THE BIOMEDICAL RESEARCH COMMUNITY

By working together, the stakeholders in the biomedical research community have made and continue to make lifesaving progress against cancer for the benefit of patients, survivors, and their families. Among these stakeholders are the following:

- patients, survivors, and their families and friends;
- clinicians;
- academic researchers from a wide range of specialties;
- biotechnology, pharmaceutical, and diagnostics companies;
- citizen advocates, advocacy groups, and philanthropic organizations;
- policymakers;
- regulatory agencies;
- funding agencies; and
- payers.

American Association for Cancer Research Cancer Progress Report 2015
THE NATIONAL INSTITUTES OF HEALTH BY THE NUMBERS

- **27** Institutes and Centers make up the National Institutes of Health (NIH).
- **$30.3** Billion for fiscal year 2015.
- **50,000** Competitive Grants awarded by the NIH each year to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state and around the world.
- **6,000** In-House Scientists funded by the NIH annually.
- **402,000** U.S. Jobs directly supported by NIH-funded research in fiscal year 2012.

Source: NIH.gov
CANCER HEALTH DISPARITIES IN THE UNITED STATES

According to the NCI, cancer health disparities in the United States are defined as differences that should not exist in cancer incidence, prevalence, death, survivorship, and burden of cancer among certain segments of the U.S. population, including:

- racial and ethnic minority groups,
- individuals with low socioeconomic status,
- individuals who lack or have limited access to healthcare,
- residents in certain geographical locations, including rural areas,
- members of the lesbian, gay, bisexual, and transgender community,
- immigrants,
- individuals with disabilities; and
- the elderly.

Examples of cancer health disparities in the United States are:

- **28% higher**: The overall cancer death rate among black men is 28 percent higher than among white men.
- **31% lower**: The overall cancer death rate among Hispanic men is 31 percent lower than among non-Hispanic men.
- **23% more likely**: Hispanic children are 23 percent more likely to develop leukemia than non-Hispanic children.
- **2X RISK**: Asian and Pacific Islanders are about twice as likely to develop and die from stomach cancer as their white counterparts.
- **34% lower**: The overall cancer death rate among non-Hispanic women is 34 percent lower than among Hispanic women.
- **32% less likely**: Colorectal cancer death rates in the lower Mississippi Delta, west central Appalachia, and eastern Virginia/North Carolina are twice as elevated compared with the rest of the United States.
- **Advanced-stage ovarian cancers**: Patients of low socioeconomic status are 32 percent less likely to receive standard overall care compared with those of high socioeconomic status.

Complex and interrelated factors contribute to cancer health disparities in the United States. These factors may include, but are not limited to, differences or inequities in:

- access to and use of health care,
- treatments received,
- exposure to environmental cancer risk factors,
- genetics,
- social and economic status,
- cultural beliefs, and
- health literacy.

The interdependent nature of many of these variables makes it difficult to isolate and study the relative contribution of each to cancer health disparities. However, given that a significant proportion of the U.S. population falls into one or more risk categories, it is important that research into these specific issues continues. Only with new insights will we develop and implement interventions that will eliminate cancer for all.

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Cancer is a leading cause of morbidity and mortality globally, accounting for about 15 percent of deaths worldwide. Its devastating impact will grow significantly in the coming decades if more effective approaches to cancer prevention, early detection, and treatment are not developed.

Cancer is a universal challenge.

Estimates for less-developed regions:
- 8.7 million new cases in 2015
- 5.8 million deaths in 2015

Estimates for more-developed regions:
- 6.4 million new cases in 2015
- 3.0 million deaths in 2015

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WHY ME? WHY THIS CANCER?

Cancer arises predominantly as a result of the accumulation of genetic mutations. An individual may inherit some of these mutations and acquire others during his or her lifetime. At birth, nearly every cell in the body has the same genetic makeup that the person inherited; however, each cell has a different chance of acquiring mutations over time based on a combination of factors. Together, these individual events come together to determine the overall risk that a person will develop a particular cancer type.

ACQUIRING GENETIC MUTATIONS

Many complex and interrelated factors affect the chance that a cell will acquire a genetic mutation, including: exposure of the cell to factors like chemicals in tobacco smoke and ultraviolet (UV) light from the sun; and the number of times the cell multiplies.

INHERITING GENETIC MUTATIONS

Only 5 to 10 percent of all new U.S. cancer cases are linked to inherited genetic mutations (i.e., mutations that you are born with).

RISK OF DEVELOPING A PARTICULAR CANCER

Approaches to cancer prevention and early detection rely on understanding the relative contributions of each cause of genetic mutations, because it is possible for a person to modify some of these causes. For example, a person can stop smoking but cannot alter his or her genetic makeup. Below are simplified estimates of the relative contribution of inherited mutations, mutations caused by preventable factors, and mutations caused by cell multiplication to four different types of cancer, based on a recent study.

Basal Cell Carcinoma

The cells of the dermis are constantly multiplying to replace damaged cells. Thus, the number of cell multiplications is the primary, but not the only, contributor to the risk of developing the most common form of skin cancer. Although cell replication is not under an individual’s control, everyone should continue to take measures to reduce his or her exposure to UV; a cause of acquired genetic mutations.

