WORLD CANCER INSTITUTE

CANCER RESEARCH

MOLECULAR TARGETS AND CANCER THERAPEUTICS

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The World Cancer Institute is a global forum and catalyst for worldwide dialogue about the most challenging disease of our time. The Institute's primary objective is to enlarge the clinical framework and therapeutic possibilities resulting from the convergence of integrative cancer care conjoined with treatment programs which may also provide enhanced quality of life.

HEALTHMEDICA

Longevity Medical Centers

Imagine...If we could Regain, Maintain and Sustain our Desired Quality of Life During and After Treatment for Cancer?

Introducing

HealthMedica OncoSpa

IntraTherapies AlphaProgram

Commencing in 2008, HealthMedica, in conjunction with its clinical research affiliate, World Cancer Institute, has studied the complex and contradictory aspects of cancer, and the psychophysical and functional effects of Standard of Care cancer treatments, as defined by the American Society of Clinical Oncology (ASCO).

HealthMedica's focus was observing the impact of numerous treatment protocols and assessing the effects of chemotherapy and radiation on near and long term wellness ranging from state of mind / mood and continuity of physical energy to overall perceived Quality of Life (QoL) in men women and children.

HealthMedica then initiated research to explore a broad range of ideas and technologies which could possibly provide a healthier journey during the challenging aspects of all categories of cancer treatments.

Clearly, as millions of cancer patients and families have painfully recognized, surviving cancer inevitably means surviving the treatment process as well.

HealthMedica
OncoSpas

Quality of Life and Wellness Support During and After Treatment for Cancer

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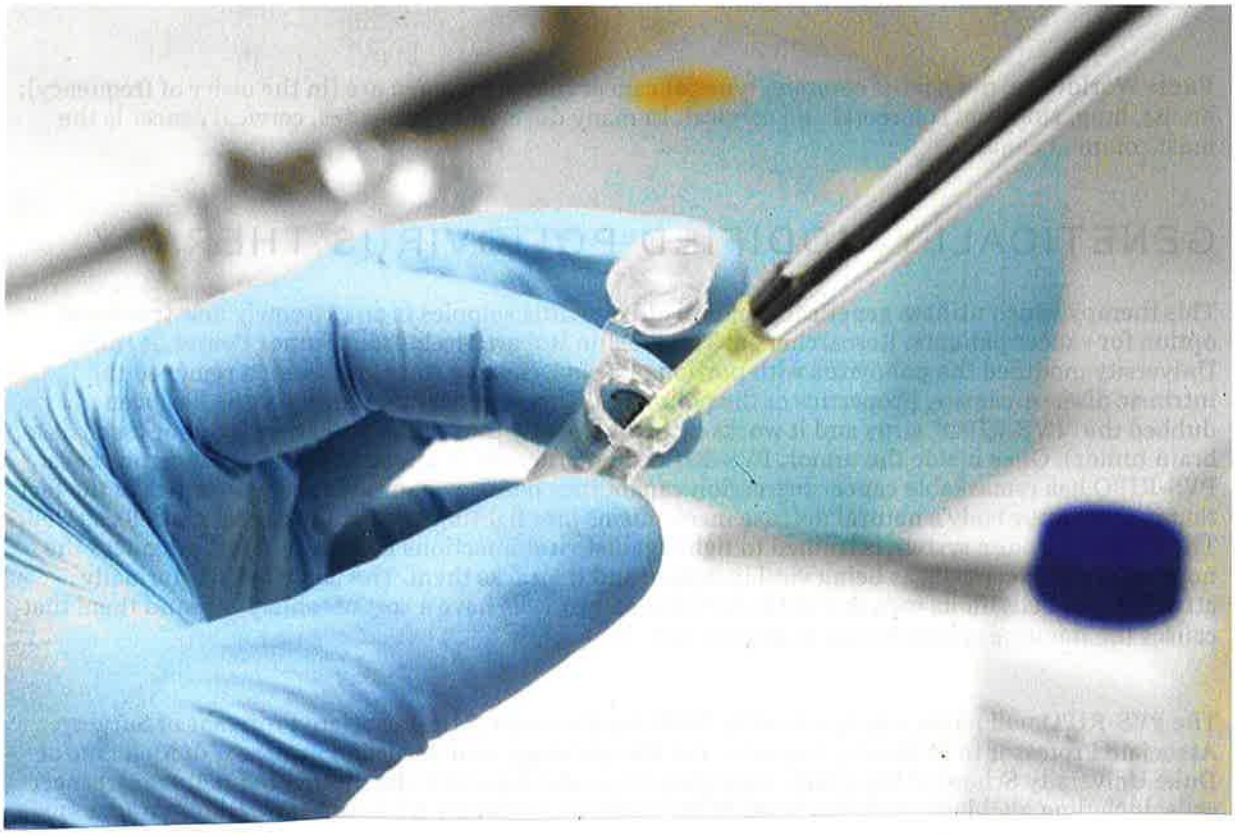

WORLD CANCER INSTITUTE INC.
IECT -INTRATHERAPIES EPIGENETIC CANCER THERAPEUTICS
CANCER VX / ONCO VX

Targeting Cancer

The dawn of precision medicine

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INTRODUCTION

The World Cancer Institute is a global forum and catalyst for worldwide dialogue and the advancement of clinically-validated and evidence-based treatment modalities directed toward the most challenging disease of our time. The Institute's primary objective is to enlarge the clinical framework and therapeutic possibilities resulting from the convergence of integrative cancer care conjoined with treatment programs which also have demonstrated promising indications in providing measurable, enhanced quality of life during treatment programs.

A New Perspective in Global Cancer Treatment

World Cancer Institute's global initiatives are directed toward advancing Oncology Clinical Protocols conjoining new cancer discoveries as pathway-specific monotherapies, with important new DNA targeting drugs based on molecular cancer genetics, Epigenetics, DNA programmable genetic pharmacology and other emerging integrative cancer therapies and immunotherapeutics.

World Cancer Institute's mandate for proactive care conjoins clinical objectives targeting a broader spectrum of balanced intervention and cancer preventive modalities during cancer treatment programs combined with the more informed use of biologic therapeutics for enhancing the body's internal restorative capacities to heal.

World Cancer Institute initiates proactive, leading edge oncologist reviewed processes and clinical assessment of diverse but clinically compatible integrative platforms. The resultant therapeutic programs and protocols target deeper systemic processes enabling the body's internal cellular restorative resources to intervene in the treatment regimen. These continuing objectives are directed toward advancing progressive treatment programs with clinically validated, evidenced-based outcomes targeting:

- Progression Free Survival (PFS)
- Overall Survival (O/S) inclusive of measurable enhanced Quality of Life (QOL) during treatment
- Reduction of traditional chemotherapy treatment side effects and toxicity in late stage cancers of all types. Driven by the dynamics of personalized medicine for optimal near and long term benefit, World Cancer Institute, and most all established and responsible medical institutions, recognize chemotherapy's clinically acknowledged and documented history of contributing to poor prognostic outcome which may often be the prime cause, or certainly a major factor, in the acceleration of overall physical, mental and emotional decline in a patient's condition within virtually all second, third and fourth line 'standard of care' chemotherapy treatment settings.

The Medical Weapon that Raises our DNA IQ to Eradicate Cancer

Increasing Rates of Cancer

Treating cancer is a healthcare priority internationally – and the needs for effective and cost-efficient treatment are increasing. In 2008, the World Health Organization (WHO) estimated that there were 12 million cases around the globe. WHO predicts that this figure will rise to more than 20 million new cases in 2025. The financial ramifications are enormous, and growing as well; as of 2009, anti-cancer drug sales exceeded $50 billion and this number will only increase as the number of cases grows.

Challenges of Current Oncological Treatment

The challenges that we face in oncological treatment are not only the increasing disease rates and financial costs associated with traditional Western cancer treatments. The truly critical issues are patient-focused. Despite extensive time, investment, and research into the topic, current cancer treatment is inadequate to meet the needs of many, if not most, patients. Traditional treatments include chemotherapy, surgery, radiation, and hormone therapy in various combinations and orders of administration, depending on the particular type of cancer and the specific diagnosis and co-morbidities. These approaches, however, are only effective for a small percentage of cancers. Traditional treatment often does not eliminate all cancer cells from the body; often rogue cells are left, which can lead to recurrence or metastasis. In addition, drug-resistant cancer cells are on the rise; drug resistance is often an issue when high levels of medication are used frequently.

From the patient's perspective, one of the biggest challenges is that traditional oncology treatments are often more severe to patient than the cancer was in the first place. Chemotherapy drugs are typically designed to target rapidly dividing cells, which can include both cancer and normal cells. The standard approach is to administer the maximum tolerable dosage and then manage the side effects, rather than to consider the negative effects on the body as well as on the cancer cells when establishing the dosage. As a result, the side effects of these chemotherapy drugs produce a very poor quality of life for patients, both in terms of physical symptoms, including pain and fatigue, as well as mental health issues such as bewilderment and disruption in mood and emotional well being. Cancer therapeutics has historically presumed that the patients has the psycho-emotional ability to withstand treatment that will most likely make them violently ill while they're on the path to ostensibly "restored health." As a result, patients don't so much as survive the disease as adapt to the treatment and its effects, some of which can be quite long lasting, potentially extending years after the end of treatment.

Epigenetics: A New Approach to An Old Problem

Epigenetics may show a new possible solution to this conundrum. For years, scientists thought that cancer was caused by "errors" in a critical stretch of DNA. But we have become increasingly aware of the role of epigenetic factors in cancer which, unlike genetic damage, can be reversed. A relatively new scientific field, epigenetics has been considered "alternative" and fringe, but has recently become increasingly accepted in the mainstream. While DNA may be set in stone, epigenetic markers can be modified, particularly methyl groups – carbon-hydrogen molecules that attach to genes and can functionally turn them on or off. For instance, pregnant women who take folic acid and vitamin B-12 may be affecting their fetuses epigenetics, thereby decreasing the risk of asthma and brain and spinal cord defects. In short, aging is a struggle between good and bad genes and epigenetics can tip the balance for 'good.'

At IntraTherapies Epigenetic Cancer Therapeutics (IECP), we have developed the concept of DNA IQ. We define this term to mean: "Self enhancing neuro-cellular and onco-algorithmic biochemical/biomedical mechanisms, protocols and therapeutics which conjoin neurobiology and epigenetic factors, affecting systemic homeostasis across the spectrum of epigenomic functions, principally driven by exogenous and endogenous factors including human senescence."

Epigenetic therapy avoids the pitfalls of conventional chemotherapy drugs by using a targeted pathway-specific approach. Also, they are much less toxic than chemo drugs. And they do not lead to the development of chemotherapy-resistant cancer cells. Another advantage to epigenetics is that

cancer treatments that reverse cancer-inducing epigenetic changes can be less toxic to patients than conventional chemotherapy drugs.
The two most common approaches to epigenetic treatment is DNA methylation and histone acetylation. DNA methylation, which involves adding a methyl group to a gene molecule. DNA methylation can act as an on-off switch – typically stopping rather than encouraging gene expression.

Similarly, histone acetylation can affect genetic expression. It occurs by addition of an acetyl group to the gene molecule. An imbalance in the equilibrium of histone acetylation has been linked to cancer.

A relatively new alternative to traditional cancer treatment, IECT is a clinical protocol based on molecular
cancer and DNA programmable genetic pharmaceuticals to inhibit the growth, replication, and proliferation of human cancer cells. Specifically, the approach takes advantage of DNA demythlation techniques conjoined with histone deacetylase inhibitors to target cellular mitochondria and to modulate and regulate the mitotic spindle and microtubule interface. Developed by the World Cancer Institute, Inc., headed by Nathan Sassover, the approach is poised to make a real difference in the cancer world.

The Global Cancer Perspective:

The aging of populations, lifestyle changes in the developing world, together with significant advances in pharmacotherapy and diagnostics, will drive cancer treatment.

These new treatment options include:

- . Immunotherapies
- . Novel antineoplastic drugs.
- Epigenetics
- DNA Programmable Genetic Pharmacology

World Cancer Institute | HealthMedica

The World Cancer Institute is an affiliate of HealthMedica — a proactive health sciences group that views transformative medicine as the basis for transformative healthcare.

HealthMedica was founded by inventor / technologist, Nathan Sassover, whose cross-industry innovations have resulted in medical discoveries and therapeutic platforms addressing the neurobiology of aging as well as clinical developments based on molecular cancer genetics and DNA programmable genetic pharmacology.

His patented inventions and discoveries further extend to diverse technology venues ranging from micro-electronics to advanced Internet broadcast network architecture.

With a background that consistently demonstrates awareness of technology-driven opportunities before they are generally recognized, Nathan Sassover's leading edge innovations have created several industry sectors and unique market segments.

