism by which DNA encodes proteins. (41)

1961 Thelma B. Dunn is the first woman elected as president of the AACR.

1962 Epithelial growth factor discovered.
A heat-stable, antigenic factor responsible for the accelerated development of the incisors and eyelids was identified (which was later called the epithelial growth factor). (42)

1963 Chemotherapy cures Burkitt lymphoma.
The geographical distribution of Burkitt lymphoma in parts of sub-Saharan Africa, described in the early 1960s, suggested that it was caused by a vector-transmitted virus. The first successful treatment of a human cancer thought to be caused by a virus, later shown to be Epstein Barr virus, was reported. (43)



1964 RAS is identified.
Research on RAS began with the first observation that a preparation of a murine leukemia virus isolated from a leukemic rat induced sarcomas in newborn rodents. (44)

1964 The World Medical Association adopts the Declaration of Helsinki for governing research on human subjects.

1964 Seven physician members of the AACR found the American Society of Clinical Oncology (ASCO).

1964 U.S. Surgeon General Luther L. Terry publicly affirms that smoking leads to lung cancer.

1965 Chemoprophylaxis is demonstrated in animal models of chemical carcinogenesis.
A variety of chemicals were shown to prevent cancer induced by chemicals by activating the detoxification system, competitively inhibiting the carcinogen, preventing initiation of carcinogenesis and other unknown mechanisms. The term chemoprevention was later coined as a new area of focus in cancer research. (45)

1965 Federal Cigarette Labeling and Advertising Act requires printing of warnings on cigarette packs.

1966 Combination chemotherapy and maintenance treatment prolong remission.
Preliminary studies of pediatric leukemia had shown synergistic effects of dual-drug treatments. By selecting agents with different side effects, it was proposed that it might be possible to combine several chemotherapy drugs to give greater efficacy without prohibitive toxicity. One of the first of these was MOPP (nitrogen mustard, vincristine, prednisone, and procarbazine), a successful treatment for Hodgkin disease that was described in a study published in *Cancer Research*. Other combination chemotherapies followed. (46)

1966 The first dedicated mammography machine is developed.
For several decades prior to the invention of this machine, breast images had been obtained using standard X-ray technology. Subsequent developments allowed for reduced exposure and, eventually, digital mammograms.

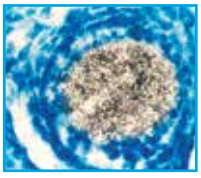
1966 U.S. Surgeon General requires institutional review of clinical research, leading to the establishment of institutional review boards.

1967 Estrogen receptor is identified.
Targets in uterine tissue were identified that interact specifically with estrogen. This finding was the first step that led to the detection of estrogen receptors in breast cancers and the design of specific and effective therapies for hormone-dependent breast cancer. (47)

1969 Rhabdomyosarcoma is an inherited familial cancer syndrome.
A study of children with rhabdomyosarcoma who had relatives who developed other organ-site cancers at an early age led to the identification of a familial cancer syndrome, later shown to be primarily influenced by inherited mutations in p53. (48)

1969 Tumors are successfully heterotransplanted into athymic "nude" mice.
Heterotransplantation had only been possible in certain immune-privileged sites in the mouse, such as the eye chamber, and eventually those grafts were rejected. The removal of the thymus, and thus the T-cell immune response, from young mice permitted transplantation of human tumors into mice for their characterization in a whole organism. (49)

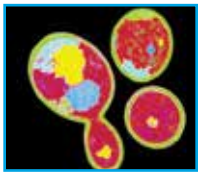
1969 In situ hybridization is introduced.
This method enabled detection of the location of specific genes within chromosomes. Today, a wide variety of probes ranging from whole chromosome fluorescent paints to probes for individual genes and gene segments can be used to detect changes in genome copy number, structure, or nuclear location. Combining these with image analysis techniques and multiplex labeling strategies enables today's multicolor cytogenetics assays termed SKY or M-FISH in which all human chromosomes can be separately visualized. (50)



1970 Multidrug resistant (MDR) cell lines are described.
Resistance to multiple cytotoxic agents is one of the major causes of chemotherapy failure. Research published in *Cancer Research* would lead to the identification of drug transporters present in the cell membranes that control entry of drugs in and out of the cell and are important for the pharmacokinetics of drug action. (51)

1970 Reverse transcriptase is identified.
The discovery of reverse transcriptase had implications for how viruses caused cancer and also challenged the "central dogma" that the transfer of cellular information passed from DNA to RNA to protein, and not in reverse. (52)

1970 Cell cycle is an ordered process.
By fusing mammalian tissue culture cells at different stages of the cell division cycle and by observing the division of mutant yeast cells under the microscope, it was determined that the order of the cell division cycle is regulated and genes involved in cell cycle regulation were identified and ordered. This work laid the groundwork for the discovery of checkpoint proteins and how cancer cells derail checkpoints. (53)



1970 Chromosome banding technique is developed.
Q-banding using alkylating fluorochromes allowed individual chromosomes and aberrations therein to be identified with high accuracy. This technique was followed by a large number of different banding chemistries. (54)

1970 DNA restriction enzymes are discovered.
Restriction enzymes cut DNA at specific and reproducible locations.They would become an important tool in molecular biology, enabling basic characterization of genomes through early mapping techniques prior to sequencing. Once it was determined that they recognized specific sequence motifs surrounding cleavage sites, they would be used for many functions including cloning, transfer, and testing of genes and genotyping. (55)

1970 The U.S. Environmental Protection Agency forms and provides regulatory enforcement against environmental carcinogens, such as asbestos.

1970 The U.S. Public Health Cigarette Smoking Act bans advertisements for cigarettes.

1971 Two-hit hypothesis is proposed.
Using retinoblastoma as a model and observing patients with one or both eyes affected and those with and without a family history of disease, it was shown how cancer can be caused by two mutational events. In the inherited form of the disease, the first mutation or "hit" occurs in the germline cells and the second in the somatic cells. In the nonhereditary form of the cancer, both "hits"occur in somatic cells over time. (56)

1971 Daughters of mothers who used diethylstilbestrol during pregnancy can develop vaginal cancer.
Vaginal cancer is rare, particularly in young women. A small group of women aged 14-25 with vaginal cancer showed a highly significant association with treatment of their mothers during the first trimester of pregnancy with diethylstilbestrol (DES). In 1971, the FDA issued a warning against prescribing DES for pregnant women. Between the time that DES was first manufactured in 1938 and the discovery of health problems in 1971, an estimated 5-10 million pregnant women and their children were exposed to the drug. (57)

1971 National Cancer Act of 1971 enables the NCI Director to expand and designate Cancer Centers and Comprehensive Cancer Centers. AACR leaders advocated for the passing of the Act and attend the signing at the White House.

1971 President Richard Nixon declares "War on Cancer" in State of the Union Address.

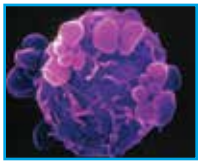
1971 Tumor growth is dependent on angiogenesis.
Starting from the observation that transplanted tumors that did not grow blood vessels were unable to increase in size, serial experiments demonstrated that tumors secrete factors that encourage new blood vessels to grow into and feed the tumor. Eventually, the genes for these factors would be identified and would become a target for molecular therapies. (58)

1971 Taxol, a natural plant product, is developed for chemotherapy.
A component of the Pacific yew tree, taxol was shown to actively inhibit leukemia cell lines in vitro. The isolated molecule was later produced by chemical synthesis, allowing the increased production necessary for it to be used as a drug treatment. Taxol was approved by the FDA in 1992 for treating ovarian cancer and subsequently for breast cancer. (59)

1971 Cells within a tumor can be differentiated into benign cells.
Shown previously with teratomas (tumors that contain differentiated tissues), it was also demonstrated with squamous cell carcinomas that some cells within a tumor are capable of differentiating into benign cells incapable of forming a tumor when transplanted. This finding, which was published in *Cancer Research*, supported the idea of a cancer stem cell. (60)

1972 Bone marrow transplantation is established as a cancer treatment.
Bone marrow transplants were used to replace blood cell-generating hematopoietic cells in patients with leukemia who had radiation therapy. Initially, transplants were from twin donors and later from donors matched by cell surface antigens. More recently, culturing stem cells extracted from the patient's blood before treatment has been the method. (61)

1972 Apoptosis, programmed cell death, is triggered by cancer therapies.
Apoptosis is the process of controlled destruction of unwanted cells, the opposite of cell replication. Cells exhibit characteristic stages of DNA and cytoplasmic condensation, followed by the breaking of the cell into apoptotic bodies and their degradation. Apoptosis can also be triggered by cytotoxic drugs. It would later be shown that tumors can arise from mutations in the apoptosis machinery, making cells resistant to death signals. (62)



1972 Computerized axial tomography (CAT) scanner is invented.
Previous imaging techniques had been unable to distinguish between tissues of similar density. The development of the CAT system, which uses a series of sectional X-rays, allowed a greater sensitivity of imaging, particularly for detecting abnormalities in soft tissue. (63)

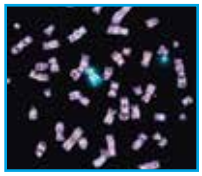
1972 Regression models and life tables are applied.
The Cox regression model and its generalizations represented an important biostatistical advance with application to cancer research as well as many other areas. It affected the conceptualization of follow-up studies in a manner that led to nested case-control and case-cohort sampling methods and other applications relevant to clinical trial design. (64)

1973 NCI begins the Surveillance, Epidemiology and End Results (SEER) Program, a model for large-scale cancer registries worldwide.