Smoking-dependent Lung Cancer

Acquired genetic mutations related to exposure to the toxins in cigarette smoke are the primary, but not the only, contributors to the risk of developing lung cancer. Eliminating tobacco use and exposure to smoke can prevent lung cancer from developing.

Hepatitis C Virus (HCV)-dependent Liver Cancer

Chronic infection with the HCV virus is the primary, but not the only, contributor to the risk of developing liver cancer in the infected individual depicted. HCV infection is treatable and preventable.

Familial Adenomatous Polyposis-dependent Colorectal Cancer

For individuals who inherit a mutation in the APC gene, the inherited genetic mutation is the primary, but not the only, contributor to their risk of developing colorectal cancer. Such individuals, however, can alter their personal prevention plans to proactively survey for the earliest signs of disease and intercept it.
GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

The genetic material of a cell comprises strands of four deoxyribonucleic acid (DNA) units called bases.

The entirety of a person’s DNA is called the genome. And almost every cell in their body contains a copy of the individual’s genome. The genome is packaged together with proteins called histones into structures called chromosomes.

DNA bases are organized into genes, and the order, or sequence, of the bases provides the code for producing the various proteins a cell needs to function.

Special chemical marks, called epigenetic marks, on the DNA and histones together determine whether a gene is accessible for decoding. The sum of these chemical marks across the entire genome is called the epigenome.

The accessible genes within each cell are deciphered to produce the proteins that ultimately define the function of the cell and the tissue in which the cell resides.
GENETIC MUTATIONS

Below are some of the various genetic mutations known to lead to cancer; however, genetic mutations do not always result in cancer.

Single base changes
• Some mutations can lead to new proteins that may cause cancer to develop.
• Deletion or insertion of DNA sequences can lead to new proteins or loss of protein function that can lead to cancer.

Extra copies of genes (gene amplification)
Higher quantities of certain proteins can lead to enhanced cell survival and growth, leading to cancer.

Large deletions
Loss of DNA can result in loss of genes necessary to stop or control the growth of cancer.

Genetic recombination
Exchange of DNA across different parts of the genome can lead to entirely new proteins that can drive the development of cancer.

Mutations that alter the epigenome
Mutations in the genes that produce proteins that alter the epigenetic marks on DNA or the histones around which it is packaged can lead to cancer.
CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

The **matrix** of proteins that surrounds the cancer cells can influence cancer formation, metastasis, and other processes.

Cancer cells can stimulate the growth of **blood and lymphatic vessel networks**, which supply the cancer cells with nutrients and oxygen required for rapid growth and survival and provide a route for cancer cell escape to distant sites (metastasis).

**Systemic factors** in the circulation, such as hormones and nutrients, influence the development and growth of cancer.

The **immune system** can identify and eliminate cancer cells, although in many cases this system is suppressed, permitting the formation and progression of a tumor. However, in some situations of chronic inflammation, the immune system can promote cancer development and progression.

*American Association for Cancer Research Cancer Progress Report 2015*
TRANSFORMING LIVES ONE SEQUENCE AT A TIME

RITA PORTERFIELD / VIRGINIA

"Has Her Life Back" Thanks to the Clinical Use of Genomics

In May 2006, Rita Porterfield was diagnosed with Erdheim-Chester disease, which is caused by excessive multiplication of a particular white blood cell. Genetic sequencing showed that Rita's disease was driven by mutations in a gene called BRAF, which is also mutated in about 50 percent of cases of cutaneous melanoma. Importantly, several BRAF-targeted therapeutics are approved for the treatment of BRAF-mutant cutaneous melanoma, and Rita was treated with one of these, vemurafenib (Zelboraf), as part of a basket clinical trial at Memorial Sloan Kettering Cancer Center (MSKCC). Within three days of taking her first dose of vemurafenib, Rita felt an improvement. She has now regained her ability to walk—when she first arrived at MSKCC she needed a motorized scooter—and you would never know she was ill.

ZACHARY (ZACH) WITT // AGE 10 // PENNSYLVANIA

Overcoming Anaplastic Large Cell Lymphoma Thanks to a Treatment for Lung Cancer

In 2010, Zach was diagnosed with anaplastic large cell lymphoma and began receiving traditional chemotherapy at the Children's Hospital of Philadelphia. In 2011, Zach's cancer stopped responding to treatment. Genetic sequencing of Zach's tumor identified a particular chromosomal alteration—an ALK translocation—that made him eligible for a clinical trial of the ALK-targeted therapeutic crizotinib (Xalkori), which had already been FDA approved for the treatment of patients with non–small cell lung cancer carrying ALK translocations. Just three days after starting crizotinib, Zach was already feeling better and playing; he remains cancer free to this day.