Surviving Cancer

COMING AT CANCER

IN WAYS CANCER

DOESN'T SEE COMING

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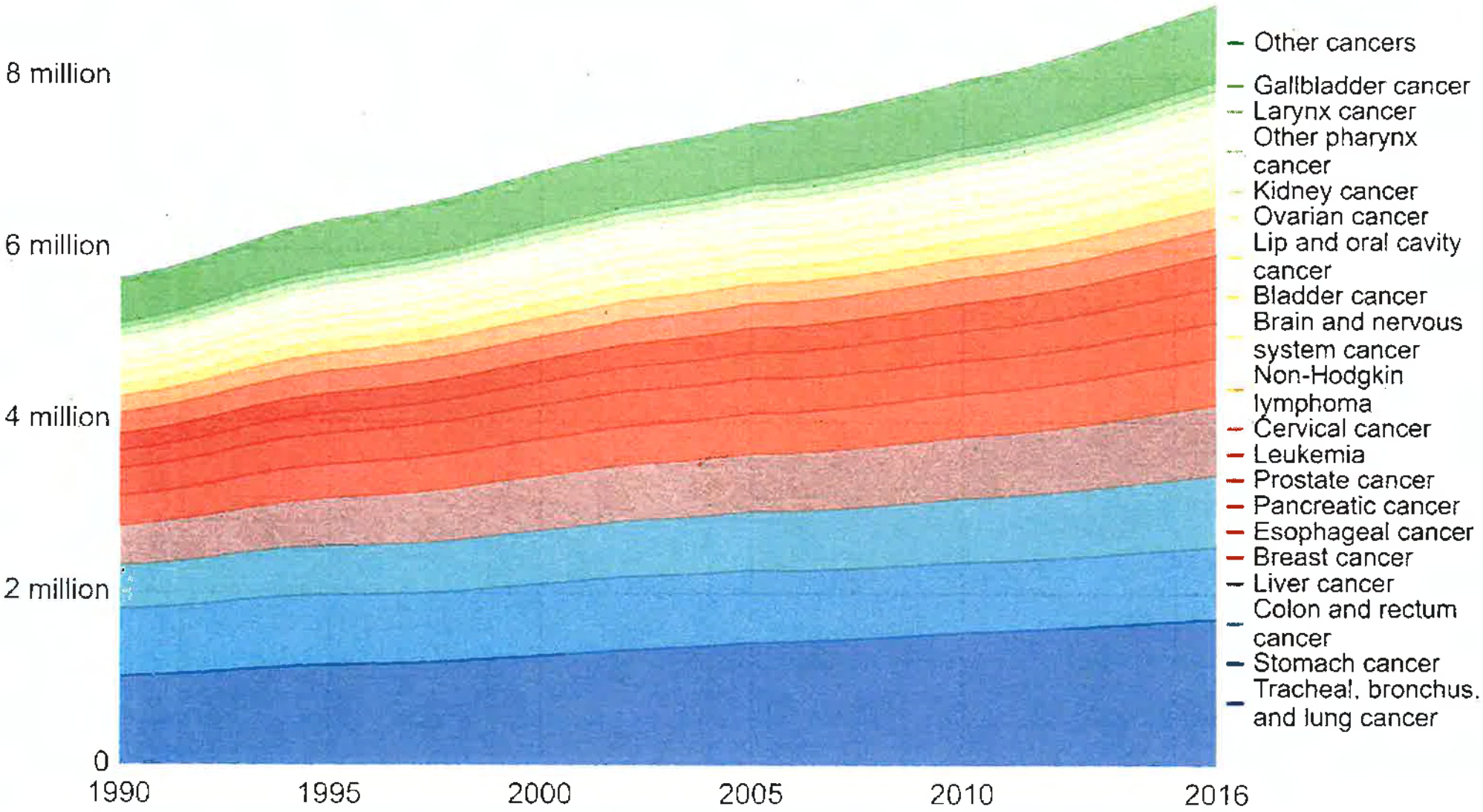
Cancer deaths by type, World

Annual cancer deaths by cancer type, measured as the total number of deaths across all age categories and both sexes. Smaller categories of cancer types with global deaths <100,000 in 2016 have been grouped into a collective category 'Other cancers'. See sources for list of grouped cancers.

Our World in Data



Source: IHME, Global Burden of Disease (GBD)

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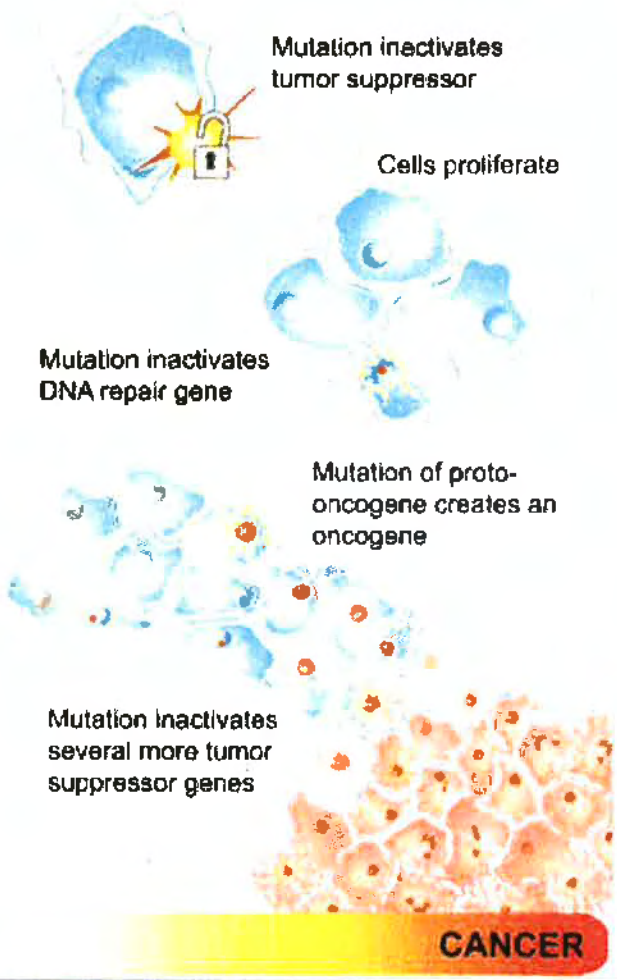


Credit: Mariana Ruiz Villarreal (LadyofHats) for CK-12 Foundation

World Cancer Institute Inc.
IECT-IntraTherapies Epigenetic Cancer Therapeutics

How Cancer Develops. Mutations in tumor-suppressor genes and proto-oncogenes leads to cancer.[Figure2]

Oncogenes

The products of proto-oncogenes are required for normal growth, repair and homeostasis. However, when these genes are mutated, they turn into oncogenes and play a role in the development of cancer. Proto-oncogenes may be growth factors, transcription factors, or other proteins involved in regulation. A very common oncogene, ras, is normally a regulatory GTPase that switches a signal transduction chain on and off. Ras and Ras-related proteins are products of oncogenes found in 20% to 30% of human tumors. The transcription factor myc is an oncogene often seen mutated in Burkitt's lymphoma, a rare type of lymphoma, a cancer of the lymphocytes.

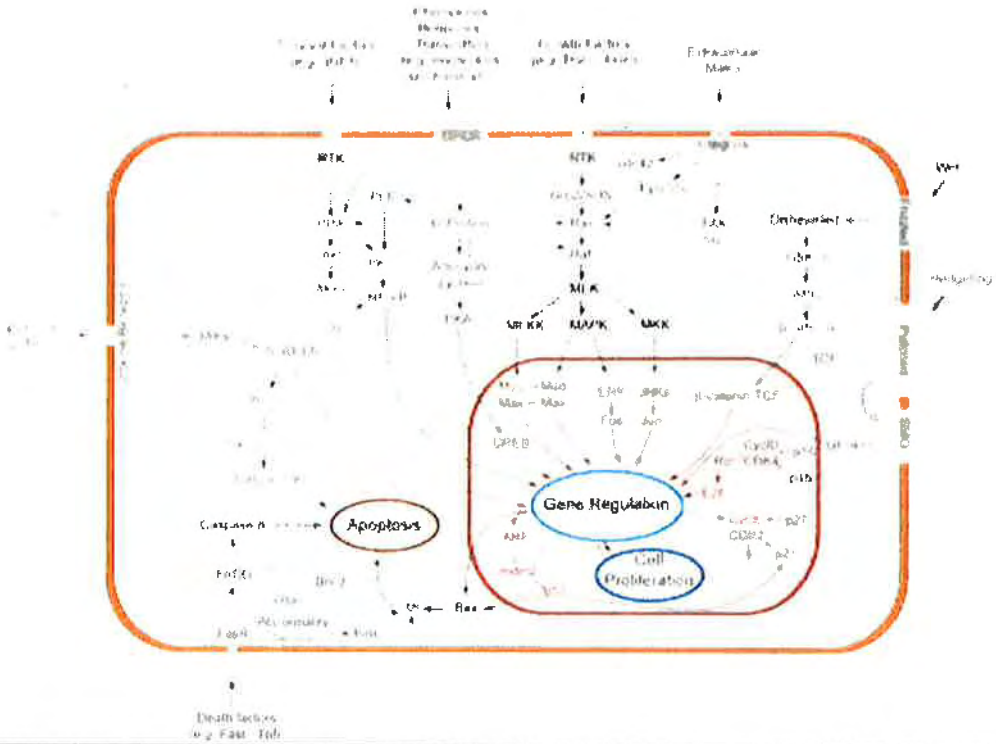
Ras is a G protein, a regulatory GTP hydrolase that cycles between an activated and inactivated form. When a growth factor binds to its receptor on the outside of the cell, a signal is relayed to Ras. As a G protein, Ras is activated when GTP is bound to it. The active Ras then passes the signal to a series of protein kinases, regulatory proteins that eventually activate transcription factors to alter gene expression and produce proteins that stimulate the cell cycle (Figure below). One important recipient of Ras signaling is the mitogen-activated protein kinases (MAPK). Once activated, MAPK transmit signals downstream to other protein kinases and gene regulatory proteins. This cascade of reactions is typical of a signal transaction pathway.

Many of the genes and proteins involved in signal transduction pathways are interconnected to Ras. Any mutation that makes Ras more active or otherwise interrupts the normal signal transduction pathways (Figure below) may result in excessive cell division and cancer.

IECT- IntraTherapies Epigenetic Cancer Therapeutics and the Re-Activation of Tumor Suppressor Genes

Tumor suppressor genes, as their name implies, normally suppress tumorigenesis. When this process is disturbed, such as by a mutation, tumor suppression may not be inhibited as normal. An example of a tumor suppressor gene is p53, which encodes a 53,000 dalton (53kd) protein,

The p53 gene is activated by DNA damage. DNA may be damaged by ultraviolet light, and any damaged DNA may be harmful to the cell. Mutations causing problems with any of the components of Figure below, may lead to the development of cancer. So that damaged DNA is not replicated, the cell cycle must be temporarily stopped so that the DNA can be repaired. The p53 tumor suppressor gene encodes a transcription factor that regulates the synthesis of cell cycle inhibiting proteins (Figure below). p53 often activates a gene named p21, whose protein product temporarily stops the cell cycle. If the DNA can not be repaired, p53 activates other genes that lead to cell death, or apoptosis. This prevents the cell from passing on damaged DNA. If the p53 tumor suppressor gene is defective, as by mutation, DNA damage in the cell may accumulate and the cell may survive to replicate the damaged DNA. The damaged DNA would then be passed to other cells through many cell divisions, and cancer could develop.



Signal transduction pathways.

Ras (upper middle section) activates a number of pathways but an especially important one seems to be the mitogen-activated protein kinases (MAPK). MAPK transmit signals downstream to other protein kinases and gene regulatory proteins. Note that many of these pathways are initiated when a signal binds to its receptor outside the cell. Most pathways end with altered gene regulation and cell proliferation. The p53 tumor suppressor protein is shown at the lower section of the figure stimulating p21. The interrelated complexity of the pathways demonstrate the significant role these play in the cell.[Figure3]

Summary

- At least two separate mutations are necessary to develop cancer. These mutations may occur in proto-oncogenes and/or tumor suppressor genes.
- Proto-oncogenes and tumor suppressor genes have an interconnected relationship within the cell; many are involved in signal transduction cascades.

TO BEAT CANCER THINK LIKE CANCER

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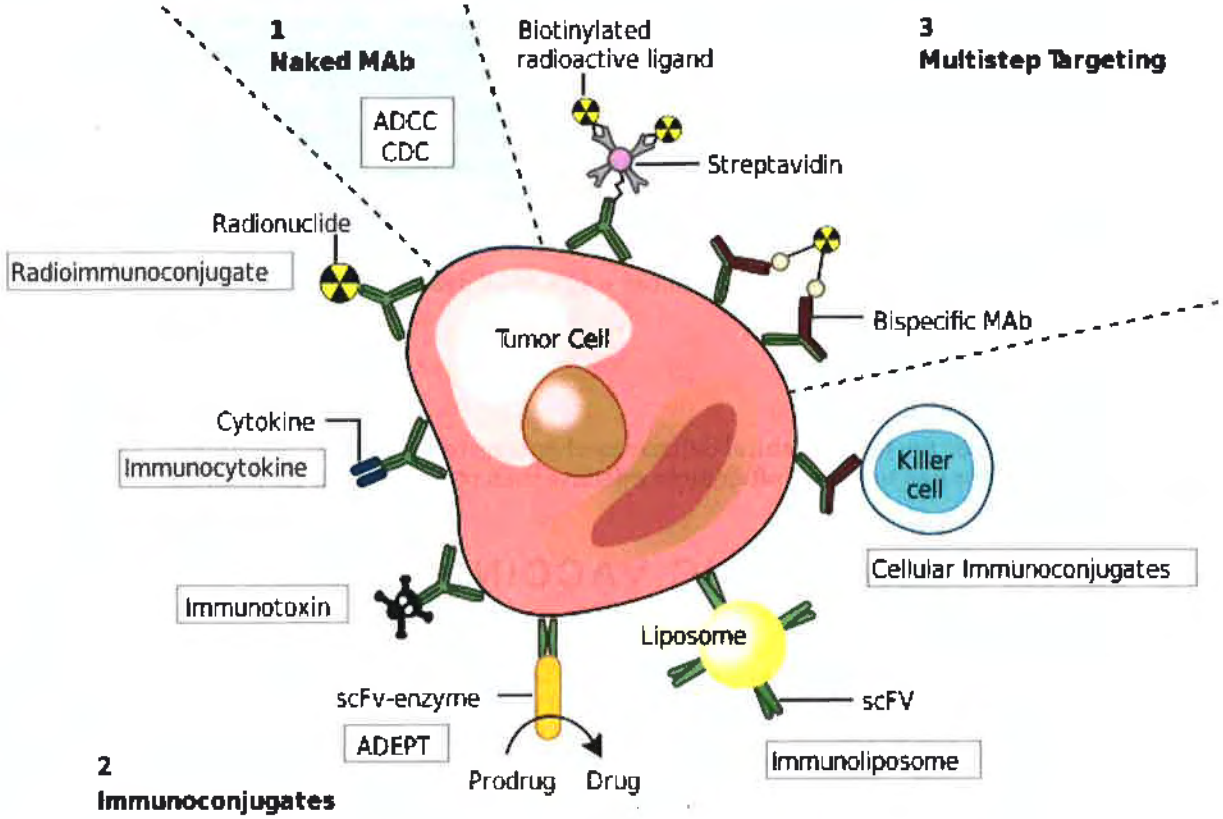
CANCER VX / ONCO VX
SPECTRUM OF PROTOCOLS



(*Image Source*)