1974 Errors in DNA replication are responsible for tumor oncogenesis.
In a study published in *Cancer Research*, it was proposed that as DNA was synthesized the polymerase might make errors in which bases were incorporated either during replication or repair. These mutations might be the consequence of an error-prone polymerase or the presence of carcinogens. (65)

1974 First Lady Betty Ford undergoes a mastectomy and speaks publicly about breast cancer.

1974 Specific chromosome rearrangements are characteristic of types of leukemia.
Cytogenetics and the evolution of molecular diagnostics for leukemia and lymphoma laid the groundwork for future targeted therapies. The Philadelphia chromosome of chronic myelogenous leukemia, with its characteristic translocation from chromosome 22 to 9, will later be shown to generate the fusion protein Bcr-Abl, against which the molecular treatment imatinib (Gleevec) acts. (66)



1974 DNA cloning methods are developed.
A method for isolating DNA fragments and introducing them into autonomously replicating bacterial plasmids provided the ability to isolate, identify, and amplify DNA fragments from any organism. The availability of pure and abundant sources of specific DNA fragments enabled the determination of the sequence of bases they contain, and the detection of mutations that cause cancer and heritable diseases. Ultimately, the ability to clone DNA was the basis for determining the sequence of the human and other genomes. (67)

1975 Method is developed to detect specific DNA fragments in mammalian genomes (Southern blotting).
A method to detect unique sequence genes in complex genomes enabled more precise study of the genetic basis of inherited diseases and cancer. Modifications to the original technique made in 1979 substantially shortened the time needed to do the nucleic acid hybridization and increased the sensitivity to the point that single-copy genes in the human genome could be detected within a few days. (68)

1975 BrdUrd labeling techniques are introduced.
Immunochemical techniques were developed to detect incorporation of BrdUrd labeled nucleotides. This was enabled by development of an antibody against BrdUrd labeled DNA, and later by development of a flow cytometric technique that simultaneously measured DNA content and incorporated BrdUrd. (69)

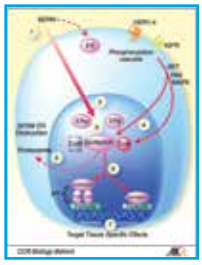
1975 Monoclonal antibodies are produced.
By fusing an antibody-deficient myeloma cell with a B-cell it was possible to create a line of cells or hybridoma that would produce large quantities of identical or monoclonal antibodies that all recognize the same part of a molecule. Monoclonal antibodies are used in a wide range of applications, diagnostics as well as drug therapies such as trastuzumab (Herceptin). (70)

1976 Viral oncogenes exist in a related proto-oncogene form in normal cells.
By using hybridization techniques (because this work occurred before the advent of DNA sequencing), researchers showed that there were forms of cancer-causing viral oncogenes in chicken cells. These were later shown in other species, including mice and humans. (71)

1976 Combination chemotherapy regimen cures pediatric leukemia.
By applying the previously proved theory of combining chemotherapies in different phases and based on different toxicities, and including radiotherapy, a regimen was developed that prolonged remission in 80% of patients with acute lymphocytic leukemia. (72)

1977 American Cancer Society sponsors first "Great American Smokeout" to curb tobacco use.

1977 Tamoxifen is approved for treatment of breast cancer.



This was the first "antihormone" therapeutic approved by the FDA. Building on earlier work on oophorectomy and estrogen removal as a treatment for breast cancer, tamoxifen was shown to inhibit growth of mammary tumors in mice, leading to its approval for treatment of breast cancer. It was also shown that tamoxifen was a selective estrogen receptor modulator (SERM), acting in opposition to estrogen in some tissues but acting like estrogen in others. (73)

1977 Individual cells within a tumor have different potential for metastasis.
Taking individual cells from a tumor and transplanting them into mice showed that not all cells are capable of forming new tumors and only some cells within a tumor may be capable of metastasis. (74)

1977 RNA splicing is demonstrated.
That the linear sequence of bases in mRNA results from transcription of a corresponding sequence of DNA had been accepted. New work, first done in viruses and later extended to the cellular genome, showed that mRNA is made from much larger precursors, from which segments are removed by a process called RNA splicing. Alternative splicing patterns are found in many genes to produce different protein products, such as in the p16-ARF locus, which encodes two important tumor suppressors. (75)

1977 Medical magnetic resonance imager (MRI) scanner is developed.
The medical MRI allowed sensitive visualization of internal structures without the use of X-rays. MRI provides clearer and more detailed images of the soft tissue structure than other imaging methods, making it an invaluable tool in early diagnosis and evaluation of tumors. (76)

1977 The inaugural AACR-Richard and Hinda Rosenthal Memorial Award, which recognizes research that has made, or promises to soon make, a notable contribution to improved clinical care in the field of cancer, is presented to Paul P. Carbone.

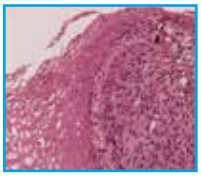
1977 The first AACR science policy committee, the Public Issues Committee, is formed.

1977 DNA sequencing is developed.
The introduction of DNA sequencing led to many advances. Over time, sequencing techniques have been refined and improved to use fluorescent dyes rather than radiolabeling, reduce sample volumes, increase the lengths of sequence read, and use automated robotic systems. (77)

1978 Tobacco-specific nitrosamines are identified as carcinogenic components of cigarette smoke.
Nitrosamines derived from nicotine were shown to cause cancer in animal models. These substances will later be shown to contribute to human lung and oral cancers. (78)

1979 The human homolog of v-gag–myc is discovered.
Using hybridization studies, the transforming sequence of the avian tumor virus MC29 was identified. This sequence was later named myc, for myelocytomatosis, a virus-induced disease. (79)

1979 p53 is discovered.
Discovered as a cellular protein bound by the monkey oncogenic virus SV40, or as a transformation-associated protein in chemically induced tumors, p53 was originally thought to be an oncogene. Later studies showed that it is a tumor suppressor gene that is mutated in the germline of individuals with the Li-Fraumeni cancer predisposition syndrome and in 50% of diverse human tumors. (80)



1979 DNA damage products are detected in human DNA.
As described in a study published in *Cancer Research*, DNA adducts were detected in cells incubated with the carcinogen benzo(a)pyrene. The adducts were more common in cells from older persons. The detection of DNA damage products would be useful for identification of carcinogens and in epidemiologic studies. (81)

1979 Tyrosine phosphorylation and protein tyrosine kinases are discovered.
The discovery of a new type of protein kinase that phosphorylates tyrosine residues in proteins, associated with the polyomavirus middle T antigen transforming protein and the Rous sarcoma virus v-Src oncoprotein, led to the conclusion that dysregulated tyrosine phosphorylation by an activated tyrosine kinase can cause malignant transformation. In subsequent years, inhibitors that target disease-causing tyrosine kinases would be approved for treatment. (82)

1979 Method is developed to detect gene transcripts (Northern blotting).
Identification of the RNA products of transcription is essential for addressing many biologic problems. The ability to separate RNA by size on gels, transfer it to a solid support, and then detect specific molecules by nucleic acid hybridization provided a critical technical link to enable detection of the transcripts produced by any gene. (83)

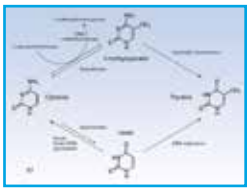
1979 Method is developed to detect specific proteins (Western blotting).
Establishing how particular genes elicit specific phenotypes requires detection of the protein products encoded by their transcripts. A rapid and sensitive method combining gel electrophoresis for fractionation, and electrophoretic transfer to a solid support for subsequent detection by specific antibodies, enabled this detection. Now proteins can also be detected using mass spectrometry. (84)

1979 U.S. Department of Health, Education and Welfare creates The Belmont Report, ethical guidelines for research on humans.

1980 Degradation of collagen in tumor environment promotes metastasis.
For tumors to metastasize they must pass through the epithelial and endothelial basement membranes and gain access to the bloodstream. Studies showed that tumors secrete proteases that degrade collagen and that cell lines with the highest levels of collagenase had the highest potential for metastasis. (85)

1980 Prostate specific antigen is a marker for prostate cancer.
The association of levels of prostate specific antigen (PSA) with risk for prostate cancer—in a study published in *Cancer Research*—led to the first routine protein biomarker test used in cancer screening and prevention. (86)

1980 DNA methylation is shown to be important in cancer.



Methylation of DNA can prevent a gene from being switched on. Chemotherapy drugs were shown to affect methylation and activate genes, suggesting that targeting methylation of specific genes may provide a way of controlling gene expression and lead to future therapies. It was later demonstrated that the methylation patterns of some genes were different in tumors compared with cells in the same tissue that were not part of the tumor. (87)

1980 The inaugural Award for Outstanding Achievement in Cancer Research, which recognizes a young investigator (not more than 40 years of age) on the basis of meritorious achievement in cancer research, is presented to Malcolm A. S. Moore.