MARYANN ANSELMO // AGE 60 // NEW JERSEY

Surviving Glioblastoma Thanks to a Treatment for Melanoma

In 2013, MaryAnn Anselmo was diagnosed with glioblastoma, the most deadly form of brain cancer. In 2014, genetic sequencing, performed at Memorial Sloan Kettering Cancer Center (MSKCC), of 410 of the genes in MaryAnn's glioblastoma revealed a glimmer of hope. Her tumor contained a mutation in BRAF, a gene commonly mutated in cutaneous melanoma, for which there are very effective FDA-approved BRAF-targeted therapeutics. One such therapeutic, vemurafenib (Zelboraf), although unused in glioblastoma, is making a big difference for MaryAnn. When she first arrived at MSKCC, she was refused by prior chemotherapy and radiation treatments. Now, her tumor has shrunk by over 50 percent in the past year and she is focused on returning to singing professionally.

WARREN RINGROSE // AGE 55 // MASSACHUSETTS

Hoping to Help Others Become the Rule Rather Than the Exception

Warren started 2013 with a bang: a diagnosis of locally advanced olfactory neuroblastoma, a rare cancer of the sinus and nasal tracts that occurs at a rate of only 0.4 per 1 million people in the United States. Following two months of treatment with traditional chemotherapeutics, computed tomography (CT) scans showed that Warren's cancer was not responding to treatment. His oncologist at the Dana-Farber Cancer Institute suggested that Warren participate in a clinical trial of sorafenib (Nexavar), a therapeutic approved for the treatment of liver and kidney cancers. Warren is a rare responder, as he was one of the few individuals on the trial who responded to sorafenib. He continues to respond to this day. Researchers are using genomics to study why Warren benefited from sorafenib, to help not only Warren, but also other individuals like him, now and in the future. Warren continues to take four pills a day, works full time, and considers himself lucky, as a cancer survivor, as a rare responder, as a beneficiary of cancer research, and that he has access to the Dana-Farber Cancer Institute.

American Association for Cancer Research Cancer Progress Report 2015
REASONS TO ELIMINATE TOBACCO USE

1 IN 5 U.S. DEATHS is attributable to cigarette smoking.

18 TYPES OF CANCER are causally related to tobacco use.

6.5 MILLION AMERICANS died of a smoking-related cancer between 1965 and 2014.

U.S. ADULTS WHO SMOKED ARE 25X MORE LIKELY to develop lung cancer than those who do not, but those who quit cut their chance of dying from lung cancer in half within 10 years.

250k+ U.S. LUNG CANCER DEATHS between 1965 and 2014 were caused by exposure to second-hand smoke.

American Association for Cancer Research Cancer Progress Report 2015

Cigarette smoking is not the only cause of cancer; cigars, tobacco in pipes, and smokeless tobacco products can also cause cancer.

Continued tobacco use after a cancer diagnosis can reduce the effectiveness of treatment and decrease overall survival.

No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke.
# E-Cigarettes: What We Know and What We Need to Know

## What We Know

<table>
<thead>
<tr>
<th>460+ BRANDS</th>
<th>More than 460 brands of e-cigarettes and other electronic nicotine delivery systems (ENDS) are available.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More than 7,700 flavors of nicotine solutions are available.</td>
</tr>
<tr>
<td></td>
<td>E-cigarette use among U.S. middle and high school students is rapidly increasing.</td>
</tr>
<tr>
<td></td>
<td>E-cigarettes are not currently regulated by the U.S. Food and Drug Administration.</td>
</tr>
</tbody>
</table>

## What We Need to Know

### ENDS and Health

- What are the health effects of acute and chronic ENDS use?
- Does switching from cigarette smoking to ENDS use confer a health benefit?
- Do different ENDS products vary in potential for addiction?

### ENDS Use

- Who uses ENDS and why?
- Does this change over time?
- Do flavorants affect the appeal and use of ENDS?
- Does the marketing and availability of ENDS affect perception and use of ENDS?
- Do tobacco-control policies affect the use of ENDS?

### ENDS and Cigarette Smoking Cessation

- Do ENDS aid cigarette smoking reduction and cessation?
- Can ENDS be used with current FDA-approved cessation medications?
- Should behavioral counseling be changed for ENDS cessation trials?
- Does short- or long-term ENDS use affect smoking relapse among those who have previously stopped using cigarettes?

### ENDS Products

- How do ENDS products differ from one another?
- Can ENDS product testing be standardized?
REDUCE YOUR RISK FOR CANCERS LINKED TO BEING OVERWEIGHT OR OBESE, BEING INACTIVE, AND/OR CONSUMING A POOR DIET

Research from the World Cancer Research Fund International shows that about a third of the most common cancers are attributable to being overweight or obese, being inactive, and/or eating poorly. As such, among their recommendations are the following:

- Be as lean as possible without becoming underweight, because 10 types of cancer have been causally linked to being obese or overweight.

- Be physically active for at least 30 minutes every day, because regular physical activity can decrease risk for colorectal, endometrial, and postmenopausal breast cancers.

- Limit consumption of energy-dense foods (foods high in fats and/or added sugars and/or low in fiber) and avoid sugary drinks, because these contribute to weight gain.

- Eat more of a variety of vegetables, fruits, whole grains, and beans, because these foods have a low energy density and, therefore, promote healthy weight.

- Limit intake of red meat and avoid processed meat (e.g., hot dogs, bacon, and salami) because these foods can increase risk for colorectal cancer.