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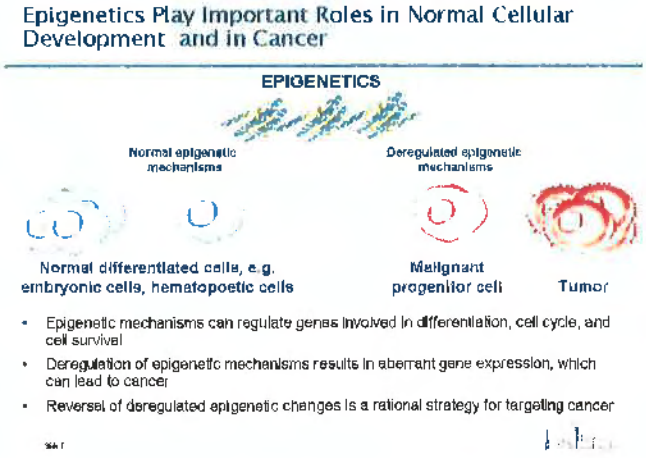

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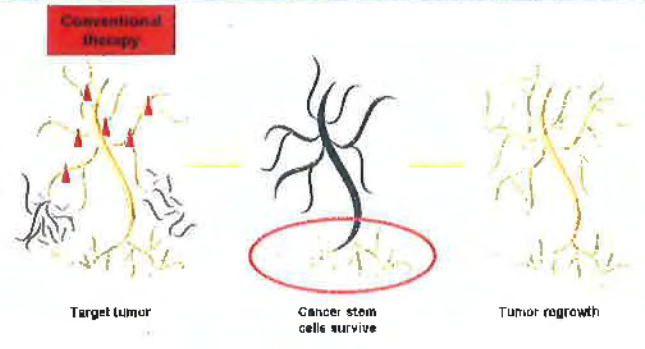

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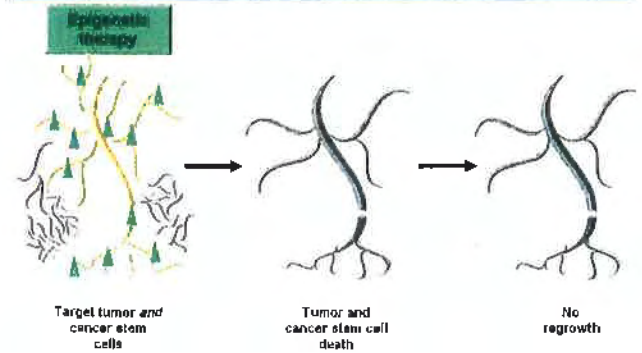


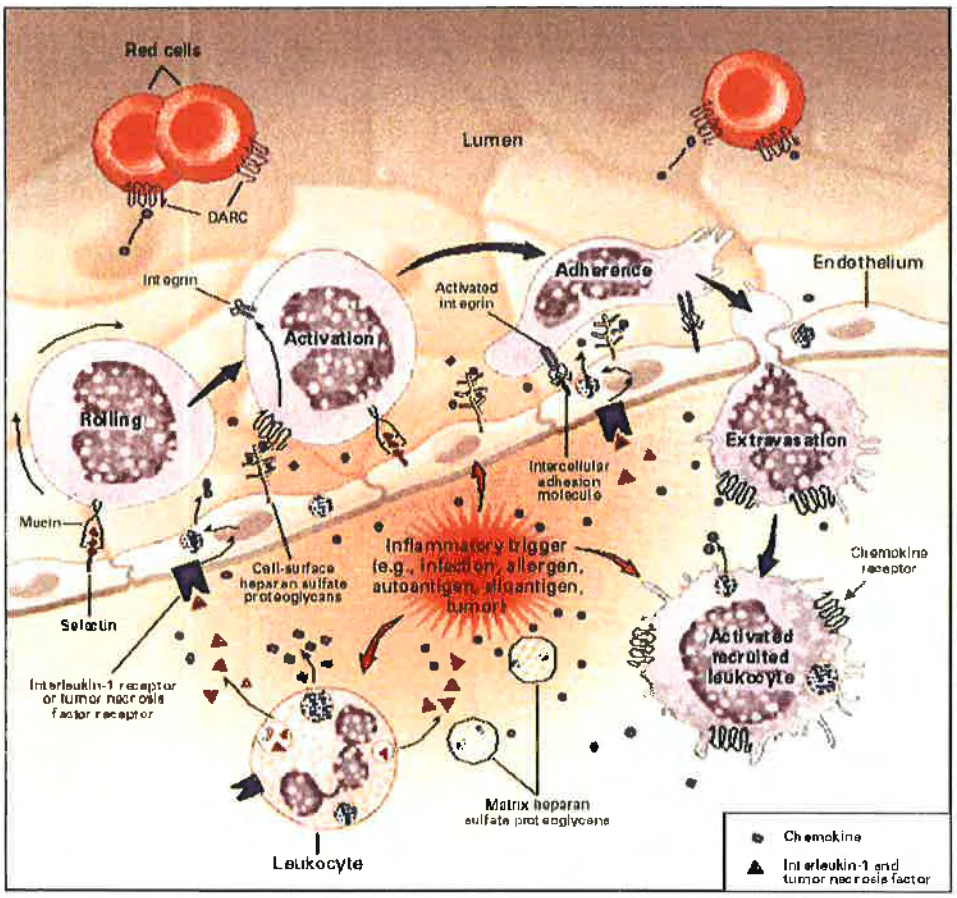
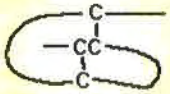
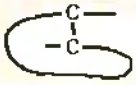
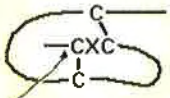
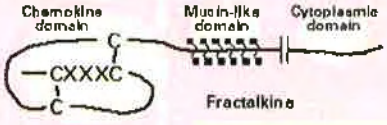


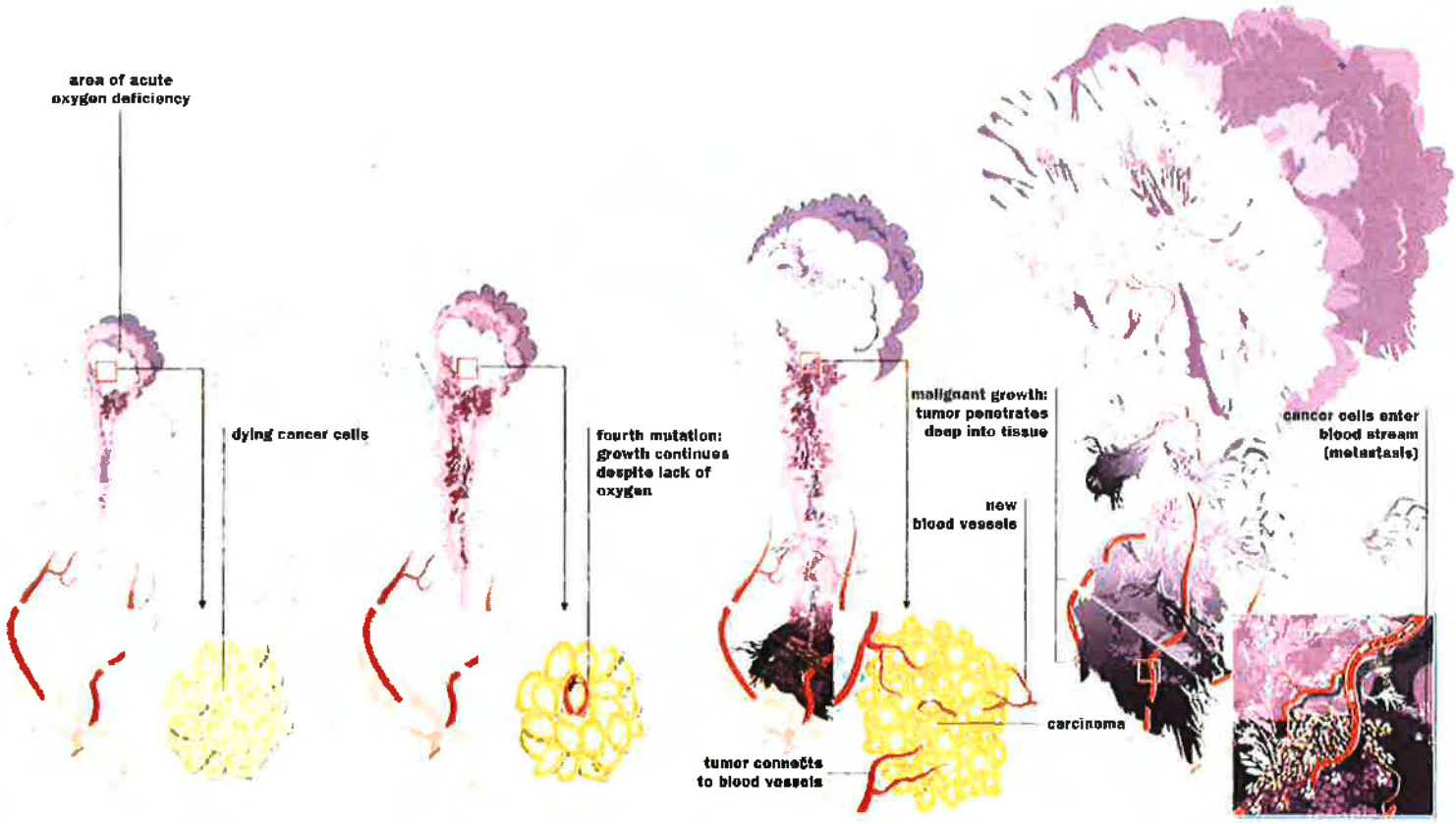
Fig. 2: Chemokines and Leukocyte Movement.

Chemokines are secreted at sites of inflammation and infection by resident tissue cells as well as, resident and recruited leukocytes. Chemokines are locally retained on matrix and cell-surface heparan sulfate proteoglycans. An established chemokine concentration gradient is surrounding the inflammatory stimulus. Leukocytes rolling on the endothelium in a selectin-mediated process are brought into contact with chemokines recruiting cell-surface heparan sulfate proteoglycans. Chemokine signaling activates leukocyte integrins, leading to firm adherence and extravasation. The Duffy antigen receptor for chemokines (DARC), a promiscous erythrocyte chemokine receptor, functions as a sink, removing chemokines from the circulation and thus helping establishing a tissue-bloodstream chemokine gradient (adapted from Luster A.D., 1998).

Chemokine	Receptor	Cell Type
Chemokine receptor		
MCP-3, -4; MIP-1α; RANTES MCP-3, -4; eotaxin-1, -2; RANTES	CCR1 CCR3	Eosinophil 
MCP-1, -2, -3, -4, -5 MCP-3, -4; eotaxin-1, -2; RANTES	CCR2 CCR3	Basophil 
CC  MCP-3, -4; MIP-1α; RANTES MCP-1, -2, -3, -4, -5 MIP-1α, MIP-1β, RANTES I-309 MDC, HCC-1, TECK	CCR1 CCR2 CCR5 CCR8 ?	Monocyte 
Fractalkine	CX_3CR1	
SDF-1	CXCR4	
MCP-3, -4; MIP-1α; RANTES MCP-1, -2, -3, -4, -5 TARC MIP-1α, MIP-1β, RANTES MIP-3β (ELC) PARC, SLC, 6CKine (Exodus-2)	CCR1 CCR2 CCR4 CCR5 CCR7 ?	Activated T cell 
Fractalkine	CX_3CR1	
IP-10, MIG, I-TAC	CXCR3	
C  PARC, DC-CK1	?	Resting T cell 
Lymphotactin	?	
SDF-1	CXCR4	
CXC  MCP-3, -4; MIP-1α; RANTES MCP-1, -2, -3, -4, -5 MCP-3, -4; eotaxin-1, -2; RANTES TARC MIP-1α, MIP-1β, RANTES MIP-3α (LARC, Exodus-1) MDC, TECK	CCR1 CCR2 CCR3 CCR4 CCR5 CCR6 ?	Dendritic cell 
SDF-1	CXCR4	
Glutamic acid–leucine–arginine Interleukin-8, GCP-2 Interleukin-8, GCP-2; GRO-α, -β, -γ; ENA-78; NAP-2; LIX	CXCR1 CXCR2	Neutrophil 
CXXXC  MCP-1, -2, -3, -4, -5 MIP-1α, MIP-1β, RANTES	CCR2 CCR5	Natural killer cell 
Fractalkine	CX_3CR1	
IP-10, MIG, I-TAC	CXCR3	

Cancer Out of Control

Of one thing we can be sure: the entire process is set in motion by defects in the genes. They initiate a chain of events that eventually enable cancer cells to travel across natural boundaries and spread to other tissue. From mutation to metastasis – the insidious path of an illness



Crisis
Prolific growth leads to an acute shortage of oxygen and other nutrients in the polyp's interior (grey area). Most cells in this area die

Deadly Trick
Within this mass of cells, only those survive that have acquired a fourth mutation, on chromosome 17. Normally, the protein created with the aid of the p53 gene orders cells suffering from stress or genetic damage to self destruct. If this mechanism fails, cancer cells escape their pre-programmed fate. Some cells even become capable of dividing in the absence of oxygen