1980 NCI commissions National Research Council to review data linking diet and cancer.

1981 Cell surface antigens of lymphocyte subtypes aid further classification of leukemias and lymphomas.
A study published in *Cancer Research* described the development of monoclonal antibodies that recognized specific cell surface receptors characteristic of stages of lymphocyte differentiation. This allowed subclassification of different diseases and more accurate prognosis. (88)

1981 Ubiquitin system for protein degradation is identified.
How ubiquitin acts as a tagging system to mark proteins that need to be destroyed by the proteosome was demonstrated. Ubiquitination controls proteins involved in many fundamental cell processes important for cancer such as cell cycle, DNA repair, and apoptosis. Later work involved targeting drugs to this pathway as a mechanism to promote apoptosis. (89)

1981 First mouse ES cell line is established.
This technology allows the generation of mouse embryos with directed mutations such as transgenics or knockouts. (90)

1982 The Susan G. Komen Breast Cancer Foundation is founded.

1982 Proto-oncogenes are involved in cancer.
Building on earlier work, research showed that the endogenous proto-oncogenes of normal cells could become mutated, becoming oncogenes and causing cancer. (91)

1982 The inaugural Bruce F. Cain Memorial Award, for outstanding preclinical research that has implications for the improved care of cancer patients, is presented to John A. Montgomery.

1982 *Helicobacter pylori* is isolated from human stomach ulcers.

Many decades previously, work had shown viruses involved in causing cancer, but it took years for it to be widely accepted that infection with *H. pylori* could cause stomach ulcers and that continuous infection and inflammation could result in cancer. (92)

1983 Human papillomavirus is identified as the causative agent of cervical cancer.
Early epidemiologic work documenting the low incidence of cervical cancer in nuns suggested that the disease might be caused by an infectious agent transmissible by sexual contact. The isolation of human papillomavirus (HPV) DNA from biopsy samples identified the HPV 16 and 18 strains as highly associated with cervical cancer. This work would lead to the development of vaccines to prevent cervical cancer. (93)

1983 National Academy of Sciences issues report, "Diet, Nutrition and Cancer," leading NCI to introduce dietary guidelines to reduce cancer.

1983 Oncogene cooperation for malignant transformation is demonstrated.
The observations that normal cells required multiple genetic events to become oncogenically transformed provided a model for the molecular basis for the multistep nature of cancer. (94)

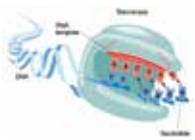
1983 Polymerase chain reaction is developed.
The polymerase chain reaction (PCR) uses a heat-stable DNA polymerase from thermophilic bacteria, allowing replication of multiple copies of a DNA sequence in vitro. This technique permitted an explosion of new methods for cloning, sequencing, and diagnostics and is used in virtually every genetics and molecular biology laboratory. (95)

1984 Electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) techniques are invented.
These techniques, used in mass spectrometry, allow the analysis of biomolecules such as DNA, proteins, peptides, polymers, dendrimers, and sugars, which were too fragile to be analyzed by more conventional ionization methods. Much of our understanding about biomolecules is dependent on mass spectrometry. (96)

1984 Bcl-2 links apoptosis and cancer.
Links between Bcl-2 and apoptosis provided the first evidence of a role for programmed cell death in cancer development. (97)

1985 Health Research Extension Act expands the NCI mission to include research on the continuing care of patients and their families.

1985 Lumpectomy is a viable alternative to mastectomy.
Clinical studies showed that lumpectomy plus radiation therapy resulted in improved survival compared with radical mastectomy for women with early-stage breast cancer. (98)

1986 Telomerase is discovered.

The mechanism of replication at the ends of chromosomes, or telomeres, had been unclear. The discovery of an enzyme capable of synthesizing telomeric DNA onto chromosome ends, thus replenishing them as cells divided, had implications for aging and cancer. (99)

1986 The National Coalition for Cancer Survivorship (NCCS) is founded.

1986 Retinoblastoma gene, RB, is identified.
The retinoblastoma gene, RB, was identified in children with hereditary retinoblastoma and shown to be a tumor suppressor gene. (100)

1987 Her-2/neu receptor is overexpressed in some breast cancers.
The growth factor receptor gene Her-2/neu was shown to be amplified in approximately 15% of stage I breast cancers.The degree of amplification is associated with decreased survival. This biomarker would later become the target of the highly successful molecular therapy, trastuzumab (Herceptin), improving survival in Her-2/neu-positive patients. (101)

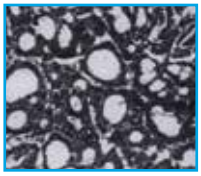
1987 Technique is developed to use homologous recombination in mouse ES cells to create genetically engineered mouse strains.
Technology to generate mice lacking specific genes, or containing specific mutations, has provided insights into the function of genes involved in development that underlies many inherited diseases and contributes to cancer. Generation of strains with mutations found in human cancers enables modeling of the initiation and progression of cancers in mice that resemble their human counterparts. Such models should prove useful for testing of biologically targeted therapies. (102)

1988 AACR hosts its first Special Conference, "Gene Regulation and Cancer" (Chair: Phillip A. Sharp). This in-depth exchange of the latest developments in an emerging area sets the tone for future AACR Special Conferences on focused topics, an ongoing series that contributes in a major way to advances in the field.

1988 AACR launches Women in Cancer Research (WICR), a membership group within the AACR committed to recognizing women's scientific achievements and fostering their career development and advancement in cancer research.
The WICR Council acts as an advisory body to the AACR leadership on issues of concern to women investigators and is also responsible for organizing the activities of WICR through its committees.

1988 Associate Membership, a new category of AACR membership for early-career scientists, is established.
The Associate Member Council develops programs that address the needs of early-career scientists and acts as an advisory body to the AACR leadership on issues of concern to the next generation of cancer researchers.

1988 Tumor suppressor genes are mutated in cancer and are the targets of tumor viruses.
Mutations in tumor suppressor genes have been shown to be responsible for several familial cancers such as retinoblastoma (Rb) and Li- Fraumeni syndrome (p53);



these genes are also spontaneously mutated in many types of noninherited cancer. They are also the targets of viral oncogenes such as the E1A proteins of adenovirus and E7 of human papillomavirus, which bind and inactivate Rb. (103)

1989 Original innovation behind the engineering of chimeric antigen receptors on T cells is reported.
In an effort to direct T cells, researchers generated a chimeric T cell receptor, composed of the TCR constant domain and an antibody's variable domains, to activate the T cell when it recognizes antigen specific to the antibody. The T cell does not need to be educated by MHC-peptide pairs, and is specifically activated by the antigen it is engineered for. This will give researchers the tools to create chimeric antigen receptors that can combat specific cancer cells expressing common antigens in the near future. (104)

1990 Americans with Disabilities Act protects cancer survivors against discrimination in the workplace.

1990 AACR adds a second journal to its publishing program, *Cell Growth & Differentiation* (succeeded in 2002 by *Molecular Cancer Research*).

1990 Specific molecular alterations are correlated with stages of cancer progression.
Expanding on the two-hit hypothesis of carcinogenesis in colorectal tumors, researchers showed that a number of events occurred, including activation of oncogenes and inactivation of tumor suppressor genes, totaling mutations in at least four to five genes, which influenced progression from a benign polyp to a large metastatic malignant tumor. (105)

1990 BRCA1 mutations are associated with breast cancer.
The identification of gene variants associated with a family history of breast cancer allowed screening of high-risk women and the choice for those with known increased risk to take preventive measures such as tamoxifen therapy or mastectomy. (106)

1990 Breast and Cervical Cancer Mortality Prevention Act provides grants to improve programs for breast and cervical cancer prevention.

1990 NIH and the U.S. Department of Energy formally begin the Human Genome Project.

1990 San Luis Obispo, California, becomes the first city in the world to ban smoking in all public buildings.

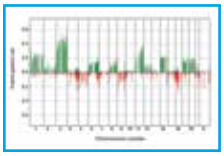
1991 AACR publishes the first issue of the journal, *Cancer Epidemiology, Biomarkers & Prevention*.

1991 Fifteen U.S. departments and agencies join to create the Federal Policy for the Protection of Human Subjects, informally known as the "Common Rule."

1991 Specific mutation in p53 in liver cancer is associated with exposure to the environmental carcinogen aflatoxin.
Mutations in codon 249 of p53 in hepatocellular carcinoma, a cancer endemic to locations in southern Africa and Asia, were shown to be associated with aflatoxin exposure. (107)

1992 American Cancer Society recommends widespread use of prostate-specific antigen test for prostate cancer.

1992 Comparative genomic hybridization is developed.
A new technique allowed changes in genome copy number to be mapped onto normal representations of the human genome. Initial mapping representations were



metaphase chromosomes, but these have now been supplanted by a wide range of microarray technologies, including some that allow allele-specific analysis. (108)

1992 The inaugural AACR-American Cancer Society Award for Research Excellence in Cancer Epidemiology and Prevention is presented to Pelayo Correa.

1992 The first AACR Workshop, "Molecular Biology in Clinical Oncology," is held in Aspen, Colorado.

1992 Mammography Quality Standards Act regulates mammography screening facilities, providers, and equipment.

1992 The U.S. Department of Defense is mandated to fund the Breast Cancer Research Program.

1992 The first Joint Meeting of the Japanese Cancer Association and AACR is held.

1993 The Prostate Cancer Foundation (PCF) is founded.

1993 The inaugural AACR-Gertrude B. Elion Cancer Research Award is presented to Benjamin G. Neel. The award is intended to encourage and support tenure-eligible junior faculty by providing a one-year grant for expenses related to a research project.