- If consumed at all, limit alcoholic drinks, because alcohol consumption can increase risk for five types of cancer: breast, colorectal, esophageal, liver, and mouth/throat cancers.

Source: http://www.wcrf.org/htf/research-we-fund/wcrf-cancer-prevention-recommendations
WAYS TO PROTECT YOUR SKIN

To reduce your risk of skin cancer, the Centers for Disease Control and Prevention recommend that you:

- seek shade and limit time in the sun, especially around midday;
- wear clothing that covers your arms and legs;
- wear a wide-brimmed hat;
- wear wrap-around sunglasses;
- apply a sunscreen rated sun protection factor (SPF) 15 or higher at least every two hours and after swimming, sweating, and towelinging off; and
- avoid indoor tanning with UV devices like sunlamps, sunbeds, and tanning booths.

American Association for Cancer Research Cancer Progress Report 2015
## Preventing or Eliminating Infection with the Four Major Cancer-Causing Pathogens

<table>
<thead>
<tr>
<th>Pathogen / Ways to Prevent Infection</th>
<th>Ways to Eliminate or Treat Infection</th>
<th>U.S. Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori</td>
<td>Treatment with a combination of stomach-acid suppressants and antibiotics can eliminate infection.</td>
<td>CDC recommends testing and treatment for people with active or a documented history of gastric or duodenal ulcers, low-grade gastric MALT lymphoma, or early gastric cancer that has been surgically treated.</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Vaccination has been part of the childhood immunization schedule since 1991.</td>
<td>U.S. Preventive Services Task Force recommends screening high-risk individuals—those from countries with high rates of HBV infection, HIV-positive persons, injection drug users, household contacts of HBV-infected individuals, and men who have sex with men—for HBV infection.</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Treatment with any of several antiviral drugs can eliminate infection.</td>
<td>CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection.</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>None available.</td>
<td>CDC recommends HPV vaccination for: boys and girls age 11 or 12, women up to age 26 and men up to age 21 who did not receive the vaccine or complete the three-dose course as a preteen.</td>
</tr>
</tbody>
</table>

American Association for Cancer Research Cancer Progress Report 2015
CANCER SCREENING

BENEFITS OF SCREENING

**Reduced cancer incidence.** Screening tests can detect precancerous lesions. Removal of the abnormal tissue can reduce, or even eliminate, an individual's risk of developing the screened cancer. For example, the Pap test can detect lesions before they develop into cervical cancer.

**Reduced incidence of advanced disease.** Screening tests that detect cancers that have already developed can reduce the individual's risk of being diagnosed with the screened cancer at a stage when it has spread to other parts of the body.

**Reduced mortality.** Diagnosis at an early stage of disease increases the likelihood that a patient can be successfully treated, and thereby reduces the individual's risk of dying of the screened cancer. For example, mammography can detect breast cancers at an early stage, when surgery may be curative.

POTENTIAL RISKS OF SCREENING

**Adverse events.** Screening tests are medical procedures; as a result, they carry some risk. However, the chance that an adverse event will occur during a screening test approved by the USPSTF is low.

**Anxiety.** Screening individuals who are not at high risk of disease can cause unnecessary anxiety during the waiting period for the test results.

**False-positive tests.** Not all individuals who have a positive screening test have the screened cancer. The rates of false-positive tests are generally low, but a false-positive screen can result in additional unnecessary medical procedures, treatments, and anxiety.

**False-negative tests.** Not all individuals who have a negative screening test are free from the screened cancer. The rates of false-negatives are generally low, but a false-negative screen can lead to missed opportunities for early treatment.

**Overtreatment and overdiagnosis.** Not all cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, leads to overtreatment, which carries its own risks. The rates of overdiagnosis and overtreatment vary between screening tests and are difficult to quantify.

*American Association for Cancer Research Cancer Progress Report 2015*
Below are the U.S. Preventive Services Task Force (USPSTF) recommendations related to population-based screening for early detection of several cancers as of July 31, 2014. Not listed are the screening programs for which the USPSTF believes there is insufficient evidence to make a recommendation. These recommendations do not take into account an individual's unique medical history and risk; thus, everyone should always consult his or her physician prior to making any decision regarding cancer screening.

**BREAST CANCER**
As of November 2013, the USPSTF recommended*:  
Women ages 50–74 have a screening mammography once every two years.  
Women younger than 50 should make a decision in concert with their physician about when to start regular screening after taking into account their own personal situation.

*Breast cancer screening guidelines are currently under review and will be updated in the near future.

**CERVICAL CANCER**
Women ages 21–29 should have a Pap test every three years.  
Women ages 30–65 should have either a Pap test every three years or a Pap test and human papillomavirus (HPV) testing every five years.

**COLORECTAL CANCER**
As of January 2014, the USPSTF recommended**:
Adults ages 50–75 should be screened through fecal occult blood testing yearly, sigmoidoscopy every 5 years with fecal occult blood tests every 3 years, or colonoscopy every 10 years.

**LUNG CANCER**
As of December 2013, the USPSTF recommended:
Adults ages 55–79 who have smoked one pack of cigarettes per day for 30 years, or the equivalent (two packs per day for 15 years, etc.), and who currently smoke or have quit within the past 15 years, should be screened annually through low-dose computed tomography.