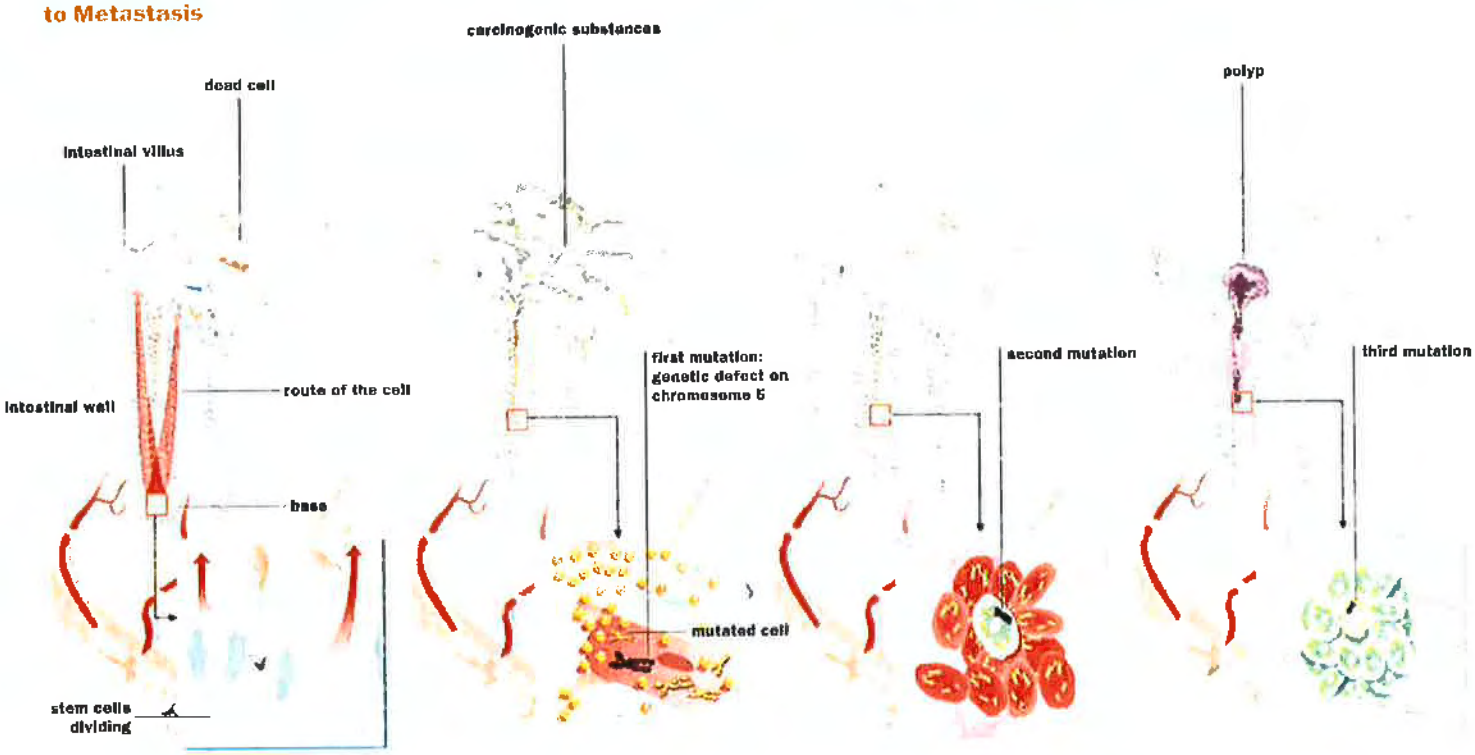
Malignancy
Gradually the tumor grows out of control. In almost 85 percent of all malignant tumors, crucial repair systems have been destroyed and genetic abnormality increases with each cell division. The cancerous growth forces surrounding tissue to connect it to adjacent blood vessels, ensuring a steady supply of nutrients – and thus the cancer's long term survival (angiogenesis)

Invasion
In this stage, the tumor becomes irreversibly malignant. It leaves its tissue of origin and penetrates deep into the layers of fat and muscle. Further mutations are necessary for this metastasis to take place. The tumor cells must learn to ignore all signals from the surrounding tissue. Metastasis now takes place in the liver. The tumor strives to neutralize the body's remaining defense mechanisms by radically reordering its genetic material, thus thwarting the immune system's attempts to deal with the invader. Resistance to cell toxins also develops rapidly within the cancerous mass

Cancer

A tumor needs time to become malignant. That's why cancer usually only strikes in old age. Once active, it gradually neutralizes all the body's natural defenses

From Mutation to Metastasis



Calm before the Storm
Here we see an intact section of colon wall. The task of the light blue cells is to digest food particles. Individual stem cells are constantly dividing at the base of each villus. The daughter cells then migrate up the villus to its tip, where life is tough and very short: after six days, the entire intestinal mucous membrane is replaced.

Beginning
The process commences when carcinogenic substances damage the genetic material, creating a mutation (red cell). In most cases, this first step involves a malfunction of the so-called APC gene on chromosome 5, which regulates the migration of cells from the base to the tip of the villus. Once this mechanism is disturbed, irregularities begin to appear during cell division.

Uninhibited Growth
In the next stage, the villi start to grow more rapidly. In 50 percent of all cases, the cause is a second mutation in the so-called ras gene (green cell). The protein whose production is governed by this gene forms part of a cellular signal chain that transmits hormonal instructions to the cell nucleus, triggering the cell division process. If the ras protein or one of its partners mutates, the cell starts to divide without receiving the signal to do so, instigating irregular cell growth.

Polyp
The tumor grows in size. At this stage, polyps are benign: they respect tissue boundaries, and the body is able to regain control over many of these so-called adenoma or no malignant growths, causing them to waste away. In rare cases, however, a third mutatio takes place – usually on chromosome 18 (yellow cell). Such cells become immortal, dividing without regard to the growth restriction signals being sent out by their neighbors. The stage of uncontrolled growth begins.

Stages of Tumor Growth

1

Avoiding Programmed Cell Death
Before a cell divides, its genes are examined for defects to prevent mutations being passed on to new cells. Surveillance proteins institute repair procedures as necessary, allowing only those cells whose genes have been successfully repaired to duplicate. Should genetic defects prove irreparable, these surveillance proteins order the damaged cells to self-destruct – a process called apoptosis. Since cancer cells contain a large number of mutations, they have to short-circuit this natural control mechanism to survive. Only then can they propagate in peace, despite their massive genetic instability.

2

Imitating Growth Signals
Cells in an organism do not replicate without permission. They require growth instructions from the body that are transmitted into the heart of the cell via complex chains of signals. Cancer cells have to imitate these signals if they are to grow at all. By short-circuiting the signals within the cell and leaving them permanently on green, the cancer cells give themselves the authorization they need to proliferate.

3

Colonization and Spread
A whole range of contact molecules and messenger substances ensure that cells cannot leave their native tissue without permission from their neighbors. Cancer cells become dangerous when they learn to break out of their natural boundaries and colonize other types of body tissue. The metastases that then form often attack vital organs and develop into aggressive tumors.

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Plasmonic Nanobubbles Speed Detection and Destruction of Cancer

platform can find and kill specific cancer cells while sparing normal cells.

BY EKATERINA Y. LUKIANOVA-HLEB, RICE UNIVERSITY; XIAOYANG REN, UNIVERSITY OF TEXAS; XIANGWEI WU, UNIVERSITY OF TEXAS; JOSEPH A. ZASADZINSKI, UNIVERSITY OF MINNESOTA; MALCOLM K. BRENNER, BAYLOR COLLEGE OF MEDICINE; AND DMITRI O. LAPOTKO, RICE UNIVERSITY

Some cancers are nearly impossible to remove without damaging important healthy organs. When such cancers appear to have a high resistance to drugs and radiation, they become practically incurable – and have a high rate of recurrence. The strategic solution would be to use a cell-level tool for detecting, modifying or killing specific cells without influencing surrounding cells and tissues. Unfortunately, modern materials and technologies cannot provide cell-specific, rapid, multifunctional processing and treatment of only the cancer cell.

But a new cell-level theranostic platform rapidly detects, modifies or kills target cells while sparing normal cells with plasmonic nanobubbles (PNBs).

Plasmonic nanobubbles

Metal plasmonic nanoparticles (NPs) are the best converters of light into heat through the mechanism of surface plasmon resonance. This unique photothermal property was developed to allow precise manipulation of thermal energy at the nanoscale through engineered plasmon resonances.

Enhancement of the photothermal efficacy and spectral selectivity of such engineered NPs is associated with several principal limitations: Most commonly, stationary optical excitation creates high thermal losses that, in turn, require additional excitation energy, while the pulsed excitation involves high optical intensities that destroy NP structure that provides optical absorbance. Spectral width of absorption spectra of single NPs is tens of nanometers at best, while random clustering of NPs further broadens their spectra to hundreds of nanometers. An ability to deliver high photothermal efficacy with high spectral resolution and minimal thermal losses will therefore significantly improve current applications of plasmonic materials.

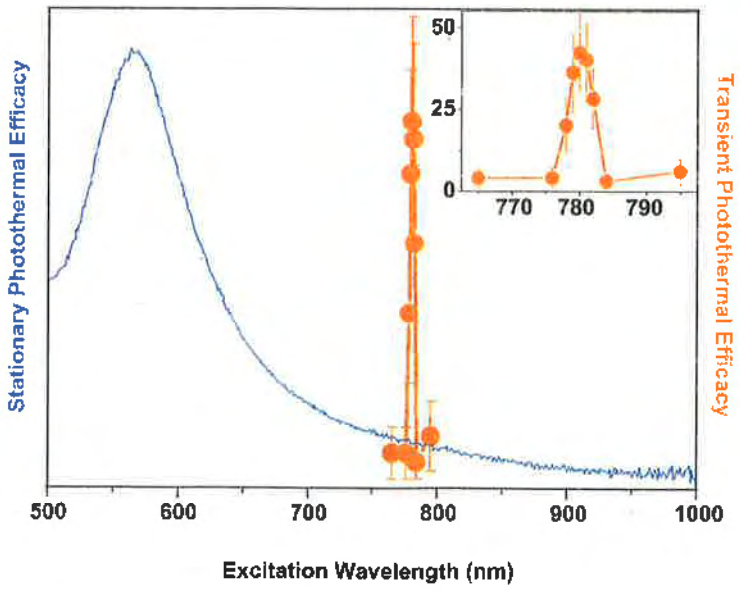

Figure 1. Spectra of the photothermal efficacy of gold solid spheres under stationary (blue) and nonstationary (red) transient high-energy optical excitation with a 70-ps single laser pulse. Images courtesy of the authors.

Until now, the photothermal and spectral properties of metal NPs have been set during their synthesis and have been assumed to stay constant during their excitation. This is a stationary paradigm, but an alternative approach can be based on the nonstationary excitation of NPs: the plasmonic nanobubble method.

The PNB is not a particle but, instead, a transient nanosecond event, a vapor nanobubble. It emerges in liquid overheated by a short-laser-pulse gold nanoparticle, expands and then collapses in nanoseconds. As a photothermal phenomenon, it can precisely deliver the localized mechanical impact and, at the same time, prevent bulk heating because it insulates all heat produced by an NP inside the vapor so the outside temperature does not rise.

PNBs have the benefit of nonstationary optical excitation of gold nanoparticles with a very short picosecond optical pulse. For example, for solid gold spheres (known also as gold colloids), we achieved with this method an approximately hundredfold transient amplification of the photothermal efficacy and the unprecedented narrowing of the photothermal spectra to 2 to 3 nm for solid gold nanospheres under off-resonant nonstationary optical excitation at 780 nm. This amplification and spectral narrowing were achieved with a 70-ps laser pulse for a wide range of fluences starting from 10 mJ/cm $^{-2}$ and a range of gold nanoparticle properties, such as size, aggregation state and environment, including living matter.

The transient nature and high spectral selectivity of the observed effect can be associated not with the nanoparticle itself, but with the nonstationary formation of a transient nanostructure with new optical properties. Thus, nonstationary optical excitation of metal nanoparticles can significantly improve their photothermal efficacy and spectral selectivity, and this can be reliably reproduced using the methodology described above. In particular, it allows the successful use of

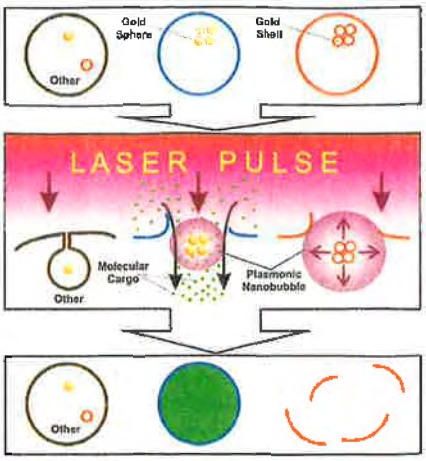

Figure 2. Multifunctional cell-specific processing of heterogeneous cell system is illustrated, with plasmonic nanobubbles that are selectively generated around clusters of gold spheres in spheres-targeted cells (blue) and around clusters of gold shells in shells-targeted cells (red) with a single laser pulse. This results in simultaneous delivery of molecular cargo into blue cells resulting from injection of the molecules (green dots) with small plasmonic nanobubbles (PNBs) and mechanical destruction of red cells with large PNBs without damage to other cells, all realized in a single pulse treatment.

solid nanospheres, which are cheap, easily available, biologically safe and stable NPs for near-infrared applications.

Gene and cell therapy

Most of the cell and gene therapies that have shown promise against human diseases such as cancer require ex vivo processing of human cell grafts to eliminate unwanted cells from a heterogeneous suspension and to genetically modify one or more cell subsets to increase their therapeutic efficacy. Ideally, both elimination and transfection should be highly efficient, selective, fast and safe for cells.

Existing methods, however, lack such characteristics, especially multifunctionality and selectivity when applied to a heterogeneous cell system. As a result, current cell processing often is slow, expensive and labor-intensive and is compromised with high cell losses and poor selectivity, limiting the efficacy and availability of cell therapies.

We have developed a universal technology for multifunctional simultaneous guided transfection of target cells and elimination of subsets of unwanted cells in heterogeneous grafts that has single-cell-type selectivity, high efficacy and processing rate, and low toxicity. We have shown that the ability of each NP type to generate PNBs of different sizes – under identical optical excitation, coupled with the cell-specific targeting and clustering of NP conjugates – allows simultaneous delivery of molecular cargo into gold sphere-targeted T-cells, and destruction of gold shell-targeted unwanted cells in a single bulk treatment of the mixed cell suspension with high efficacy, speed and selectivity and with low toxicity. This technology will create a universal platform for cell and gene therapy and for stem cell transplantation.

The long-term objective of this research is to improve the outcome of diseases whose treatment requires ex vivo cell processing. The ability to simultaneously genetically modify target cells and eliminate other specific cells from a highly heterogeneous cell system (graft), with single-cell selectivity and without compromising other important cellular components, will enhance the feasibility and effectiveness of cell engineering in general and gene therapies in particular. The technology may subsequently be applied to process any liquid tissues to improve the outcome of other cell-based interventions in cancer and other disorders.

Drug delivery

Some aggressive cancers are still difficult to treat because of 1) incomplete removal of cancer cells by surgery, especially when complicated by micrometastasis and colocalization of cancer cells with functionally or cosmetically important structures; 2) multidrug resistance of cancer cells; and 3) acute and long-term toxicities of radio- and chemotherapies. Therefore, new treatment strategies are needed to provide cell-level selectivity of cancer diagnosis and treatment, and high efficacy against drug-resistant cells.