1994 AACR membership passes 10,000.

1994 Carcinomas originate from normal stem cells that become cancer stem cells.
Investigations showed that a determined stem cell required for normal tissue renewal is the most likely cell of origin of carcinomas. (109)

1995 AACR publishes the first issue of the journal, *Clinical Cancer Research*.

1995 Microarray technology is developed for molecular profiling.
A chip that can assay the expression of thousands of genes from one sample rapidly expands the generation of data on molecular targets and diagnostics and drives the need for computational analysis methods. This hardware and software can be applied to gene expression, measuring genetic variation at SNPs and gene copy number and examining alternative splicing to measure biomarkers for individual cancers, which ultimately can lead to personalized therapies. (110)

1995 SAGE (Serial Analysis of Gene Expression) technology is described as another method to analyze gene expression profiles.
SAGE was described in the same year as microarray technology and provides another method for gene-expression analysis. Short nucleotide sequence tags (~9-14 bps) are designed to a unique portion of a transcript and are sufficient to identify this transcript with specificity from the sample mRNA pool. Sequence tags are linked together (concatemers), cloned, and sequenced. The number of times a particular tag is observed quantifies the expression level of that transcript in the original mRNA sample. For example, conducting SAGE on mRNA derived from tumor and normal adjacent tissue can evaluate differential gene expression, if any, in the transcript the sequence tags are designed to identify. (111)

1995 Computer-guided technology improves delivery of radiation therapy.
Computerized systems improve the accuracy of radiation therapy with better focusing on the tumor, reducing damage to surrounding healthy tissue. (112)

1996 AACR in partnership with ASCO launches "Methods in Clinical Cancer Research: A Workshop," held in Park City, Utah.

1996 The inaugural AACR-Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research is presented to Samuel A. Wells, Jr.

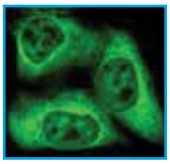
1996 The inaugural AACR-DeWitt S. Goodman Memorial Lecture is delivered by David J. Mangelsdorf. The lectureship is awarded for significant contributions to the field of nutrition and cancer and cancer prevention.

1997 AACR holds its first Special Conference on "DNA Methylation, Imprinting, and the Epigenetics of Cancer" (Cochairs: Stephen B. Baylin, Timothy H. Bestor, and Peter A. Jones).

1997 Rituximab (Rituxan) approved by the FDA for the treatment of B-cell non-Hodgkin lymphoma resistant to other treatments.
Rituximab was the first monoclonal antibody FDA approved for the treatment of cancer. Rituximab, in combination with CHOP chemotherapy (RCHOP), is now standard of care in the treatment of diffuse large B-cell lymphoma and many other B-cell lymphomas.

1998 Use of a monoclonal antibody (trastuzumab, Herceptin) significantly improves survival in advanced Her-2/neu breast cancer.
Patients with Her-2/neu-positive metastatic breast cancer who were treated with chemotherapy plus trastuzumab (Herceptin) lived longer and their tumors showed a greater decrease in size compared with those in patients who received chemotherapy alone. (113)

1998 Selective estrogen receptor modulators prevent breast cancer in high-risk women.
A study showed reduction of breast cancer incidence by 44% in women at high risk for developing breast cancer who were treated with selective estrogen receptor modulators. This led to FDA approval of tamoxifen for prevention of breast cancer in women at high risk of developing the disease. (114)

1998 PTEN is a lipid phosphatase.

This observation focused attention on the PI3K pathway in cancer development, which is currently an important area of drug development. (115)

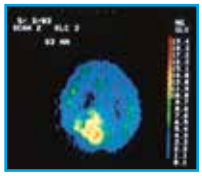
1998 The inaugural AACR-Women in Cancer Research Charlotte Friend Memorial Lecture is delivered by Frances M. Visco. The lecture is intended to give recognition to an outstanding female or male scientist who has made meritorious contributions to the field of cancer research and who has, through leadership or by example, furthered the advancement of women in science.

1998 250,000 people take part in "THE MARCH: Coming Together to Conquer Cancer," a rally on the National Mall in Washington, DC, in support of increased cancer research funding.
THE MARCH Research Task Force Report was published in *Cancer Research*. (116)

1998 The inaugural Pezcoller Foundation-AACR International Award for Cancer Research is presented to Anthony J. Pawson.

1998 RNAi knockdown is demonstrated.
RNA interference provides a method to switch off the actions of genes and can be performed in a high-throughput manner, unlike the creation of knockout mice, which is very time consuming. Researchers are using RNAi to identify genes that might be involved in cancer by switching them off and examining the consequences. It is hoped that therapies might one day be enhanced through RNAi, for example, by using RNAi to switch off genes involved in drug resistance to make chemotherapy more effective. (117)

1998 Master Settlement Agreement forces tobacco companies to pay $246 billion to U.S. states over next 25 years as restitution for violating antitrust and consumer protection laws.

1998 Positron emission tomography (PET) scanner is approved for functional imaging.

PET uses an injected dye to view tissues that are highly metabolically active. PET can identify tumors that are fast growing and active. It is more sensitive at detecting small tumors and metastatic tumors than CT or MRI and so may aid in early diagnosis. (118)

1998 Human embryonic stem cells are grown for the first time.
Embryonic stem cells have the capacity to become any cell type. Various possible applications have been suggested for how stem cells might be used to cure cancer, from generating host-identical replacement cells for tissues that have been surgically removed or destroyed by radiation therapy to generating immune cells that recognize tumors and can enhance the body's own defense system to kill cancers. (119)

1998 U.S. Congress enacts a plan to double the 1998 NIH budget by 2003.

1999 The AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics is launched. This conference, which alternates between locations in the U.S. and Europe each year, has become the most important drug development meeting in the world and an important collaboration among the organizing bodies.

1999 AACR launches the Scientist↔Survivor Program to unite scientific, cancer survivor, and patient advocacy communities worldwide.

1999 AACR Molecular Epidemiology Working Group is formed. This first AACR Working Group brings multiple disciplines together to foster advances in molecular epidemiology. Its success has motivated the formation of other Working Groups, all of which contribute in major ways to AACR programs, including the Annual Meeting.

1999 Pancreas Cancer Think Tank is held by AACR.

2000 Massively parallel signature sequencing method is published.
This method launched the development of a variety of "next-generation" sequencing platforms. (120)

2000 The da Vinci robotic surgical system is the first robotic surgery system approved by the FDA for general laparoscopic surgery.
The da Vinci robotic surgical system is less invasive than previous surgical techniques and is used to treat a number of cancers.

2000 Minorities in Cancer Research (MICR) is established by the AACR to meet the professional needs and advance the careers of minority scientists.
The MICR Council acts as an advisory body to the AACR leadership on issues of concern to minority investigators and is also responsible for organizing the activities of MICR through its committees.

2000 The AACR Foundation for the Prevention and Cure of Cancer (now renamed the American Association for Cancer Research Foundation) is launched.

2000 Breast and Cervical Cancer Treatment Act passes to provide treatment for low-income women diagnosed with cancer.

2001 AACR Journals Online first offers the full text of all AACR scientific publications.

2001 NCI establishes the Center to Reduce Cancer Health Disparities to help reduce the disproportionate impact of cancer on underserved populations.

2001 First commercial PET/CT scanner is developed.
The first prototype began clinical evaluation at the University of Pittsburgh in 1998. The results from over 300 cancer patients were published in peer-reviewed journals two years later. The impressive results of high-resolution structural, anatomic data coupled with functional data created a market for commercial design. The first commercial PET/CT scanner, Discovery LS, was announced in 2001. (121)

2001 The FDA approves CyberKnife Robotic Radiosurgery System.
This noninvasive alternative to surgery allowed for more accurate targeting of radiation therapy to treat cancers, tumors, and other lesions.

2001 The Children's Oncology Group is formed.
Formed from four of NCI's pediatric cooperative groups (the National Wilms Tumor Study Group, the Children's Cancer Group, the Pediatric Oncology Group, and the Intergroup Rhabdomyosarcoma Study Group), the Children's Oncology Group directs most of the pediatric cancer clinical trials in the U.S. Fifty to sixty percent of eligible children participate in clinical trials.

2001 National Nanotechnology Initiative (NNI) is established.
The National Nanotechnology Initiative (NNI) is a research and development initiative of the U.S. government and comprises the individual and cooperative nanotechnology-related activities of 20 departments and federal agencies. NNI's common goals are to: 1) advance a world-class nanotechnology research and development program; 2) foster the transfer of new technologies into products for commercial and public benefit; 3) develop and sustain educational resources, a skilled workforce, and a dynamic infrastructure and toolset to advance nanotechnology; and 4) support responsible development of nanotechnology. (122)

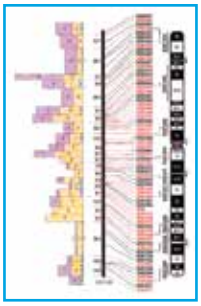
2001 Guidelines and recommendations for the implementation of intensity-modulated radiotherapy (IMRT) are published by the National Cancer Institute Intensity Modulated Radiation Therapy Collaborative Working Group.
Intensity-modulated radiotherapy (IMRT) represents one of the most important developments in radiation therapy. It enables the delivery of high-dose radiation targeted to the tumor and minimal dose to the surrounding healthy tissue. IMRT is now how radiation therapy is most commonly delivered. (123)

2001 Two ligands for inhibitory PD-1 are identified.
Engagement of PD-1 by either of its two newly discovered ligands B7-H1 and B7-DC (PD-L1 and PD-L2, respectively) drastically inhibits T cell receptor-mediated proliferation and cytokine production. Researchers believe this is a way to regulate T-cell responses as dysregulation of this pathway can lead to autoimmunity. This pathway will become a major target for cancer immunotherapy, as blocking PD-1 from binding either of its two immunomodulatory ligands can shift the balance toward heightened T-cell cytotoxicity activity, directing it towards the cancer. (124)

2001 AACR publishes the first issue of the journal, *Molecular Cancer Therapeutics*.

2001 Imatinib, the first FDA-approved small-molecule kinase inhibitor, is effective in treating chronic myelogenous leukemia.
Earlier work established that the Bcr-Abl fusion protein, a result of the Philadelphia chromosome translocation event, was characteristic and causative of chronic myelogenous leukemia (CML). The kinase inhibitor imatinib (Gleevec) selectively shuts down Bcr-Abl signaling in leukemic cells resulting in remission. (125)

2001 Draft sequence of the human genome is published.



A public, free-access, complete human genomic sequence allows researchers to perform many experiments, including but not limited to studies of comparison with other organisms, predictions of gene functions, identification of new genes involved in cancer, and design of new diagnostics and therapeutics. The race to sequence the genome advanced technologies for sequencing and analysis, and it is believed that the $1000 genome sequence may be possible within a few years. This opens up the possibility that patients might sequence and store their full genetic information and that it might be used for personalized medicine, such as determining customized drug treatments and preventive measures. (126)

2001 AACR introduces two new categories of membership: Affiliate Membership, for health professionals working in support of cancer and biomedical research, and Student Membership, for high school and undergraduate students.