*Breast cancer screening guidelines are currently under review and will be updated in the near future.

**Colorectal cancer screening guidelines are currently under review and will be updated in the near future.
**HOW DO I KNOW IF I AM AT HIGH RISK FOR DEVELOPING AN INHERITED CANCER?**

Among the factors to consider are whether, in your family, there is one or more of the following:

- many cases of an uncommon or rare type of cancer (such as kidney cancer);
- many cases of a particular cancer, such as breast cancer, among those on the same side of the family;
- members diagnosed with cancers at younger ages than usual (such as colon cancer in a 20-year-old);
- one or more members who have more than one type of cancer (such as a female relative with both breast and ovarian cancer);
- one or more members with cancers in both of a pair of organs simultaneously (both eyes, both kidneys, or both breasts); and
- more than one childhood cancer in a set of siblings (such as sarcoma in both a brother and a sister).

*American Association for Cancer Research Cancer Progress Report 2015*
*Adapted from: cancer.org/Cancer/CancerCauses/GeneticsandCancer/heredity-and-cancer.*
DIRECT-TO-CONSUMER GENETIC TESTING

Direct-to-consumer (DTC) genetic tests are marketed without requiring a health care provider to consumers, in contrast to tests that are ordered by a physician for a patient. This growing form of testing, also known as at-home testing, allows a consumer or patient to obtain access to their genetic information without necessarily involving a doctor or insurance company in the process. Below are a number of important facts about DTC genetic tests.

Potential Benefits of Using DTC Genetic Tests
These tests may encourage and empower consumers to take a proactive role in their health care.

Potential Risks of Using DTC Genetic Tests
These tests may mislead or misinform people about their health status.

DTC Genetic Tests and the FDA
DTC tests that claim to provide only information such as a person’s ancestry or genealogy are not regulated by the FDA. In February 2015, however, the FDA authorized marketing of the first DTC genetic test: 23andMe’s Bloom Syndrome carrier test. This test can help determine whether a healthy person has a variant in a gene that could lead to his or her children inheriting this serious disorder.

Because of the complexities of such tests, both the FDA and Federal Trade Commission recommend involving a health care professional in any decision to use DTC testing, as well as to interpret the results.

American Association for Cancer Research Cancer Progress Report 2015
BIOMEDICAL RESEARCH: WHAT IT IS AND WHO CONDUCTS IT

Biomedical research, as defined by the Organization for Economic Cooperation and Development (OECD), comprises:

- The study of specific diseases and conditions (mental or physical), including detection, cause, prophylaxis, treatment, and rehabilitation of persons.
- The design of methods, drugs, and devices used to diagnose, support, and maintain the individual during and after treatment for specific diseases or conditions.
- The scientific investigation required to understand the underlying life processes that affect disease and human well-being, including such areas as the cellular and molecular bases of diseases, genetics, and immunology.

Biomedical researchers are often categorized by the type of work they do, although some individuals perform several types of work and can be included in a number of categories. The types of biomedical researchers include, but are not limited to, the following:

- Basic researchers study animals, cells, molecules, or genes to gain new knowledge about cellular and molecular changes that occur naturally or during the development of a disease.
- Clinical researchers conduct clinical trials; study a particular patient or group of patients, including their behaviors; or use materials from humans, such as blood or tissue samples, to learn about the way the healthy body works, disease, or response to treatment(s).
- Population scientists, such as epidemiologists, social and behavioral scientists, and health services researchers, study the patterns, causes, costs, and effects of health and disease conditions in defined populations, or the effects of interventions on these conditions. These areas of research are highly collaborative and can span the spectrum from basic to clinical to population-wide research.
- Physician-scientists care for patients and conduct research. They may perform population, clinical, translational, or basic research.
RESEARCH MODELS

Researchers use a variety of models to mimic what happens in healthy and disease conditions. Below are some of the most common models used.

- **Cell lines** are cells of different origins that can be grown continuously in the laboratory.
- **Primary cells** are cells that are obtained directly from healthy or diseased tissues of either human or animal origin.
- **Tissues** are pieces of or entire healthy or diseased tissues from humans or animals. They are obtained through biopsies or surgery.
- **Organoids** are engineered 3-D structures generated from healthy or diseased components, that resemble an organ in cellular composition and organization.
- Many different animal models are used in biomedical research. Mice are the most commonly used models, but zebrafish and dogs are emerging as very good models for certain types of cancer. Less frequently used animal models include rodents other than mice, cats, fruit flies, nematodes (worms), pigs, and primates.
- **Other models** include yeast.
**Target validation.**
Potential therapeutic targets identified in discovery research are confirmed to play a role in a given disease.

**Target to hit.**
Large numbers of chemical or biological agents are screened to identify molecules that “hit” the target.

**Hit to lead.**
Positive hits are further tested to determine which bind the target with the most specificity.

**Lead optimization.**
The properties of the lead compound are refined to enhance potency and drug availability and to reduce side effects.

**Preclinical testing.**
Animal models are used to test for effectiveness of the optimized lead, identify any potential toxicity issues, and determine an optimal starting dose for clinical testing. The final compound is called the clinical candidate.