The specificity and functionality of drug delivery to cancer cells has been improved by more than one order of magnitude through the mechanism of plasmonic nanobubbles. The PNB method effectively discriminates between cancer and normal cells under the identical treatment of both with NPs and optical radiation. By combining the threshold nature of PNBs and the enhanced accumulation and clustering of NPs in cancer cells, we have shown that PNBs, unlike NPs, can be minimized or avoided in normal cells despite the uncontrollable nonspecific uptake of NPs by such cells.

The temporally and spatially controlled initiation and collapse of PNBs create local optical and mechanical effects that can enable imaging intracellular molecular targeting, localized drug or gene delivery, and selective elimination of cells for therapeutics, theranostics and microsurgery. The optical and acoustical properties of PNBs provide a mechanism for real-time guidance of their therapeutic action. PNBs also offer improved safety as a result of their transient, on-demand nature; PNBs do not exist until activated with an optical pulse; then they disappear within nanoseconds.

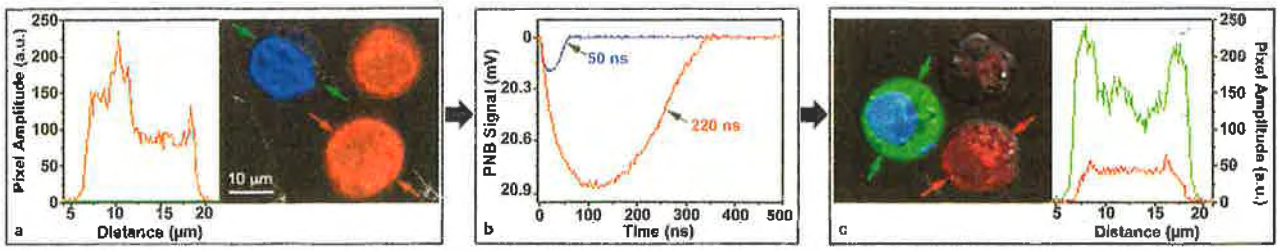

Figure 3. (a) J32 cells with intracellular clusters of gold spheres (NSP-OKT3, blue DAPI marker) and shells (NS-OKT3, Calcein Red marker); (b) optical scattering PNB-specific time responses of individual cells to a single laser pulse show simultaneous generation of small PNBs in blue and large PNBs in red cells in presence of extracellular molecular cargo FITC-Dextran (the lifetimes of PNBs are shown); (c) postlaser treatment blue cells show the injected FITC-Dextran (green fluorescence), and red cells show leaked-out Calcein Red dye and distorted membranes resulting from their destruction. The fluorescence intensity profiles of individual cells in (a) and (c) are indicated by small color-matched arrows.

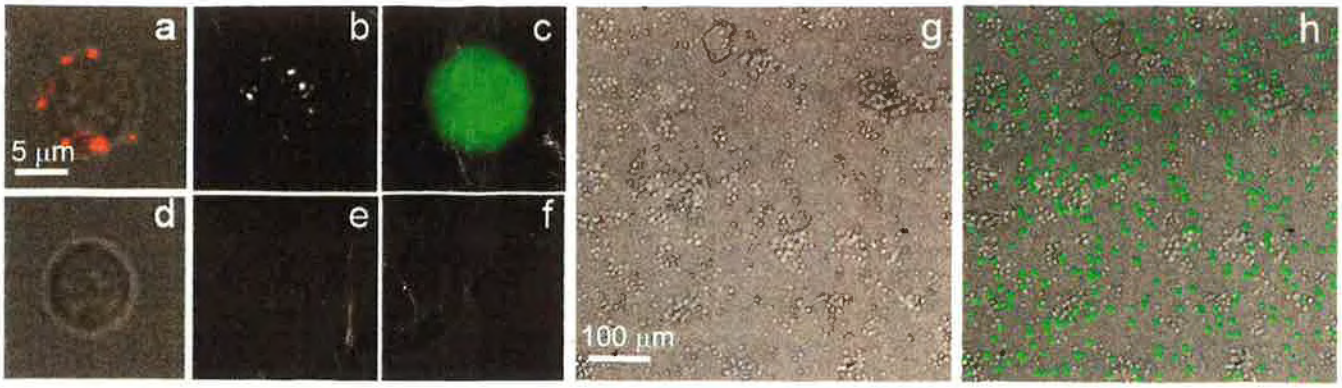

Figure 4. Images of target (CD3-positive) (a-c) and nontarget (CD3-negative) (d-f) cells. (a,d) confocal bright-field and optical scattering images show NP clusters (red) in cells; (b,e) time-resolved optical scattering images show bright PNB in target cell; (c,f) confocal fluorescent and bright-field images obtained after the PNB treatment show GFP fluorescence in target cell after 72 hours. Images of the mixture of cells (CD3-positive/CD3-negative 50:50): (g) bright-field and (h) GFP fluorescence after the PNB treatment (48 hours).

We compared three modes of the cell-level delivery of therapeutic effect with gold NPs, hyperthermia (thermal), plasmonic nanobubbles (mechanical) and a combination of drugs with plasmonic nanobubbles (chemotherapeutic). Of these, the combination of plasmonic nanobubbles with standard anti-cancer drugs demonstrated the best effect as a proof of principle for a novel nanotherapeutic mechanism for selective, efficient, safe and guided treatment of drug-resistant superficial cancer.

1. Selective intracellular delivery of standard extracellular drugs via laser-induced PNBs overcomes drug and thermal resistance of cancer cells.

2. High therapeutic selectivity is achieved through high cellular specificity of PNBs under excitation with broad laser beams in single-pulse mode at a physiologically safe level of laser radiation.

3. Drug doses required for total destruction of cancer cells are reduced by an order of magnitude, while nonspecific toxicity among normal cells is reduced sevenfold, and treatment time is reduced from days to minutes.

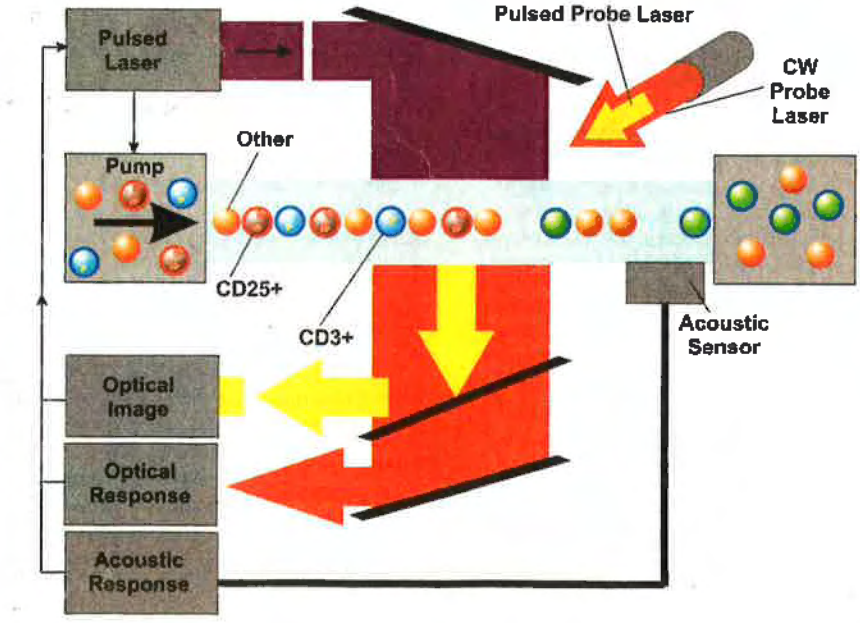

Figure 5. Functional diagram of the flow system with the pulsed broad excitation laser (purple), flow cuvette with the pump and reservoir, and three PNB detection paths: Optical time-response is detected with continuous red laser, optical scattering image is detected with yellow pulsed laser, and acoustic response is detected with acoustic sensor; all signal detectors and the flow pump are synchronized with the pulsed excitation laser.

Perspectives

Our long-term goal is to develop a universal platform that radically and selectively improves the treatment of cancer cells but spares normal cells and organs. We address several critical needs of current laser surgery and chemo-radiotherapeutics: 1) the resistance of several cancers to current therapeutics; 2) the severe nonspecific toxicities and functional impairments resulting from high doses of drugs and x-rays; 3) the cosmetic and functional morbidity after surgical resection of some tumors; 4) residual disease and local recurrences; and 5) lack of oncological specificity, efficacy and speed among new technologies and materials.

Cancer cell theranostics (united diagnosis and treatment) with PNBs offers an opportunity that is unique and distinct from current surgical and therapeutic agents due to the following: 1) Cell-level treatment is achieved through an on-demand intracellular mechanical, nonthermal process that 2) is efficiently localized only in cancer cells under identical simultaneous exposure of tumors and normal tissues to laser pulse and gold nanoparticles, 3) uses safe doses of gold nanoparticles and a single near-infrared laser pulse, 4) can be activated in superficial and deep tissue with standard clinical laser surgical tools and 5) combines detection of cancer cells with their immediate destruction in a single rapid procedure with real-time guidance.

Meet the authors

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Intratherapie's Age Management Therapeutics, available only at **HealthMedica HealthScience** centers, defines the dynamics of aging within a spectrum of ten pathophysiologies associated with age related degenerative disorders and human senescence.

These Programs unify next generation health enhancement, longevity science and personalized medicine in a physician administered clinical setting, targeting prevention of age related degenerative illness. Provided as both interventional and therapeutic protocols, designated as the '**AlphaProgram**' and the **Immunety** Program,

Founded in 2001, the IntraTherapies Institute is a catalyst in the evolution of health and wellness management and the integration of Longevity Science and Personalized Medicine within its group of proactive health enhancement programs.

Targeting the neurobiology of disease and aging, IntraTherapies is committed to the highest standards in providing a platform for both preventive as well as interventional health enhancement programs, IntraTherapies' objectives are directed toward a clinical architecture addressing primary age-related disease categories and therapeutic processes on multiple levels of the healthcare continuum.

Within a medical framework comprising the specialties of neurology, endocrinology, oncology, hematology, immunology, we strive for a comprehensive but cost effective approach enabling a new category of healthcare, Age Management Therapeutics®. From both a preventive and interventional perspective, we enable an evidence-based platform of comprehensive health optimization, while providing an innovative clinical environment to foster important new medical discoveries.

The IntraTherapies Institute actively pursues the 'leading edge' of personalized medicine, but guided by stringent oversight from a committed medical team interested in the progression from present day clinical choices to a near future of significant health enhancement within near term time frames for patients.

The ultimate objectives are to accelerate the availability of evidence-based clinically validated treatments to a broader population seeking the most promising, safe and effective medical programs addressing age-related degenerative disorders, disease prevention, disease intervention and enhanced health.

DEVELOPING CANCER

In this section you will learn:

- Cancer is not one disease; it is a collection of diseases characterized by the uncontrolled growth of cells.
- Many cancers are progressive in nature, providing distinct points for medical intervention to prevent cancer, detect it early, or treat progressive disease.
- The most advanced stage of cancer, metastatic disease, accounts for most cancer-related deaths.
- Changes in the genetic material in a normal cell underpin cancer initiation and development in most cases.
- A cancer cell's surroundings influence disease development and progression.
- The more we know about the interplay among the individual factors influencing cancer biology, the more precisely we can prevent and treat cancer.

Research has taught us that cancer is a complex disease. In fact, it is not just one disease but rather a collection of many diseases that arise when the processes that control the multiplication and life span of normal cells go awry.

In adults, cell multiplication is a very tightly controlled process that occurs primarily only to replace cells that die due to exposure to various external factors or as a result of normal wear and tear.

If the processes that control the multiplication and life span of normal cells go awry, the cells start multiplying uncontrollably, fail to die when they should, and begin to accumulate. In body organs and tissues, the accumulating cells form a tumor mass, whereas in the blood or bone marrow, they crowd out the normal cells. Over time, some cancer cells within the tumor mass gain the ability to invade local tissues. Some also gain the ability to spread (or metastasize) to distant sites.

The progressive nature of cancer provides distinct sites for medical intervention to prevent cancer, detect it early, or treat progressive disease. In general, the further a cancer has progressed, the harder it is to stop the chain of events that leads to the emergence of metastatic disease, which is the cause of most deaths from solid tumors.

Changes, or mutations, in the genetic material of a normal cell are the primary cause of cancer initiation. Over time, additional mutations are acquired by cells within a growing tumor mass, and this drives cancer progression. The number of cells within a growing tumor that carry a given mutation depends on when the mutation was acquired during tumor growth. Thus, even within the same tumor, different cancer cells may have different genetic changes. In general, the more genetically heterogeneous a tumor is, the harder it is to effectively treat.

Not all mutations acquired by a cell contribute to cancer initiation and development. In fact, the identity, order, and speed at which a cell acquires genetic mutations determine whether a given cancer will develop and, if a cancer does develop, the length of time it takes to happen. Numerous interrelated factors influence mutation acquisition and determine the overall risk that a person will develop a particular type of cancer (see sidebar on **Why Did I Get This Cancer?** p. 19).

CANCER DEVELOPMENT: INFLUENCES INSIDE THE CELL

The accumulation of mutations in the genetic material of a cell over time is the predominant cause of cancer initiation and progression (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 20). A genetic mutation is a change in the type or order of the four deoxyribonucleic acid (DNA) units, called bases, that make up the genetic

CANCER: A COSTLY DISEASE. RESEARCH: A VITAL INVESTMENT

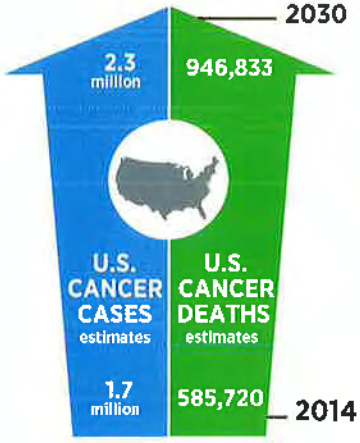
Cancer exerts an immense global toll that is felt not only through the number of lives it affects each year, but also through its significant economic impact. With the number of cancer cases projected to increase substantially in the next few decades, it is anticipated that the economic burden will rise, too. One study estimates that the global cost of new cancer cases will increase from $290 billion in 2010 to $458 billion in 2030 (21).