2002 I-SPY Trials are launched.
The I-SPY TRIALs are an adaptive approach to clinical trial design to accelerate the processes of identifying patients who would benefit from new drugs and to bring effective drugs to the market. The I-SPY TRIAL Program consists of three integrated and linked phases: phase I (I-SPY 1), phase II (I-SPY 2), and phase III (I-SPY 3). The I-SPY 1 study integrated patients' clinical, imaging, and genomic data to evaluate whether response to therapy could predict recurrence-free survival. Additionally, the trial data were used to inform and enable decisions at earlier time points for the I-SPY 2 Trial. The adaptive design of the I-SPY 2 trials allowed investigators to learn from study data as they were collected and adapt treatments to those that would be more likely to benefit the patient. Rather than waiting until the end of the trial, outcomes were assessed continually and data used to inform the ongoing trial. I-SPY 3 is designed to accelerate the phase III testing of agents.

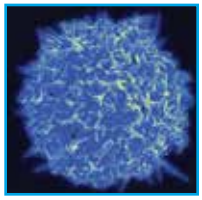
2002 BRAF gene is mutated in human cancers.
Somatic missense mutations in BRAF, a gene encoding a kinase in the RAS–RAF–MEK–ERK–MAP pathway, are described as occurring in a variety of human cancers. Mutated BRAF proteins have elevated kinase activity capable of transforming NIH3T3 cells. BRAF mutations occur most frequently in malignant melanoma. This observation provided a new therapeutic target. (127)

2002 The NSG mouse is an excellent model for engraftment of human tumors.
The NOD/SCID/gamma-deficient mouse model is functionally incompetent, lacking functional T, B, and NK cells, and is therefore a model recipient for xenotransplantation. This mouse model can be used to engraft human cancer cells so that researchers can study and understand features of patients' tumors, such as progression and metastasis. (128)

2002 First clinical trials of checkpoint inhibitor antibody are held.
Immunosuppressive CTLA-4 on T cells acts as a brake on the immune system. A specific monoclonal antibody that recognizes CTLA-4 blocks it and unleashes the potential of the immune system to destroy cancerous cells, opening the door to a new approach to cancer immunotherapy. (129)

2002 The IARC classifies secondhand smoke as carcinogenic to humans.
The International Agency for Research on Cancer (IARC), in their monograph on Tobacco Smoke and Involuntary Smoking, concluded that there is sufficient evidence that secondhand smoke, also referred to as involuntary or passive smoking, causes lung cancer in humans. (130)

2002 First successful trials using adoptive T-cell transfer are held.



Two studies showed that adoptive transfer of in vitro expanded, antigen-specific CD8+ T-cell clones generated from peripheral blood of patients with advanced, metastatic melanoma persisted in vivo, and led to elimination of antigen-specific tumor cells and tumor regression. (131)

2002 AACR holds first multidisciplinary Frontiers in Cancer Prevention Research conference.

2002 AACR publishes the first issue of the journal, *Molecular Cancer Research* (successor to *Cell Growth & Differentiation*).

2002 The inaugural AACR-Prevent Cancer Foundation Award for Excellence in Cancer Prevention Research is presented to Michael B. Sporn. (In 2013, the award is renamed the AACR Award for Outstanding Achievement in Cancer Prevention Research.)

2002 The inaugural Kirk A. Landon-AACR Prize for Basic Cancer Research is presented to Robert N. Eisenman.

2002 The inaugural Dorothy P. Landon-AACR Prize for Translational Cancer Research is presented to Elwood V. Jensen and V. Craig Jordan.

2002 The FDA approves ibritumomab tiuxetan for the treatment of patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma.
Ibritumomab tiuxetan was the first radioimmunotherapy drug approved by the FDA to treat cancer. It was approved for the treatment of patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin lymphoma (NHL), including patients with rituximab refractory follicular NHL.

2003 Obesity is associated with increased cancer death rates.
In a prospective study of more than 900,000 U.S. adults, the death rates from all cancers combined in men and women with a body-mass index (BMI) of 40 or above were 52% and 62% higher than in men and women with normal BMI, respectively. The study estimated that 90,000 cancer-related deaths could be prevented each year in the U.S. if men and women could maintain normal weight. (132)

2003 The FDA approves the first EGFR inhibitor.
Gefitinib was approved by the FDA in 2003 for patients with locally advanced or metastatic non-small cell lung cancer after failure of both docetaxel- and platinum-based treatments. The surrogate endpoint for clinical efficacy was tumor response rate. Erlotinib, another EGFR inhibitor, was approved by the FDA in 2004 for this same cohort, but clinical efficacy was based on improved overall survival. Two follow-up clinical trials with gefitinib did not demonstrate survival benefit. This led to the FDA relabeling of gefinitib in 2005 for cancer patients who, in the opinion of their treating physicians, are currently benefiting or have previously benefited from gefitinib treatment. Approval of gefinitib as a first-line therapy was granted in 2015 for patients with metastatic NSCLC whose tumors express either of two specific EGFR mutations (exon 19 deletions or exon 21 L858R substitution gene mutations). Erlotinib received the same first-line therapy indication for the specific EGFR-mutant cohort in 2013. (133)

2003 The Institute of Medicine of the National Academies publishes report on disparities in health care.
In 1999 Congress requested an IOM study on the extent of disparities in health services received by U.S. racial and ethnic minorities. The report from that study, "Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care," found the U.S. racial and ethnic minorities received lower quality health services and were less likely to receive routine medical procedures. The report recommended several policies to decrease these disparities, including raising awareness about health disparities, developing guidelines for providers, and increasing the numbers of minority health care providers and interpreters in clinics and hospitals. (134)

2003 Loss of function of some tumor suppressor genes occurs through hypermethylation.
Some genes that are frequently hypermethylated in cancer, but are not themselves mutated, can be important tumor suppressor genes. Tumor suppressor genes can be silenced through hypermethylation of their promoter regions, allowing cells to grow and reproduce uncontrollably. (135)

2003 Database of target genes responsive to Myc is developed.
The database serves as a warehouse for information about Myc-responsive genes. Genes are clustered based on their responsiveness to the transcription factor Myc and paired with phylogenetic sequence comparisons to predict the target-binding sites of c-Myc. It also provides information and references on alterations of MYC genes in human cancers and links to a c-Myc protein-protein interaction database. (136)

2003 Large-scale mutation analysis of tyrosine kinome identifies mutations in genes, including NTRK and PIK3CA, implicated in cancer.
The large-scale sequencing-based approach helped identify previously unknown gene mutations providing potential targets for drug development. Therapies targeting NTRK fusions and PIK3CA mutations were developed subsequently and are currently being tested in clinical trials. (137)

2003 AACR membership passes 20,000.

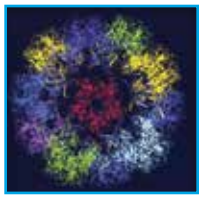
2003 Ubiquitin-proteosome pathway inhibitor bortezomib (Velcade) receives accelerated approval.
Bortezomib (Velcade), a member of a new class of anticancer drugs that target the ubiquitin protein degradation system, was shown to be active in patients with relapsed multiple myeloma that was refractory to conventional chemotherapy. (138)

2003 The inaugural AACR Distinguished Lecture is delivered by James E. Darnell, Jr. (In 2013, the lectureship is renamed the AACR-Irving Weinstein Foundation Distinguished Lecture.)

2004 5-Azacitidine (Vidaza), the first-in-class drug targeting an epigenetic mechanism, is approved.
5-Azacitidine targets an epigenetic mechanism in cancer. It is a hypomethylating agent and a chemical analogue of the nucleoside cytosine. It works by inhibiting DNA methyltransferase, leading to DNA hypomethylation. The FDA approved this drug for the treatment of several subtypes of myelodysplastic syndrome.

2004 According to the American Cancer Society, the absolute number of cancer deaths in the United States declines for the second year in a row, confirming a trend in cancer-related mortality.