**Investigational new drug (IND).**
Prior to clinical testing, one or more clinical candidates are submitted to the FDA for approval to be used in clinical trials.

American Association for Cancer Research Cancer Progress Report 2015
WHAT IS THE FDA?

The U.S. Food and Drug Administration (FDA) is an agency within the Department of Health and Human Services that is responsible for protecting public health in numerous ways, including:

- Assuring the safety, efficacy, and security of therapeutics and medical devices.
- Regulating the manufacturing, marketing, and distribution of tobacco products, with an emphasis on reducing tobacco use by minors.
- Working with stakeholders across the biomedical research community to develop and disseminate new methods and technologies that make medicines safer and more effective.
- Providing the accurate, science-based information necessary to use medicines appropriately to maintain and improve health.

American Association for Cancer Research Cancer Progress Report 2015
Adapted from: http://www.fda.gov/AboutFDA/CentersOffices/default.htm
Phase I studies are designed to determine the optimal dose of an investigational therapy and how humans process it, as well as to identify any potential toxicities. These first-in-human studies can also demonstrate early efficacy or clinical results.

Phase II studies are designed to determine initial efficacy of an investigational therapy in a particular disease or selected group of patients, in addition to continually monitoring for adverse events or potential toxicities.

Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care (placebos are rarely used in cancer clinical trials).

Phase IV studies are also known as post-marketing studies. They are conducted after a therapy is provisionally approved by the FDA and provide additional effectiveness or “real-world” data on the therapy.
FDA’S EXPEDITED REVIEW STRATEGIES

The FDA has developed four evidence-based strategies to expedite assessment of therapeutics for life-threatening diseases like cancer.

**Accelerated approval.** Accelerated approval is based on assessing the effect of a therapeutic at an earlier stage by using a surrogate endpoint. Any therapeutic approved in this way must undergo additional testing following approval to verify that it provides clinical benefit. Olaparib (Lynparza) for the treatment of advanced ovarian cancer associated with deleterious germline BRCA mutations was approved under this pathway in December 2014.

**Fast track.** This designation is given to drugs that fill an unmet medical need and can be granted solely on the basis of preclinical data or data from nonhuman studies. Fast track applications may be evaluated through a “rolling” or continual review procedure, rather than waiting until study completion. Ipilimumab (Yervoy) for the treatment of metastatic melanoma was approved through fast track in March 2011.

**Breakthrough therapy.** A drug that shows substantial improvement over available treatment in early clinical studies can receive breakthrough therapy designation, making it eligible for all features of fast track designation (see above) and additional guidance from the FDA throughout the drug development process. One example of a therapeutic that was FDA approved, in December 2014, after receiving a breakthrough therapy designation is blinatumomab (BlinCYTO) for the treatment of acute lymphoblastic leukemia.

**Priority review.** Drugs that have the potential to significantly improve safety or effectiveness may be granted priority review after all clinical trials are completed. This allows the drug to be assessed within six months as opposed to the standard 10 months. Radium Ra 223 dichloride (Xofigo) was granted priority review and approved in May 2013 for the treatment of prostate cancer that has spread to the bone.
HOW DO THE THREE FDA-APPROVED HPV VACCINES DIFFER?

12 strains of HPV can cause cancer:
HPV6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59

3 vaccines can prevent infection with some of these strains.

CERVARIX
- Protects against infection with HPV16 and HPV18.
- FDA approved in 2009.
- FDA approved for:
  - preventing cervical cancer and precancers.
  - vaccination of females ages 9 to 25.

GARDASIL
- Protects against infection with HPV16 and HPV18, and HPV6 and HPV11 which cause genital warts.
- FDA approved in 2006.
- FDA approved for:
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of males and females ages 9 to 26.

GARDASIL 9
- Protects against infection with HPV6, 11, 16, 18, 31, 33, 45, 52, 58, and HPV6 and HPV11 which cause genital warts.
- FDA approved in 2014.
- FDA approved for:
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of females age 9 to 26 and males ages 9 to 15.

American Association for Cancer Research Cancer Progress Report 2015
Information is current as of July 31, 2015
# Using Radiation in Cancer Care

## Radiotherapy

Radiotherapy is the use of high-energy rays (e.g., gamma rays and X-rays) or particles (e.g., electrons, protons, and carbon nuclei) to control or eliminate cancer. It works chiefly by damaging DNA, leading to cell death.

## Types of Radiotherapy

### External Beam Radiotherapy
Directs radiation at the tumor from outside the body, it is the most common form of radiotherapy. Standard linear accelerators use electromagnetic fields to accelerate electrons, which can be used directly or collided with a metal target to generate high-energy X-rays. Electrons and photons (X-rays) are the most common sources of radiation in external beam radiotherapy.

**Conventional (2-D) external beam radiation therapy** delivers a high-energy X-ray beam from one or multiple directions. Imaging of the treatment area is typically performed using low-energy diagnostic X-rays. It is chiefly used in settings where high precision is not required, such as in the treatment of bone metastases.

**3-D conformal radiotherapy (3D-CRT)** uses specialized imaging, usually computed tomography, and/or magnetic resonance imaging and planning software to deliver high-energy X-rays via multiple beams that more precisely fit the shape and size of the tumor.