Data from (21)

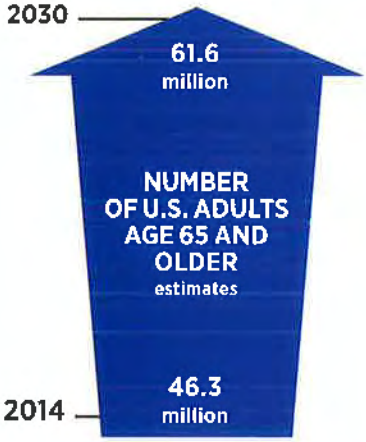
In the United States, the direct medical costs of cancer care are projected to rise from nearly $125 billion in 2010 to $156 billion in 2020. These costs stand in stark contrast to the NIH budget for fiscal year (FY) 2016, which is $32.31 billion, of which $5.21 billion is dedicated to the NCI.

The increasing personal and economic burden of cancer underscores the urgent need for more research so that we can accelerate the pace of progress against cancer. Recent advances, some of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers from across the spectrum of research disciplines. Much of their work, as well as the federal regulatory agency that ensures the safety and efficacy of medical device and therapeutic advances—the FDA—is supported by funds from the federal government. Although the $2 billion increase to the NIH budget in FY 2016 was a welcome boost, it is imperative that Congress and the Administration provide sustained, robust, and predictable increases in investments in the federal agencies that are vital for fueling progress against cancer, in particular the NIH, NCI, and FDA, in the years ahead.

THE GROWING PUBLIC HEALTH CHALLENGE OF CANCER IN THE UNITED STATES



Cancer is a leading cause of morbidity and mortality in the United States (16, 17). It is expected that the public health challenge it poses will grow considerably in the coming decades if more effective strategies for cancer prevention, early detection, and treatment are not developed (8, 18).



This growing challenge will be fueled by an increase in the number of U.S. adults age 65 and older (19), continued use of cigarettes by 15 percent of U.S. adults (20), and high rates of obesity and physical inactivity (17).

The research that powers the significant advances that have been and continue to be made against cancer is made possible by investments from governments, philanthropic individuals and organizations, and the private sector the world over. Of particular importance in the United States are federal investments in biomedical research and government agencies conducting research such as the FDA and the Centers for Disease Control and Prevention (CDC). Most U.S. government investments in biomedical research are administered through the 27 institutes and centers of the National Institutes of Health (NIH). The largest component of the NIH is the National Cancer Institute (NCI), which is the federal government's principal agency for cancer research and training.

CANCER: AN ONGOING CHALLENGE

Although we have made tremendous progress against cancer, this collection of diseases continues to be an enormous public health challenge worldwide, accounting for one in every seven deaths that occur around the world (6) (see **Figure 1**). In the United States alone, it is predicted that 595,690 people will die from some form of cancer in 2016, making it the second most common cause of death after heart disease (3).

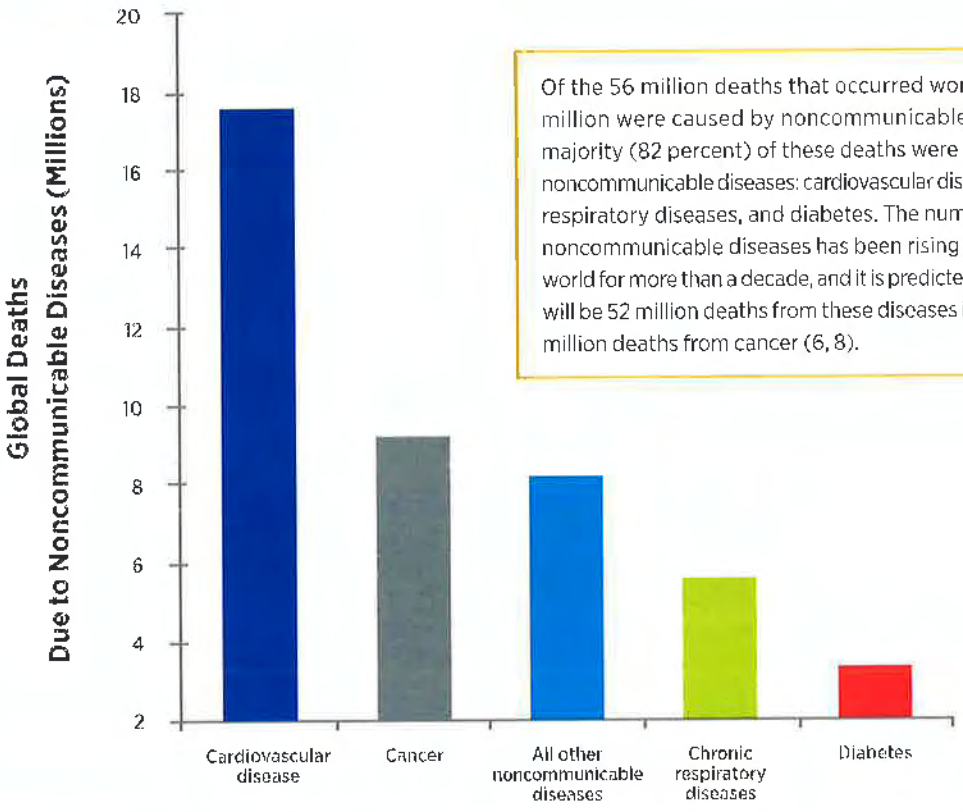
By 2013, cancer had overtaken cardiovascular disease as the leading cause of death in

23

U.S. states (7).

One of the challenges we face is that advances have not been uniform for all forms of cancer (see **Table 3**, p. 14). For example, while the incidence rates for many of the most commonly diagnosed cancers in the United States—including breast, colorectal, lung, and prostate cancer—have been declining for more than a decade, those for other forms of cancer—most notably kidney, liver, and pancreatic cancer, as well as melanoma and childhood cancer—have been increasing (2). Overall 5-year relative survival rates for U.S. patients also vary widely depending on the form of cancer diagnosed (3). Overall 5-year relative survival rates for women with invasive breast cancer and men with

FIGURE 1 CANCER: A GLOBAL CHALLENGE



Of the 56 million deaths that occurred worldwide in 2012, 38 million were caused by noncommunicable diseases (6). The majority (82 percent) of these deaths were caused by just four noncommunicable diseases: cardiovascular disease, cancer, chronic respiratory diseases, and diabetes. The number of deaths from noncommunicable diseases has been rising in every part of the world for more than a decade, and it is predicted that globally, there will be 52 million deaths from these diseases in 2030 including 13 million deaths from cancer (6, 8).

TABLE 2

COMPARISON OF RELATIVE 5-YEAR SURVIVAL RATES FOR CHILDHOOD CANCERS (0-19 YRS) BETWEEN 1975-79 AND 2006-2012

*Followed into 2012

^ Cancers in children and younger adolescents are classified by histology (tissue type) using the International Classification of Childhood Cancers (ICCC)

Data from Ref. (5) and Ref. (10)

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

Strings of four **deoxyribonucleic acid (DNA)** units called bases comprise the genetic material of a cell.

DNA bases are organized into **genes**. The order, or sequence, of the bases provides the code used by the cell to produce the various proteins it needs to function.

The entirety of a person's DNA is called the **genome**. Almost every cell in the body contains a copy of the genome. The genome is packaged together with proteins known as histones into structures called **chromosomes**.

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

The accessible genes within each cell are read to produce the proteins that ultimately define the **cell and tissue function** in which the cell resides.

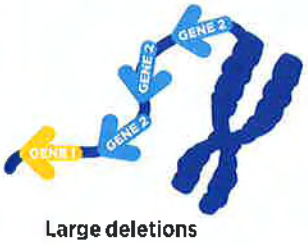
Adapted from (1)

GENETIC MUTATIONS

The following are some of the types of genetic mutation known to lead to cancer. Of note, genetic mutations do not always result in cancer.

Single base changes

- Some mutations can lead to the generation of altered versions of normal proteins, and these may cause cancer to develop.
- Deletion or insertion of a single base can result in new proteins or loss of protein function, which can lead to cancer.



Extra copies of genes (gene amplification)
Higher quantities of certain proteins can result in 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.

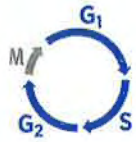
Mutations that alter the epigenome
Several proteins read, write, or erase the epigenetic marks on DNA or the histones around which it is packaged. Mutations in the genes that produce these proteins can lead to cancer.

Adapted from (1)

WHY DID I GET THIS CANCER?

Cancer initiation and progression are predominantly caused by the accumulation of changes, or mutations, in the genetic material of a cell over time. Some genetic mutations are inherited from your parents and are present in each cell of the body from birth but most genetic mutations are acquired during your lifetime.

Five to 10 percent of all new U.S. cancer cases are linked to inherited genetic mutations (22).



Some mutations are acquired during cell multiplication, and the number of times a cell multiplies increases the chance it will acquire a mutation.

Some mutations are acquired as a result of exposure to factors that damage genetic material, such as toxins in tobacco smoke and ultraviolet (UV) light from the sun.

These factors come together to determine the chance that an individual cell has of acquiring mutations over time. This, in turn, helps determine the overall risk that a person will develop a particular type of cancer.

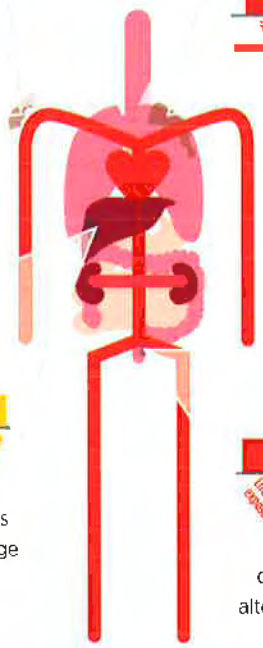
Simplified estimates of the relative contribution of each of the various sources of mutations to developing particular types of cancer are illustrated based on a recent study (23). This understanding can influence approaches for prevention and early detection of these and other types of cancer. Because cancer is caused by the accumulation of mutations over time, the older a person gets, the more likely he or she is to have a cell that has acquired a combination of genetic mutations causing it to become cancerous.

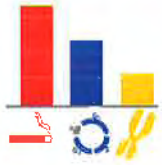
Basal Cell Carcinoma

Basal cells in the outermost layer of the skin are constantly multiplying to replace skin damaged by normal wear and tear. Thus, the number of cell multiplications is the primary contributor to the risk of developing basal cell carcinoma. However, it is not the only contributor. Exposure to UV radiation from the sun or tanning beds can also cause basal cells to acquire genetic mutations, and a person can reduce his or her risk for this cancer by adopting sun-safe habits and avoiding UV tanning devices (see **Protect Skin From UV Exposure**, p. 32).

Hepatitis C Virus–dependent Liver Cancer

Chronic infection with hepatitis C virus (HCV) increases a person's risk for liver cancer because it causes damage to the liver, which triggers a tissue-repair process that involves extensive multiplication of cells in the liver. Thus, chronic HCV infection is the primary, but not the only, contributor to the risk of developing liver cancer in infected individuals. HCV infection is treatable and preventable (see **Prevent Infection With Cancer-causing Pathogens**, p. 33).





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 cancer from developing (see **Eliminate Tobacco Use**, p.24).

Familial Adenomatous Polyposis–dependent Colorectal Cancer

For individuals who inherit a mutation in the adenomatous polyposis coli (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 intervene as appropriate (see **Finding Cancer**, p. 38).

Adapted from (24)

material of a cell. The order, or sequence, of DNA bases is a key determinant of what proteins are produced by a cell and how much of each protein is produced. Many different types of mutation contribute to cancer initiation and development, primarily by altering the amount or function of certain proteins (see sidebar on **Genetic Mutations**, p. 20).

In addition to genetic mutations, most cancer cells also have profound epigenetic abnormalities, compared with normal cells of the same tissue. In many cases, epigenetic alterations and genetic mutations work together to promote cancer development. Although genetic mutations are permanent, some epigenetic abnormalities appear to be reversible, and harnessing this discovery for therapeutic purposes is an area of intensive investigation.

CANCER DEVELOPMENT: INFLUENCES OUTSIDE THE CELL

Genetic mutations that disrupt the orderly processes controlling the multiplication and life span of normal cells are the main cause of cancer initiation and development. However, interactions between cancer cells and their environment—known as the tumor microenvironment—as well as interactions with systemic factors, also have an important role in cancer development (see sidebar on **Cancer Growth: Local and Global Influences**). In fact, cancer cells often exploit tumor microenvironment components to promote their multiplication and survival.

CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

Solid tumors are much more complex than an isolated mass of proliferating cancer cells because cancer initiation, development, and progression are strongly influenced by interactions among cancer cells and numerous factors in their environment. Among the components of the tumor microenvironment are normal parts of the tissue in which the cancer is growing, systemic factors that transiently percolate through the tissue, and cells that are actively recruited to the tissue.

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 the 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. In some situations of chronic inflammation, however, the immune system can promote cancer development and progression.

Adapted from (1)

CANCER DEVELOPMENT: A WHOLE-PATIENT PICTURE

Research has powered an explosion in our understanding of the individual factors inside and outside a cell that cause cancer initiation, development, and progression. It is also beginning to provide us with a picture of how these factors work together and are influenced by each person's unique biological characteristics. This knowledge is the essence of precision medicine, as well as the more nascent strategy of precision prevention (see **Figure 2**).

Precision prevention and medicine aim to tailor each person's health care to the prevention and/or treatment strategies most likely to be of benefit, sparing each person the cost of and potential harms from those prevention interventions and/or treatments that are unlikely to be of benefit (25, 26). As we develop an even more comprehensive, whole-patient understanding of the way in which cancer starts, progresses, and results in sickness, we can expect to see an acceleration in the pace of progress in precision medicine and prevention for cancer (see **Anticipating Future Progress**, p. 100).

FIGURE 2

PRECISION MEDICINE AND PREVENTION

Precision medicine, sometimes referred to as personalized medicine, molecular medicine, or tailored therapy, is broadly defined as treating patients based on characteristics that distinguish them from other patients with the same disease. Factors such as a person's genome, the genome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, and other yet-to-be-discovered features (indicated by the question mark) are considered in precision medicine (25). Precision prevention is a conceptual framework that aims to tailor cancer prevention to the individual patient by accounting for the various factors that may play a role in developing a particular cancer (26); it is analogous to the manner in which precision medicine treats patients. The following factors could be considered in the implementation of precision prevention: a person's genome; age; gender; family history, including genetic predisposition to developing cancer (see **Table 5**, p. 43); lifestyle factors including tobacco and alcohol use, being overweight or obese, and levels of exercise; reproductive and medical factors; exposures to known carcinogens like viruses; socioeconomic status; and geography, as well as yet-to-be identified factors (indicated by the question mark). The order in which the factors appear in the images is not meant to imply that one factor is more important than another.