2004 The FDA approves bevacizumab (Avastin) for treating advanced colon cancer.
This is the first FDA-approved antiangiogenic therapeutic; there are now 11. Building on earlier work identifying the need of new blood vessel networks to feed tumor growth, therapies were designed to antagonize VEGF, a key molecule in angiogenesis. The addition of bevacizumab (Avastin) to conventional fluorouracil-based combination chemotherapy resulted in improved survival in patients with metastatic colorectal cancer. (139)



2004 Vaccines against human papillomavirus (HPV) are developed to prevent cervical cancer.
Vaccination against the most common oncogenic human papillomavirus types, HPV 16 and HPV 18, could prevent up to 70% of cervical cancer cases worldwide. (140)

2004 The inaugural AACR Award for Lifetime Achievement in Cancer Research is presented to Emil Frei III.

2005 First haplotype map of the human genome is published.
A large consortium published a database of 1 million SNPs in 269 DNA samples from four population groups. This resource allowed for the beginning of whole-genome association studies and the identification of susceptibility variants. (141)

2005 NCI Biorepositories and Biospecimen Research Branch of the Cancer Diagnosis Program is established.

2005 EGFR T790M mutation is reported.
Lung adenocarcinomas that contain a primary drug-sensitive mutation in EGFR initially respond to the tyrosine kinase inhibitors gefitinib and erlotinib, but eventually progress by previously unknown mechanisms of acquired resistance. This study found that the tumors that progress due to acquired resistance contain, in addition to the primary mutation, a secondary mutation in exon 20, leading to the substitution of methionine for threonine at position 790 (T790M) in the kinase domain. This information provided a basis for the development of second-generation kinase inhibitors to treat non-small cell lung cancer. (142)

2005 Proffered abstracts at the AACR Annual Meeting set a new record of over 6,000.

2005 Small noncoding RNAs have a role in oncogenesis.
Traditionally, much of the focus of genomic research had concentrated on genes that code for proteins. Several studies showing that small, noncoding RNAs may play a role in the development of cancer, including one published in *Cancer Research*, have challenged the long-standing belief that proteins were the principal functional products of the genome. (143)

2005 AACR Chemistry in Cancer Research Working Group is formed.

2005 AACR Workshop on the Human Epigenome is held.

2006 The Cancer Genome Atlas is established to map cancer genes.
The Cancer Genome Atlas (TCGA), a collaboration between the National Cancer Institute and the National Human Genome Research Institute, seeks to identify the changes in each cancer's complete set of DNA in the hope of understanding how such changes drive the disease.

2006 The U.S. Surgeon General's report on secondhand smoke is released.
This Surgeon General's report updated the evidence of the harmful effects of secondhand smoke. The previous comprehensive review of this evidence by the Department of Health and Human Services was released in 1986. (144)

2006 New method of adoptive T-cell transfer is introduced.
Genetic engineering of T cells to express T-cell receptor bypasses the need to expand tumor-specific T cells. Some cancer patients have few to no tumor-reactive T cells; genetically modifying normal circulating peripheral T cells overcomes this limitation to standard adoptive transfer. (145)

2006 Cancer is described as an evolutionary and ecological process, providing insight into its clonal heterogeneity.
In 1976, a landmark paper was published on the evolutionary theory of cancer. Advances in biology and sequencing facilitated the validation of this theory. A 2006 paper decribed each neoplasm as a complex, Darwinian, adaptive system made up of a "mosaic of mutant cells" that "compete for space and resources, evade predation by the immune system and can even cooperate to disperse and colonize new organs." These papers provided insight into the clonal heterogenity of tumors and described how resistant clones arise. (146)

2006 Protein-coding genes of breast and colon cancers are sequenced.
Genomic sequencing and analysis of the 13,023 genes in 11 breast and 11 colorectal cancers revealed that only a subset of the accumulated mutations in a tumor contribute to the neoplastic process. The comprehensive data and analysis helped researchers understand the genetic landscape of breast and colon cancers, while also providing clues for new targets for diagnostic and therapeutic intervention. (147)

2006 AACR publishes *CR* (relaunched in 2011 as *Cancer Today*), the association's first magazine specifically for cancer patients, survivors, and their family members and friends.

2006 The inaugural AACR-Minorities in Cancer Research Jane Cooke Wright Memorial Lecture is delivered by Olufunmilayo I. Olopade.

2006 AACR Tumor Microenvironment Working Group is formed.

2006 AACR Council of Scientific Advisors is formed.

2007 ALK rearrangements in non-small cell lung cancer are identified.
Researchers identified a small inversion on chromosome 2p in non-small cell lung cancer (NSCLC) cells that results in a fusion gene of EML4 and ALK. Expression of the mutant EML4-ALK fusion transcript transformed

foci in normal cells and resulted in subcutaneous tumors in nude mice. In this original study, the EML4-ALK mutant fusion transcript was identified in ~6.7% of the human NSCLC patients tested. Later studies identified additional ALK fusion gene variants that encode oncogenic kinases in NSCLC patients. In fact, these mutations are most often found in NSCLC patients who are younger, female, light/never smokers, or do not harbor EGFR or KRAS mutations. This finding in a subset of NSCLC patients provided a new therapeutic target based on cancer genotype and led to landmarks in both targeted therapy and precision medicine. (148)

2007 AACR celebrates 100 years of fostering research in cancer and related biomedical science; disseminating new research findings among scientists and others dedicated to the conquest of cancer; promoting science education and training; and advancing the understanding of cancer etiology, prevention, diagnosis, and treatment throughout the world.

2007 The inaugural AACR Team Science Award is presented to the University of Michigan-Brigham and Women's Hospital Team.

2007 The inaugural AACR Award for Leadership and Extraordinary Achievements in Cancer Research is presented to AACR CEO Margaret Foti. (In 2008, the award is renamed the Margaret Foti Award.)

2007 The inaugural AACR-Princess Takamatsu Memorial Lecture is delivered by Webster K. Cavenee.

2007 AACR holds its first Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved.

2007 The inaugural AACR Award for Outstanding Achievement in Chemistry in Cancer Research is presented to Samuel J. Danishefsky.

2007 The AACR Office of Science Policy and Government Affairs opens in Washington, DC.

2007 AACR-FDA-NCI Cancer Biomarkers Collaborative is held. This body of more than 100 cancer researchers and advocates produced a definitive publication in the form of a consensus report that was published in *Clinical Cancer Research*. (149)

2007 AACR Translational Cancer Medicine Think Tank is held.

2008 Tumor burden is tracked using circulating DNA alterations in the blood.
Tumor cells can be found in the circulation of those with advanced cancers, and tumor-derived mutant DNA can be detected in the cell-free fraction of the blood. However, previous studies were unable to use sufficiently sensitive techniques to detect low levels of circulating tumor DNA (ctDNA). Modifications to the BEAMing technique (beads, emulsion, amplification, and magnetics) made it possible to detect low levels of circulating mutant DNA fragments, precisely measure the level of ctDNA, and track tumor burden in patients. This indicated that ctDNA could serve as a potential biomarker to noninvasively monitor many types of cancer and help inform clinical decision-making. (150)

2008 Whole-genome sequence of a human cancer is reported.
Treatment of acute myeloid leukemia has been particularly challenging since most of the genetic events that initiate the disease are unknown. Whole-genome sequencing of a typical acute myeloid leukemia genome and its matched normal counterpart found 10 genes with acquired mutations, eight of which were new mutations. This study established whole-genome sequencing as a method for discovering mutations that may respond to targeted therapies. (151)

2008 AACR publishes the first issue of the journal, *Cancer Prevention Research*.

2008 Stand Up To Cancer, a charitable program of the Entertainment Industry Foundation, holds its first fund-raising telecast. The AACR is the Scientific Partner of SU2C.

2008 AACR launches its collaboration with the Cancer Therapy & Research Center (CTRC) at UT Health Science Center San Antonio and Baylor College of Medicine to support the CTRC-AACR San Antonio Breast Cancer Symposium. At this symposium, the inaugural AACR Outstanding Investigator Award for Breast Cancer Research is presented to Douglas Easton, and the inaugural AACR Distinguished Lecture in Breast Cancer Research is given by Joan Massagué.

2008 AACR-NCI Think Tank, "Charting the Future of Cancer Prevention," is held.

2009 Congress passes the American Recovery and Reinvestment Act, also known as the Stimulus.
The provisions of the Act support initiatives by the Division of Cancer Control and Population Sciences related to cancer prevention, screening, treatment, and genomics.

2009 Congress passes the Family Smoking Prevention and Tobacco Control Act.
The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) was signed into law on June 22, 2009, giving the FDA authority to regulate the manufacture, distribution, and marketing of tobacco products. (152)

2009 AACR commemorates its 100th Annual Meeting in Denver, Colorado.

2009 AACR membership passes 30,000.

2010 Childhood cancer mortality rates decline by more than 50%.
Improved drugs, treatment strategies, and investments in clinical trials are some of the possible factors resulting in this decrease in childhood cancer mortality. (153)

2010 Congress passes the Patient Protection and Affordable Care Act (ACA).
The ACA was designed to expand coverage, control health care costs, and improve the health care delivery system, including improving insurance coverage for preventative care, screening services, and tobacco cessation treatments. (154)

2010 Prostate cancer vaccine composed of the patient's activated immune cells shows promise in clinical trial.
The vaccine, sipuleucel-T, composed of the patient's dendritic cells, stimulates T cells to respond to prostatic acid phosphatase, an antigen found on most prostate cancer cells. (155)

2010 The inaugural AACR Distinguished Lecture on the Science of Cancer Health Disparities is given by Charles M. Perou at the AACR Cancer Disparities meeting.