**Intensity-modulated radiotherapy (IMRT)** is a further refinement of 3D-CRT that more precisely focuses and shapes the radiation by dividing each beam into many “beamlets,” each of which can have a different intensity. IMRT is particularly useful when a sharp dose gradient is required between the tumor and sensitive tissues, as when the optic nerves.

**Intraoperative radiation therapy** uses electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures.

**Stereotactic radiotherapy** is used in both stereotactic surgery (SRS) and stereotactic body radiotherapy (SBRT). It uses many (typically more than eight) beams with a highly sophisticated imaging system to deliver radiation to very well-defined smaller tumors. Typically, SRS is used to treat tumors of the brain and central nervous system, whereas SBRT can be used on small tumors within larger organs of the body.

### Particle Therapy
Uses protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that pass through the body, losing energy and causing damage to the nontumorous tissues through which they pass, these heavier particles deposit most of their energy in the target. In this manner, particle therapy can deliver higher doses with less damage to surrounding tissue. Although this therapy is of great interest, proton facilities are much more expensive than traditional facilities, and the overall benefit to the patient is still being determined.

### Brachytherapy
Places small radioactive sources in or near to the tumor. There are two forms of brachytherapy.

- **Permanent implantation** implants radioactive sources into the tumor, for example, placement directly into the prostate for the treatment of prostate cancer or into the tumor vasculature (see radiolabelization at right).
- **Temporary placement** of radioactive sources, in one form of this treatment, moderately active sources are placed for 1-4 days; for example, in the treatment of soft-tissue sarcoma. In “high-dose-rate” brachytherapy, a highly active source is inserted for a few minutes; for example, in the curative treatment of cervical cancer.

### Uses of Radiotherapy

**CIRTATIVE**radiotherapy seeks to completely eliminate a cancer, particularly small cancers, as well as locally advanced cancers as part of combination therapy.

**Neoadjuvant**radiotherapy is used to reduce or control a cancer so that it can be subsequently treated by a different method such as surgery.

**Adjuvant**radiotherapy seeks to eliminate any remaining cancer following prior treatment.

**Palliative**radiotherapy is used to reduce or control symptoms of disease when cure by another method is not possible.

### Interventional Radiology
Combines imaging with minimally invasive techniques designed to treat cancer locally, including:

- **Chemoembolization** is a process by which therapeutic-coated particles are injected directly into the tumor vasculature in order to prevent blood flow and increase the therapeutic concentration to very high levels.
- **Cryoadsorption** is a technique wherein needles are directly inserted into the tumor and cooled to very cold temperatures, causing tumor cell death.
- **High-intensity focused ultrasound** applies high-intensity focused ultrasound waves to locally heat and destroy tumors.
- **Microwave ablation** uses microwave radiation to locally heat and destroy tumors.
- **Radiofrequency ablation** is the injection of radiofrequency microwaves directly into the tumor vasculature for example, injection of 90Y microspheres into a liver tumor via the hepatic artery.
- **Radiofrequency ablation** is a technique wherein needles are directly inserted into the tumor and an electrical current used to heat the needle, causing tumor cell death.
THE CHALLENGE OF TREATMENT RESISTANCE

Diversity, or heterogeneity, among cancer cells within and between tumors, is ultimately what drives insensitivity to treatment, which in turn leads to treatment resistance. Some examples of heterogeneity are as follows:

Not all cells in a tumor may be rapidly dividing; those that are not are insensitive to treatments targeting rapidly dividing cells.

Some cancer cells in a tumor may contain mutations in the target of a given treatment that render the treatment ineffective.

Redundancies among signaling networks fueling proliferation can enable cancer cells to become resistant to a treatment.
COMPANION DIAGNOSTICS

The effective therapeutic use of most drugs targeting particular cancer-driving molecular abnormalities often requires tests called companion diagnostics. Companion diagnostics:

- are stringently tested for their safety, accuracy, sensitivity, and fidelity;
- are regulated by the U.S. Food and Drug Administration;
- accurately match patients with the most appropriate therapy;
- allow patients to receive a treatment to which they are most likely to respond; and
- allow patients identified as very unlikely to respond to be spared any adverse side effects of the therapy.

American Association for Cancer Research Cancer Progress Report, 2015
EDITING THE EPIGENOME

As of July 31, 2015, there were six FDA-approved anticancer therapeutics that target proteins that read, write, or erase epigenetic marks. These agents target either a family of writers called DNA methyltransferases or a family of erasers called histone deacetylases.

DNA methyltransferases add epigenetic marks called methyl groups to DNA. The anticancer therapeutics azacitidine (Vidaza) and decitabine (Dacogen), which are FDA approved for the treatment of myelodysplastic syndromes, block the ability of DNA methyltransferases to add methyl groups to DNA.