PREVENTING CANCER

In this section you will learn:

- More than half of global cancer cases are a result of preventable causes.
- Not using tobacco is the single best way a person can prevent cancer from developing.
- About 20 percent of U.S. cancer diagnoses are related to people being overweight or obese, being physically inactive, and/or consuming a poor diet.
- Many cases of skin cancer could be prevented by protecting the skin from ultraviolet radiation from the sun and indoor tanning devices.
- The number of U.S. cancer cases attributable to human papillomavirus (HPV) infection is rising, but most U.S. adolescents have not received the full HPV vaccine course.
- Exposure to environmental cancer risk factors remains a challenge for certain segments of the U.S. population.

Factors that increase the chance of developing cancer are referred to as cancer risk factors. These factors directly or indirectly increase the chance that a cell will acquire a genetic mutation and therefore increase the chance that a cell will become cancerous (see sidebar on **Why Did I Get This Cancer?**, p. 19). Decades of research have led to the identification of numerous cancer risk factors (see **Figure 3**, p. 24) (27).

Many of the risk factors that have the biggest impact on cancer incidence are avoidable (see **Figure 3**, p. 24). For example, many cases of cancer could be prevented either by individuals modifying their behaviors or through the development and implementation of new public education and policy initiatives that encourage individuals to avoid cancer risk factors or protect people from cancer risk factors in the workplace or environment. In fact, a recent study suggests that between 40 percent and 60 percent of cancer cases among white Americans could be prevented if each person did not smoke, limited alcohol consumption, maintained a healthy weight, and undertook regular physical activity (29). These lifestyle behaviors also increase risk for cancer in other U.S. racial and ethnic groups, but the absolute contributions of these factors to cancer risk in nonwhite populations remain to be determined.

50%
of all global cancer cases are preventable (30).

Many cancer risk factors are also risk factors for other chronic diseases, such as cardiovascular disease, respiratory diseases, and diabetes. Therefore, reducing or eliminating exposure to these factors through behavior modification or public education and policy initiative implementation has the potential to reduce the burden of both cancer and other diseases.

In the United States, many of the greatest reductions in cancer morbidity and mortality have been achieved through the implementation of effective public education and policy initiatives. For example, major public education and policy initiatives to combat cigarette smoking have been credited with preventing almost 800,000 deaths from lung cancer from 1975 to 2000 (31). The researchers concluded, however, that this figure represented just 32 percent of the lung cancer deaths that could have been prevented during that period if tobacco control strategies had completely eliminated cigarette smoking (31).

Clearly, a great deal more research and more resources are needed to understand why some individuals continue to engage in risky behaviors despite current public education and policy initiatives, and how best to help these individuals eliminate or reduce their risk of some cancers. One recent

Through the Division of Cancer Prevention and Control, the

Centers for Disease Control and Prevention (CDC)

work with national cancer organizations, state health agencies, and other key groups to develop, implement, and promote effective strategies for preventing and controlling cancer.

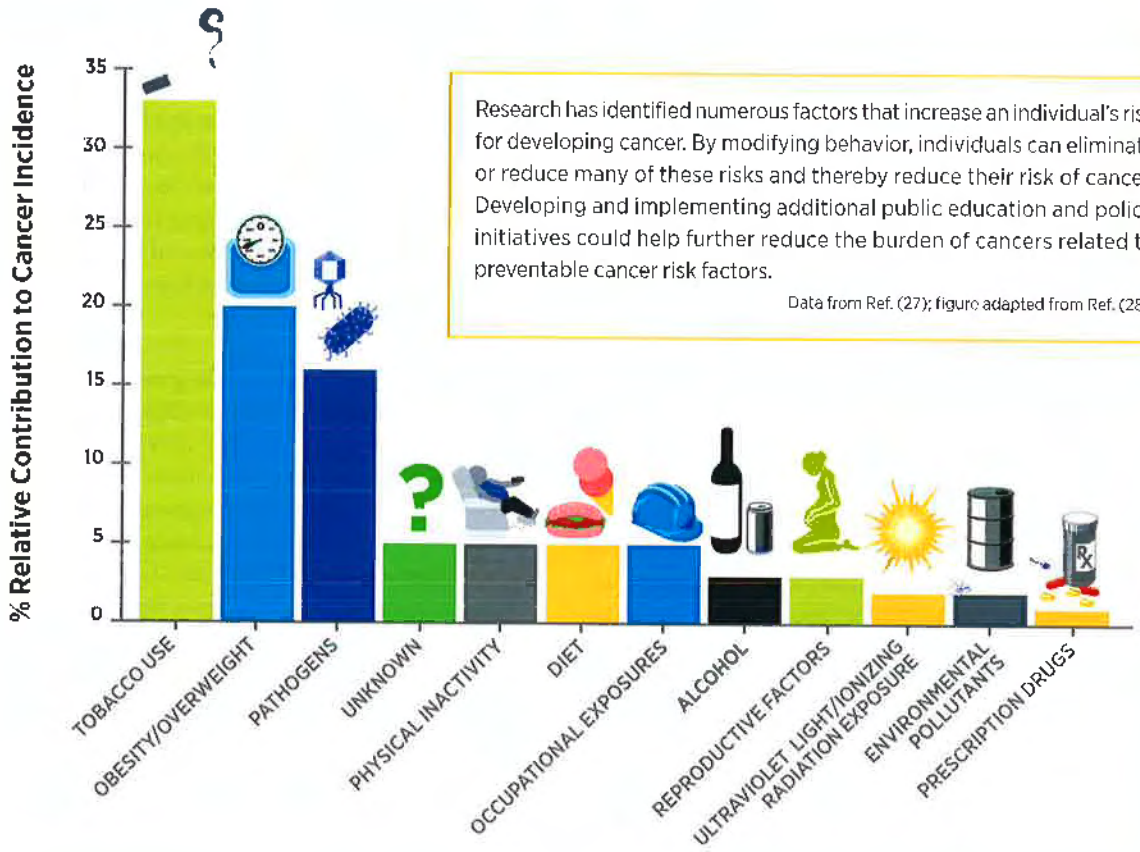
study suggested that the way that public education messages are framed can dramatically influence whether or not an individual modifies his or her behavior because it showed that dieting individuals who saw a message focusing on the negative aspects of unhealthy food actually increased their consumption of unhealthy foods (32).

ELIMINATE TOBACCO USE

Smoking tobacco exposes a person to toxicants that can cause genetic mutations, increasing his or her risk of developing not only lung cancer, but also 17 other types of cancer (see **Figure 4**, p. 25) (33). It is responsible for one in every three cases of cancer diagnosed in the United States each year (27). Therefore, one of the most effective ways a person can lower his or her risk of developing cancer, as well as other smoking-related conditions such as cardiovascular, metabolic, and lung diseases, is to avoid or eliminate tobacco use.

Since the relationship between tobacco use and cancer was first brought to the public's attention in 1964 (37), the

FIGURE 3 RISKY BUSINESS

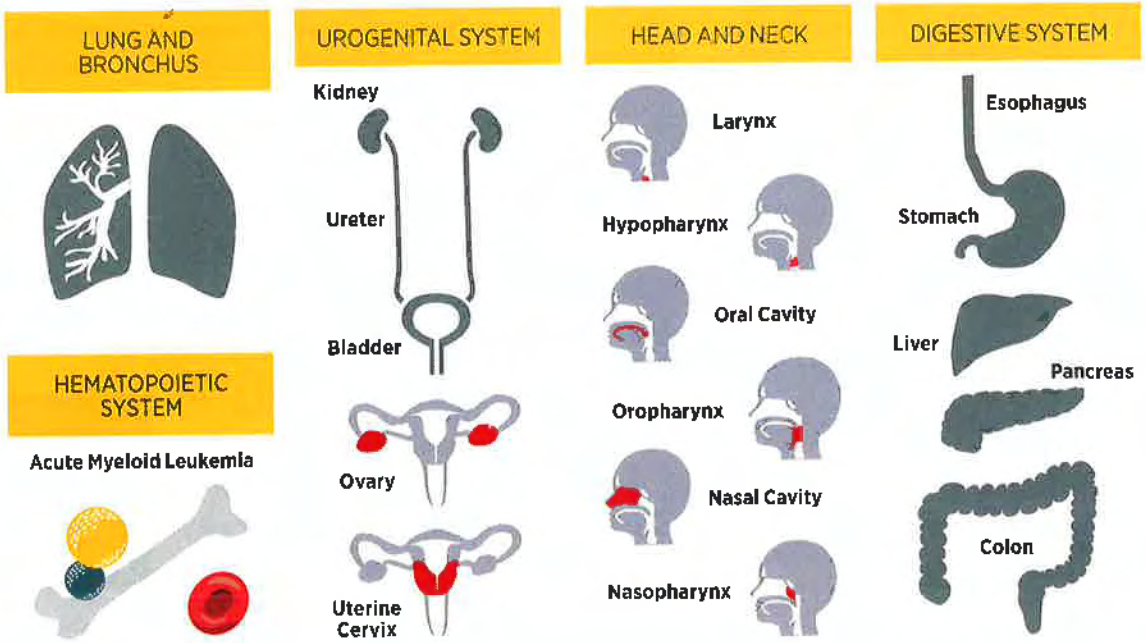


Research has identified numerous factors that increase an individual's risk for developing cancer. By modifying behavior, individuals can eliminate or reduce many of these risks and thereby reduce their risk of cancer. Developing and implementing additional public education and policy initiatives could help further reduce the burden of cancers related to preventable cancer risk factors.

Data from Ref. (27); figure adapted from Ref. (28).

FIGURE 4

BEYOND THE LUNGS: CANCERS CAUSED BY SMOKING TOBACCO



Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer (34). No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke, which is estimated to have resulted in more than 260,000 of the 5 million lung cancer deaths in the United States attributable to smoking from 1965 to 2014 (35).

Figure adapted from Ref. (1)

development and implementation of major public education and policy initiatives have driven down cigarette smoking rates among U.S. adults from 42 percent in 1965 to 15 percent in 2015 (20, 34). In addition, the most recent data show declining use of cigarettes among high school students: In 2011, 15.8 percent of high school students were current users of cigarettes, compared with 9.3 percent in 2015 (38).

We have made tremendous progress reducing the public health burden of tobacco use, with researchers estimating that more than 8 million smoking-related deaths were prevented in the United States from 1964 to 2014 as a result of declines in cigarette smoking rates (39). The reductions in cigarette smoking rates have not been evenly distributed among all segments of the population, as defined by race, ethnicity, educational level, socioeconomic status, and place of residence (40). For example, 29.2 percent of non-Hispanic American Indians/Alaska Natives, 18.2 percent of non-Hispanic whites, 17.5 percent of non-Hispanic blacks, 11.2 percent of Hispanics, and 9.8 percent of non-Hispanic Asians are smokers (40).

In addition, U.S. adult use of other tobacco products that can cause certain types of cancer—cigars, smokeless

U.S. adults who smoke are

25 times

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 (35).

Quitting smoking abruptly is more likely to lead to lasting smoking cessation than cutting down gradually (36).

tobacco products (e.g., chewing tobacco and snuff), and pipe tobacco—has not changed over the past decade (41). Moreover, use of emerging tobacco products, such as electronic cigarettes (e-cigarettes) and water pipes, among high school students is increasing rapidly. In 2011, 1.5 percent of high school students were current users of e-cigarettes, and 4.1 percent were current users of hookahs, compared with 16.0 percent and 7.2 percent, respectively, in 2015 (38).

Given that tobacco use and addiction mostly begin during youth and young adulthood, more research into the health consequences of using e-cigarettes and water pipes is urgently needed (43). In particular, we need to fully understand whether e-cigarettes have value as cigarette-smoking cessation aids and how they affect use of other tobacco products by smokers and nonsmokers (see sidebar on **E-cigarettes: What We Know and What We Need to Know**, p. 27) (44). We also need more research into the health consequences of smoking marijuana; for example, there is concern it could cause cancer because it involves the

Tar is the major source of tobacco carcinogens, and one water pipe tobacco smoking session delivers

25 times the tar

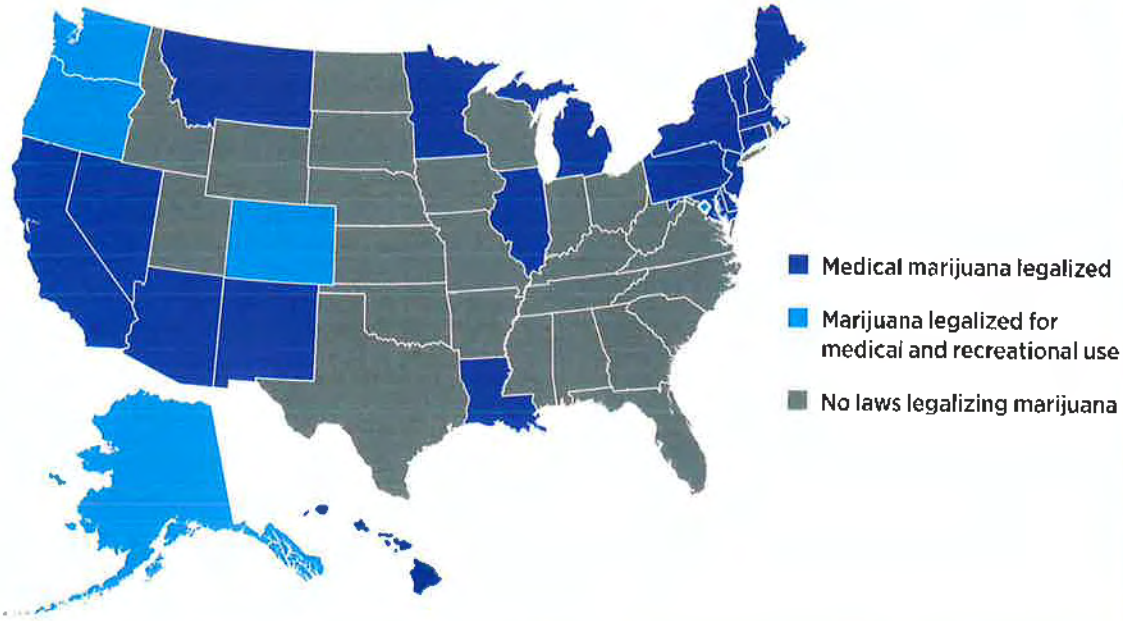
of a single cigarette (42).