2010 AACR is certified as a provider of Continuing Medical Education (CME).

2010 AACR forms the Cancer Immunology and the Behavioral Science in Cancer Research Working Groups.

2010 AACR launches Task Forces on the Cancer Epigenome, Survivorship Research, and Membership Development.

2011 Organoids derived from human tissue are described.
In 2009 researchers described how a single small intestinal stem cell could expand to crypt-villus organoids in culture without a mesenchymal niche. In 2011 this work was extended to describe how to generate organoids from mouse colon and human small intestine and colon. (156)

2011 A novel technique for adoptive T-cell transfer leads to complete responses in two patients with chronic lymphocytic leukemia.
Genetically engineered T cells expressing chimeric antigen receptors that target CD19 and contain a costimulatory domain from CD137 and the T-cell receptor zeta chain display potent activity in vivo. (157)

2011 Ruxolitinib (Jakafi), the first drug to treat myelofibrosis and first-in-class JAK1 and 2 inhibitor, is approved.
This was the first FDA approval supported by patient reported outcomes (PRO). Myelofibrosis is associated with dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Ruxolitinib inhibits JAK1 and 2. (158)

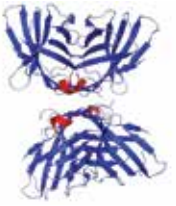
2011 Douglas Hanahan and Robert A. Weinberg update their seminal paper, "Hallmarks of Cancer," adding a decade of new discoveries.
(159)

2011 The FDA approves crizotinib (Xalkori) to treat ALK-positive NSCLC.
The FDA granted accelerated approval for crizotinib to treat locally advanced or metastatic non-small cell lung cancer (NSCLC) patients with tumors that were positive for ALK rearrangements. ALK-positive tumors are identified with an FDA-approved test. Full FDA approval was granted in 2013, just six years after the identification of mutant ALK fusion transcripts in a subset of NSCLC patients. (160)

2011 BRAF inhibitor vemurafenib (Zelboraf) and its companion diagnostic are approved by the FDA to treat melanoma tumors expressing the BRAF V600E mutation.
BRAF is mutated in approximately half of those with late-stage melanoma. Vemurafenib was approved with its companion diagnostic test, cobas 4800 BRAF V600 Mutation Test, which is used to determine whether a patient's tumor expresses the BRAF V600E mutation. (161)

2011 Abiraterone acetate (Zytiga), which decreases androgen production, is approved for metastatic, castration-resistant prostate cancer.
Abiraterone acetate targets cytochrome P450 17A1 (CYP17A1) to inhibit androgen production from the testes, adrenal glands, and tumor. (162)

2011 Ipilimumab (Yervoy), a monoclonal antibody targeting major checkpoint inhibitor CTLA-4, is approved for advanced melanoma.
Ipilimumab (Yervoy) is the first FDA-approved immune checkpoint innhibitor; there are now four. (163)



2011 Brentuximab vedotin (Adcetris), the first new drug to treat Hodgkin lymphoma in over 30 years and the first specifically indicated to treat systemic anaplastic large cell lymphoma, is approved.
Because brentuximab vedotin is an antibody-drug conjugate, the antibody is able to direct the drug to CD30, a cell membrane protein expressed on lymphoma cells. (164)

2011 Regular aspirin use may reduce the risk of several cancers and distant metastases.
Although several important questions need to be answered before aspirin can be considered for use for cancer prevention, studies suggest that aspirin use may reduce both long-term risk of cancer death and short-term cancer incidence and mortality. (165)

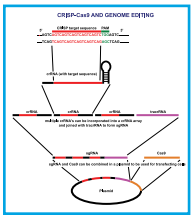
2011 AACR publishes the first issue of the journal, *Cancer Discovery*.

2011 AACR publishes its first annual *Cancer Progress Report*, a comprehensive educational document for both Congress and the public that chronicles the progress of cancer research and serves as a call to action in the fight against cancer.

2011 AACR relaunches *CR* magazine as *Cancer Today*.

2011 AACR Pediatric Cancer Working Group is formed.

2012 It is discovered that CRISPR-Cas9 is RNA-guided DNA endonuclease.
Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems were originally identified in some bacteria and archaea and conferred adaptive immunity against viruses and plasmids. After the components of the system were identified, the mechanism was studied in vitro. The CRISPR-Cas9 system is a family of endonucleases that use dual-RNAs for site-specific DNA cleavage. This paper describes "the potential to exploit the system for RNA-programmable genome editing." (166)



2012 The NIH Human Microbiome Project defines the normal microbial makeup of healthy humans.
The NIH launched the Human Microbiome Project in 2007 to characterize the human microbiota and analyze their role in health and disease. In 2012 a consortium of researchers published a series of coordinated reports, creating the first reference data for the normal human microbiome.

2012 Major checkpoint inhibitor shows dramatic clinical trial results.
An anti-PD-1 monoclonal antibody drastically shrank tumors in patients with melanoma, kidney cancer, and advanced non-small cell lung cancer. (167)

2012 Breakthrough Therapy designation is established for the FDA.
This designation expedites the development and review of drugs that treat a serious or life-threatening disease or condition and provide substantial improvement over existing therapies.

2012 The number of cancer survivors reaches an all-time high of 13.7 million.

2012 Vismodegib (Erivedge) is the first drug approved for basal cell carcinoma, the most common type of skin cancer.
Vismodegib inhibits the Hedgehog pathway. Of patients with metastatic disease who received vismodegib, 30% experienced a partial response; of those with locally advanced disease, 43% experienced a complete or partial response. (168)

2012 Whole-genome sequencing explains exceptional response to therapy in a single patient.
Massively parallel sequencing (MPS) was used to provide biologic insights and identify the molecular pathology of prostate tumors. Deep RNA and shallow DNA sequencing was performed in primary tumors and matched metastases in six patients. The results provided a foundation for developing MPS-based molecular pathology. (169)

2012 Functional consequences of intratumoral heterogeneity are described, suggesting the limitations of single tumor-biopsy samples.
Multiple, spatially separated tissue samples were obtained from primary renal carcinomas and associated metastatic sites. Exome sequencing, chromosome aberration analysis, and ploidy profiling were performed. Gene expression, IHC, and mutation functional analysis further characterized the tissue samples. Roughly 63-69% of all somatic mutations were not detectable across every regional sample from the same tumor. Gene expression signatures varied in different regions of the tumor. This heterogeneity across the same tumor presents challenges when using a single tumor biopsy and provides further evidence of the Darwinian selection of cell populations within a tumor that can lead to therapeutic resistance. (170)

2012 AACR-Pancreatic Cancer Action Network Think Tank, "The 2020 Goal for Pancreatic Cancer: Driving the Agenda Forward," is held.

2012 AACR Cancer Epigenome Think Tank is held.

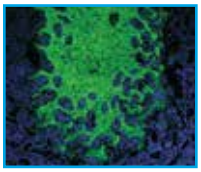
2013 The term "financial toxicity" is coined.
Financial toxicity is recognized as a potential adverse event in cancer treatment. Out-of-pocket costs related to cancer treatment can impede delivery of high-quality care and diminish quality of life. Both objective financial burden and subjective financial distress are components of financial toxicity. (171)

2013 CAR T-cell therapy achieves complete responses in acute lymphoblastic leukemia.
Two separate studies, both with T cells engineered to express chimeric antigen receptor targeting CD19 on leukemic B cells, saw dramatic results in adults and children with relapsed and refractory B-ALL. (172)

2013 Radium Ra 223 dichloride (Xofigo), which can bind with minerals in the bone and deliver radiation directly to bone tumors, is approved by the FDA to treat metastatic, castration-resistant prostate cancer that has spread to bones.
This is the first FDA-approved alpha-emitting radionuclide. Because radium Ra 223 dichloride delivers radiation directly to bone tumors, it limits the damage to the surrounding normal tissues. (173)

2013 CRISPR-Cas9 is adapted for genome editing in eukaryotic cells.

This study engineered two different type II CRISPR/Cas systems to show that Cas9 nucleases, directed by short RNAs, can facilitate site-specific cleavage in genomic loci of human and murine cells. (174)

2013 The microbiome helps to stimulate anticancer immune responses.

Resident gut bacteria have the potential to move from the intestines to lymphoid tissues such as the spleen and lymph nodes; once there, they stimulate T-cell responses that aid antitumor response. (175)

2013 T-DM1 is approved for late-stage HER2-positive breast cancer.
Ado-trastuzumab emtansine (TDM1; Kadcyla) was approved to treat patients who were previously treated with the anti-HER2 therapy trastuzumab and taxanes, a class of chemotherapy drugs commonly used for the treatment of breast cancer. TDM1 is an antibody-drug conjugate, in which the antibody trastuzumab is connected to the drug DM1 that interferes with cancer cell growth. TDM1 delivers the drug to the cancer site to shrink the tumor.

2013 The Fellows of the AACR Academy is established, and the inaugural class of Fellows is inducted.

2013 The AACR partners with over 200 organizations and institutions to conduct the first Rally for Medical Research in support of increased funding for biomedical research, April 8, Washington, DC.
About 10,000 people attended the Rally, which was held outside the Washington, DC, convention center at the time of AACR Annual Meeting 2013.

2013 AACR publishes the first issue of the journal, *Cancer Immunology Research*.

2013 The inaugural AACR-CRI Lloyd J. Old Award in Cancer Immunology is presented to James P. Allison.

2013 AACR holds its first Special Conference focused on pediatric cancer, "Pediatric Cancer at the Crossroads: Translating Discovery into Improved Outcomes" (Cochairs: John M. Maris, Stella M. Davies, James R. Downing, Lee J. Helman, and Michael B. Kastan).