Histone deacetylases remove epigenetic marks called acetyl groups from histones. The anticancer therapeutics belinostat (Beleodaq), romidepsin (Istodax), and vorinostat (Zolinza), which are FDA approved for the treatment of certain types of lymphoma, as well as panobinostat (Farydak), which is approved for the treatment of multiple myeloma, block the ability of histone deacetylases to remove acetyl groups from histones.
HOW IMMUNOTHERAPEUTICS WORK

The ways in which different immunotherapeutics work to benefit patients varies:

- Some release the brakes on the natural cancer-fighting power of the immune system, for example, nivolumab (Opdivo) and pembrolizumab (Keytruda).
- Some enhance the cancer-killing power of the immune system by triggering the cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).
- Some increase the killing power of the immune system by providing more cancer-targeted immune cells, called T cells; these are called adoptive T-cell therapies, for example, CTL019 and JCAR015.
- Some flag cancer cells for destruction by the immune system, for example, dinutuximab (Unituxin).
- Some increase the killing power of the immune system by enhancing T-cell function, for example, interleukin-2 (Aldesleukin).
- Some comprise a virus that preferentially infects and kills cancer cells, releasing molecules that trigger cancer-fighting T cells; these are called oncolytic virotherapeutics, for example, talimogene laherparepvec (T-Vec).

American Association for Cancer Research Cancer Progress Report 2015
There are two main types of adoptive T-cell therapy.

Chimeric antigen receptor (CAR) T-cell therapy. T cells are harvested from blood or bone marrow and genetically modified before being expanded in number. This modification targets the T cells specifically to the patient’s cancer and triggers them to attack when they get there.

Tumor-infiltrating lymphocyte (TIL) therapy. T cells are harvested directly from a patient’s tumor and expanded in number in the laboratory. Many of these T cells naturally recognize the patient’s cancer.
SURVIVING A CANCER DIAGNOSIS AS A CHILD OR ADOLESCENT

16,500
U.S. children and adolescents (ages 0-19) will be diagnosed with cancer in 2015.

83%
Overall five-year relative survival rates for children (ages 0-14) diagnosed with cancer.

85%
Overall five-year relative survival rates for adolescents (ages 15-19) diagnosed with cancer.

110,000
U.S. cancer survivors ages 0-19 were alive on Jan. 1, 2014.

380,000
Survivors of cancer diagnosed by the age of 19 were alive on Jan. 1, 2010.

As highlighted by Congressman Michael McCaul in the AACR Cancer Progress Report 2014, survivors of cancer diagnosed by the age of 19 face particularly demanding challenges. For example:

98%
of adult survivors of childhood cancer have one or more chronic health conditions and 68 percent have severe/disabling or life-threatening conditions.

5%
of survivors of a cancer diagnosed in childhood develop a second cancer between 5 and 30 years after their initial diagnosis.
LIFE AFTER A CANCER DIAGNOSIS IN THE UNITED STATES

When an individual becomes a cancer survivor, his or her life is changed irrevocably. Cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, psychosocial, and financial challenges as a result of the cancer diagnosis and treatment.

Among the challenges experienced from the time of diagnosis to the end of initial treatment are:

- Choosing a physician(s) and treatment facility;
- Choosing among a variety of treatment options; and
- Managing side effects of cancer and cancer treatment, many of which persist long term (see below).

Many challenges experienced by cancer survivors begin during cancer treatment and continue long term, but others can appear months or even years later. These long-term and late effects include, but are not limited to:

- Bone density loss (osteoporosis);
- Cognitive impairment sometimes referred to as “chemo brain”;
- Diagnosis with a new form of cancer(s);
- Distress, which can interfere with a person’s ability to cope effectively with cancer and its treatment;
- Fatigue that is very severe and often not relieved by rest;
- Fear of cancer recurrence;
- Heart damage (cardiotoxicity);
- Infertility;
- Lung (pulmonary) damage;
- Lymphedema, swelling, most often in the arms or legs, that can cause problems in functioning and pain;
- Pain;
- Premature aging;
- Recurrence of original cancer; and
- Sexual dysfunction.

Although all cancer survivors face challenges, some segments of the population experience more than others. In addition, pediatric cancer survivors (ages 0–14 at diagnosis) are particularly at risk for critical health-related problems because their bodies are still developing at the time of treatment; whereas adolescents (ages 15–19) and young adults (ages 20–39) have to adapt to long-term cancer survivorship while beginning careers and thinking about starting families of their own.

American Association for Cancer Research Cancer Progress Report 2015
BUILDING BLOCKS TO FURTHER PRECISION MEDICINE

To maximize the potential of precision medicine, we must:

- Provide robust, sustained, and predictable funding increase for the NIH, NCI, and FDA;
- Support regulatory science initiatives;
- Increase patient participation in precision medicine initiatives;
- Develop and train the biomedical research workforce of tomorrow; and
- Support precision prevention efforts.

American Association for Cancer Research Cancer Progress Report 2015
Precision medicine is treating patients based on characteristics that distinguish individuals from other patients with the same disease. To fully implement precision medicine, we need tests that can accurately match a patient with the most appropriate therapy. Given that these tests are essential to the treatment of patients, ensuring that they are safe, reliable, and accurate is paramount, irrespective of where and how these tests are developed. Therefore, a single, predictable, risk-based regulatory framework implemented by the FDA to evaluate diagnostic tests will not only safeguard patients, but it will also further advance precision medicine.