2013 AACR launches Task Forces on Radiation Oncology and Surgical Oncology.

2014 NCI National Clinical Trials Network (NCTN) is formed.
The NCTN was established to provide an integrated clinical trials program to take advantage of scientific advances in our knowledge of tumor biology and targeted therapies. These scientific advances created a need for cancer clinical trials with the capacity to screen large numbers of patients in order to identify those whose tumors contained distinct molecular targets.

2014 Liquid biopsy allows for noninvasive screening for early detection of cancers.
Liquid biopsy is a screening of patient blood, which is a less invasive means to detect circulating tumor DNA shed by cancer cells that can serve as a biomarker for cancer at earlier stages, when there is better potential for survival. Dying cancer cells shed their DNA into the bloodstream even at very early stages; routine screening has the potential to detect cancer earlier, before the cancer has advanced to late stages when treatment is less effective. A liquid biopsy can also monitor a patient's response to treatment and begin to help researchers understand why certain cancers become resistant to treatment. (176)

2014 CAR T-cell therapy achieves a 92% response rate in non-Hodgkin lymphoma.
(177)

2014 Blinatumomab (Blincyto) is the first bispecific T-cell engager (BiTE) approved by the FDA.
Blinatumomab (Blincyto) engages the body's T cells against Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL), an uncommon form of ALL. In earlier clinical studies, 32% of participants showed complete remission for approximately 6.7 months. (178)

2014 The NCI launches the Exceptional Responders Initiative.
The goal of this study is to understand the exceptional treatment responses of those cancer patients who respond to treatments that are not effective for most other patients.

2014 The FDA approves olaparib (Lynparza) for advanced ovarian cancer along with a laboratory-developed test (LDT) companion diagnostic to identify appropriate patients through the detection of the presence of mutations in BRCA genes in blood samples.

Olaparib is the first FDA-approved therapeutic that inhibits PARP and was approved with the genetic test, BRACAnalysis CDx, a companion diagnostic. BRACAnalysis CDx detects mutations in BRCA1 and BRCA2 genes (gBRCAm) in blood samples from patients and can guide treatment decisions for the use of olaparib. (179)

2014 Combination immunotherapy delivers dramatic results.
Combination nivolumab (anti-PD-1) and ipilimumab (Yervoy; anti-CTLA-4), both immune checkpoint inhibitors, in a phase 1b clinical trial saw 90% response rates in patients with advanced melanoma.

2014 AACR opens its first two international satellite offices in Shanghai, China, and Toronto, Ontario, Canada.

2014 AACR membership passes 35,000.

2014 AACR holds two Think Tanks, "Future of Pediatric Cancer Research and Care," and "Charting the Future of Cancer Disparities Research" (the latter jointly with ACS, ASCO, and NCI).

2015 NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trials open for enrollment.
This phase II precision medicine trial explores treating patients based on the molecular profiles of their tumors regardless of cancer type.

2015 Daratumumab (Darzalex) is the first monoclonal antibody approved for the treatment of multiple myeloma.
In clinical studies, 29-36% of patients experienced a complete or partial reduction in their tumor burden. (180)

2015 The Precision Medicine Initiative is announced.
The Precision Medicine Initiative leverages advances in genomics, methods for managing and analyzing large data sets, and health information technology to accelerate biomedical discoveries and bring precision medicine to many aspects of health care, including cancer.

2015 Mutation signatures of in vitro carcinogen exposure are extracted from mammalian genome.
Mutational processes leave characteristic marks on the genome, creating a record of the mutagenic processes that occur throughout the life of an organism. Earlier research linked exposure to environmental carcinogens to mutations in a specific gene, such as p53. With the advent of massively parallel next-generation sequencing (NGS) technology, these signatures can now be extracted from the sequences of whole genomes or all protein-coding exons, allowing greater precision in characterizing the mutational signature than can be obtained from analysis of a single gene. This opens up the possibility of identifying mutational signatures in the genome associated with exposures that contribute to the burden of human cancer. A portion of this work was published in *Cancer Research*. (181)

2015 The FDA approves osimertinib (Tagrisso) to treat EGFR T790M mutation-positive non-small cell lung cancer.
The FDA granted accelerated approval for osimertinib (Tagrisso) to treat patients whose tumors have a specific EGFR mutation (T790M) and whose disease has gotten worse after treatment with other EGFR-blocking therapy. (182)

2015 The percentage of adults in the U.S. who smoke declines from 21% in 2005 to 15% in 2015.
(183)

2015 First cyclin-dependent kinase inhibitor is approved for cancer treatment.
Palbociclib (Ibrance) is the first cyclin-dependent kinase 4/6 inhibitor approved by the FDA. Palbociclib was approved for postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. Adding palbociclib to letrozole doubled the median progression-free survival from 10 to 20 months. (184)

2015 AACR announces the launch of AACR Project GENIE (Genomics Evidence Neoplasia Information Exchange), an international data-sharing project that aggregates and links clinical-grade cancer genomic data with clinical outcomes from tens of thousands of cancer patients.

2015 Vice President Joe Biden announces that he will forgo a run for the U.S. presidency to dedicate his energy to "a moonshot in this country to cure cancer…an absolute national commitment to end cancer as we know it today."
In a statement, AACR CEO Margaret Foti, PhD, MD (hc) notes that "the vice president is absolutely correct: We are at a turning point in cancer research, … [but] future progress for cancer patients will require more research and more funding for the federal agencies that are vital for fueling progress against cancer, in particular, the NIH, NCI, and FDA."

2015 AACR Radiation Science and Medicine Working Group is formed.

2015 AACR Radiation Oncology Think Tank, "Optimizing Cancer Care through Advancements in Radiation Science and Medicine," is held.

2015 QuadW-AACR Sarcoma Expert Panel, "Envisioning the Future of Sarcoma Research and Improved Patient Outcomes," is held.

2016 On January 8, a group of 15 AACR leaders, led by AACR President José Baselga, meets with Vice President Biden's senior staff to discuss the state of cancer research and the Vice President's commitment to a national initiative to eliminate cancer. Four days later, during the State of the Union Address, President Obama announces the launch of a "new national effort" to eliminate cancer to be led by the vice president.

2016 AACR Cancer Prevention Summit, "Shaping the Future of Cancer Prevention: A Roadmap for Integrative Cancer Science and Public Health," is held.

2016 Vice President Biden addresses attendees of AACR Annual Meeting 2016, thanking the assembled researchers for devoting their lives to cancer research and encouraging them to share their ideas to accelerate progress against cancer.

2016 AACR celebrates its publishing centennial, commemorating the 100th anniversary of the publication of its first journal, *The Journal of Cancer Research*, and the 75th anniversary of the publication of its oldest continuously published journal, *Cancer Research*.

2016 NCI-Match Trials interim analysis is released at AACR Annual Meeting.

2016 The FDA approves the first liquid biopsy test.
The FDA approved a liquid biopsy test, a companion diagnostic test called cobas EGFR Mutation Test v2. The test uses plasma samples to identify patients with metastatic non-small cell lung cancer (NSCLC) eligible for treatment with the EGFR-targeted therapeutic erlotinib (Tarceva). The need for this noninvasive test is particularly important in cases in which a tumor biopsy is not possible. (185)

2016 Report to the Nation on the Status of Cancer (1975-2012) is released, showing that death rates have declined for all cancers combined.
(186)

2016 Report on E-Cigarette Use Among Youth and Young Adults is released by the U.S. Surgeon General.

2016 The first drug to target the Bcl-2 protein is approved.

Venclexta (venetoclax), also known as ABT-199, is the first FDA-approved drug that targets the Bcl-2 protein and interferes with the ability of cancer cells to evade apoptosis. Venclexta was approved for the treatment of patients with chronic lymphocytic leukemia and a 17p deletion. Phase II trials demonstrated an overall response rate of 80%. (187)

2016 AACR Think Tank on Genomics in Clinical Medicine is held.

2016 The NCI's Genomic Data Commons is launched.
The Genomic Data Commons is a data-sharing platform that provides the cancer research community with a unified data repository supporting cancer genomic studies. NCI-generated data from some of the largest and most comprehensive cancer genomic datasets as well as datasets from organizations are harmonized, allowing data from various sources to be compared directly.

2016 AACR holds two Workshops, "Childhood Cancer Predisposition, Optimizing Pediatric Surveillance and Care through Precision Genetics," and "Liquid Biopsies in Oncology Drug and Device Development" (the latter jointly with FDA).

2016 Cancer Moonshot Blue Ribbon Panel report is released and details 10 research recommendations for achieving the goals of the Cancer Moonshot to make a decade's worth of progress in five years.

2016 21st Century Cures Act is passed, including $18 billion in supplemental funding over seven years to fund Cancer Moonshot projects and initiatives.

2017 The FDA launches the Oncology Center of Excellence, making oncology the first disease area to have a coordinated review of drugs, biologics, and devices across the agency's three medical product centers.

2017 AACR announces the first public release of data aggregated through its Project GENIE initiative, consisting of nearly 19,000 de-identified genomic records and limited clinical data.
By aggregating the historical and ongoing clinical sequencing efforts from leading international institutions, AACR Project GENIE has formed a real-world registry of cancer data that will continue to grow with time. These data are already being used to answer important clinical questions, and will be a community resource that will undoubtedly catalyze numerous new research projects.

2017 NCTN/NCORP Data Archive, a new centralized repository of patient-level data from phase III clinical trials, is launched by the NCI.

2017 The AACR International Conference on New Frontiers in Cancer Research is held in Cape Town, South Africa—the first AACR meeting on the African continent.

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