70%

of U.S. middle and high school students were exposed to e-cigarette advertisements in 2014 (46).

FIGURE 5

HIGH TIME TO LEARN MORE



There are laws legalizing some form of marijuana use in 25 U.S. states and the District of Columbia. In most states, marijuana is legalized only for medical purposes, but it is legalized for both medical and recreational purposes in Alaska, Colorado, Oregon, Washington, and the District of Columbia. With more and more states legalizing some form of marijuana use, it is imperative that we conduct more research to fully understand the health consequences of marijuana use, including how it affects cancer risk.

Data are current as of July 31, 2016, and are from Ref. (45)

E-CIGARETTES: WHAT WE KNOW AND WHAT WE NEED TO KNOW

WHAT WE KNOW

While conventional cigarettes deliver nicotine by combusting tobacco, electronic cigarettes (e-cigarettes) deliver nicotine by vaporizing a nicotine solution.

460+ BRANDS

More than 460 brands of e-cigarettes and other electronic nicotine delivery systems (ENDS) are available.

More than 7,700 flavors of nicotine solutions are available (44).

E-cigarette use among U.S. middle and high school students is rapidly increasing (38).

FDA APPROVED

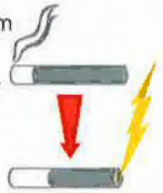
In May 2016, the U.S. Food and Drug Administration announced it would begin regulating e-cigarettes, and banned the sale of these products to anyone under the age of 18.

WHAT WE NEED TO KNOW (44)

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 other?
- Can ENDS product testing be standardized?

Adapted from (1)

burning of an organic material, much like tobacco smoking. The need for this research is driven by the growing number of states that have legalized marijuana use for medical and/or recreational purposes (see **Figure 5**, p. 26).

A number of new tobacco control policy initiatives have been recently announced in the United States, the most prominent of which is the decision by the FDA to extend its regulatory oversight to all tobacco products, including e-cigarettes, cigars, pipe tobacco, and hookah tobacco (see sidebar on **Enhancing Tobacco Control Through FDA Regulation**). In addition, a growing number of cities, counties, and states, most recently California, have passed legislation raising the minimum age of sale of tobacco products to 21 (47). This is important because nearly everyone who buys cigarettes for U.S. minors is under the age of 21 (47), and it has been predicted that if implemented nationwide, such legislation could lead to a 12 percent reduction in smoking prevalence (48).

MAINTAIN A HEALTHY WEIGHT, EAT A HEALTHY DIET, AND STAY ACTIVE

Researchers estimate that one in every five new cases of cancer diagnosed in the United States is related to people being overweight or obese, being inactive, and/or eating a poor diet (49). Therefore, maintaining a healthy weight, being physically active, and consuming a balanced diet are effective ways a person can lower his or her risk of developing or dying from cancer (see sidebar on **Reduce Your Risk for Cancer Linked to Being Overweight or Obese, Being Inactive, and/or Consuming a Poor Diet**, p. 29).

ENHANCING TOBACCO CONTROL THROUGH FDA REGULATION

The U.S. Food and Drug Administration (FDA) has had the authority to regulate tobacco products since 2009. While the agency exercised regulatory authority over some of these products, such as cigarettes, others remained unregulated—until now. In 2016, the FDA extended its authority to cover all tobacco-based products through an amendment to the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act). The key provisions of this extended rule include:

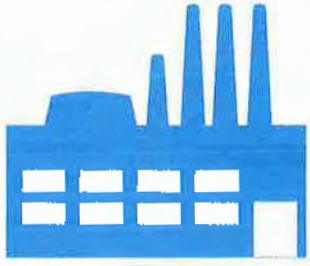
Permits FDA regulation of vaporizers, vape pens, cigars, hookah pens, e-cigarettes, e-pipes, and all other electronic nicotine delivery systems, as well as future tobacco products not yet on the market.

Prohibits the distribution of free samples.

Defines content and size of warning labels and requires additional warnings for cigar packaging.

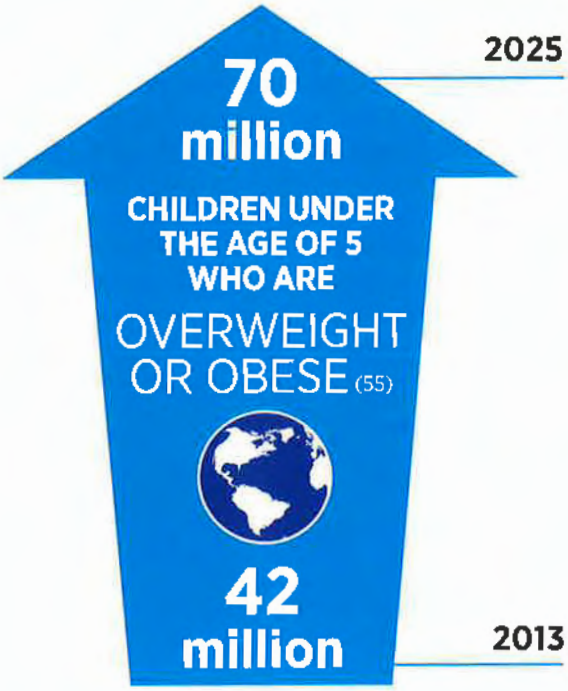
Requires a premarket review process and authorization of new tobacco products that reviews manufacturers' claims and requires the disclosure of ingredients and reporting of harmful or potentially harmful components.

Defines establishments that mix or prepare e-liquids or create or modify aerosolizing apparatus for direct sale to consumers as tobacco product manufacturers that are subject to regulation as manufacturers.



Prohibits the sale of tobacco products to individuals under the age of 18 and requires the display of health warnings in advertisements and on tobacco and tobacco-related products.

Being overweight or obese as an adult increases a person's risk for 14 types of cancer (see **Figure 6**, p. 30) (50), and it is estimated to have been responsible for about 481,000 of the new cases of adult cancer diagnosed worldwide in 2012 (51). Therefore, it is extremely concerning that in the United States, 71 percent of adults age 20 or over are overweight or obese (52), 32 percent of youth ages 2 to 19 are overweight or obese (52), and more than half of U.S. adults and 73 percent of high school students do not meet the relevant recommended guidelines for aerobic physical activity (see sidebar on **Physical Activity Guidelines**, p. 31) (20, 53).



The importance of following guidelines for leisure time physical activity is highlighted by a recent study showing that increasing levels of leisure time aerobic physical activity decreased risk for developing 13 types of cancer (56). For 10 of these cancers, this held true regardless of body mass index (BMI), the most common measure of whether or not a person is underweight, normal weight, overweight, or obese.

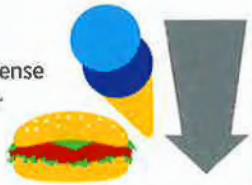
Physical inactivity cost health care systems **$53.8 billion** worldwide in 2013 (54).

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 one fifth of all U.S. cancers and one third of the most common types of cancer diagnosed in the United States 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 14 types of cancer have been causally linked to being obese or overweight (see **Figure 6**, p. 30).

Be physically active for at least 30 minutes every day, because regular physical activity can decrease risk for certain 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 six types of cancer: breast, colorectal, esophageal, liver, stomach, and mouth/throat cancers.

Source:
http://www.wcrf.org/int/research-we-fund/our-cancer-prevention-recommendations
Adapted from (24)

From 2007 to 2010,

87%

of U.S. adults did not meet U.S. government recommendations for daily fruit intake and

76%

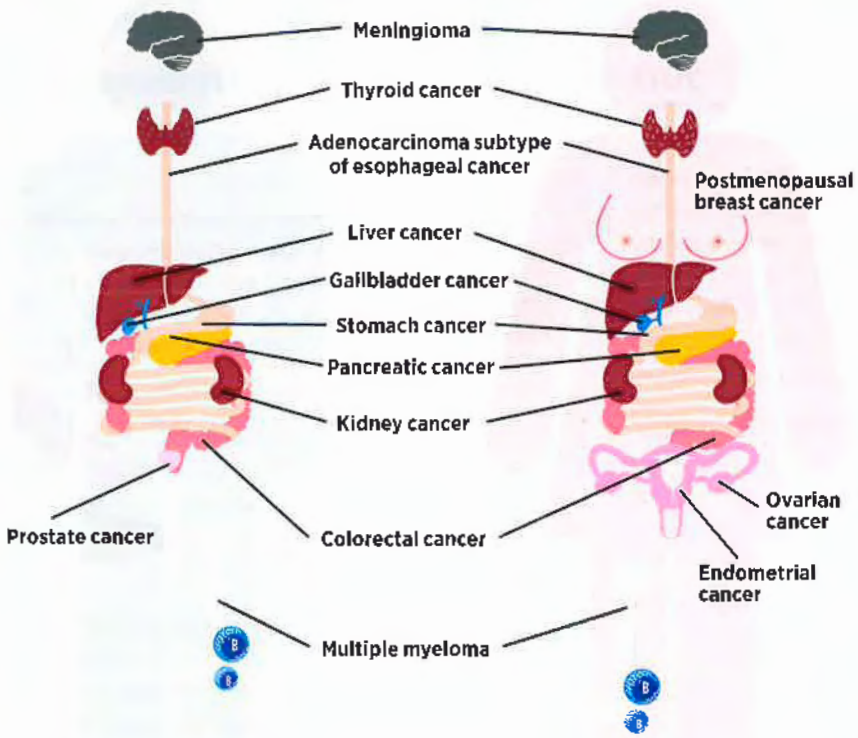
did not meet the recommendations for daily vegetable intake (61).

Several steps to promote physical activity for all segments of the U.S. population are outlined in *Step it up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities* and in the U.S. National Physical Activity Plan (57, 58). Nevertheless, concerted efforts by individuals, families, communities, schools, workplaces, institutions, health care professionals, media, industry, government, and multinational bodies are required to implement any strategy to promote the maintenance of a healthy weight and the participation in regular physical activity.

In addition, intensive efforts by all stakeholders are needed if we are to increase the number of people who consume a balanced diet, such as that recommended by the U.S. Department of Health and Human Services and the U.S. Department of Agriculture in the *2015—2020 Dietary Guidelines for Americans* (59). One recent policy initiative to help people make better informed food choices and meet the new dietary guidelines is the FDA decision to change the regulatory requirements for the information that manufacturers must provide on nutrition facts labels

FIGURE 6

WEIGHING THE EVIDENCE: CANCERS CAUSED BY OBESITY



Fourteen types of cancer—the adenocarcinoma subtype of esophageal cancer, advanced prostate cancer, meningioma, multiple myeloma, and colorectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese (50, 204).

Figure adapted from Ref. (24)

on food packaging, including the new requirement for information about how much sugar has been added to the food product (60).

The new public education and policy initiatives are important steps toward reducing the burden of cancer caused by being overweight or obese, being inactive, and/or eating a poor diet. More research is needed, however, to better understand the effect on cancer risk of exposure to these cancer risk factors at various stages of life. For example, recent data suggest that increased body weight during childhood and adolescence may increase risk for colorectal cancer later in life (62, 63), while eating plenty of fruit during adolescence may decrease risk for breast cancer in later life (64), although more research is required to confirm these findings.

New U.S. dietary guidelines recommend added sugars account for no more than

10%

of daily calories, which is equivalent to about 50 grams of added sugar per day (59).

PHYSICAL ACTIVITY GUIDELINES

The U.S. Department of Health and Human Services recommends the following minimum physical activity levels to improve the nation's health; see http://www.health.gov/paguidelines/guidelines/summary.aspx.

FOR CHILDREN AND ADOLESCENTS

Sixty minutes or more of physical activity such as running daily.

Muscle- and bone-strengthening exercises such as pushups at least three days per week.

FOR ADULTS

All adults should avoid inactivity; some physical activity is better than none.

At least 150 minutes per week of moderate-intensity activity such as a brisk walk or 75 minutes per week of vigorous-intensity activity, such as running.

Moderate- or high-intensity muscle-strengthening activities two or more days per week.

FOR SPECIFIC POPULATIONS

Older adults, those who are pregnant, and/or those with disabilities should consult their physicians and the modified guidelines.

Cancer survivors should consult their physicians and follow modified guidelines adapted for their specific cancers and treatments.

Adapted from (1)

PROTECT SKIN FROM UV EXPOSURE

For most of the nearly 5 million patients with skin cancer who are treated each year in the United States, their disease was caused by genetic mutations arising as a result of exposure to ultraviolet (UV) light from the sun, sunlamps, tanning beds, and tanning booths (65). In fact, it is estimated that exposure to UV radiation, primarily from the sun, causes as many as 90 percent of U.S. cases of melanoma, the most deadly form of skin cancer. About 8 percent of cases are attributable to indoor tanning (66). Thus, one of the most effective ways a person can reduce his or her risk of skin cancer is by practicing sun-safe habits and not using UV indoor tanning devices (see sidebar on **Ways to Protect Your Skin**).

WAYS TO PROTECT YOUR SKIN

To reduce your risk of the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—the Centers for Disease Control and Prevention recommend that you:

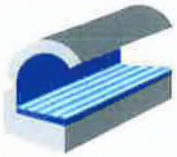
seek shade and limit time in the sun, especially around midday;

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 2 hours and after swimming, sweating, and toweling off; and



avoid indoor tanning with UV devices like sunlamps, sunbeds, and tanning booths.

Adapted from (24)

21,000 U.S. melanoma cases

each year from 2020 to 2030 could be prevented by implementing a comprehensive skin cancer prevention program (71).

INDOOR TANNING LEGISLATION

Use of an indoor UV tanning device increases a person's risk for melanoma by 20 percent, and each additional use increases risk a further 1.8 percent (73). The U.S. Food and Drug Administration is considering proposals that would ban the use of indoor UV tanning devices by people younger than age 18 and require manufacturers and indoor tanning facilities to take more actions to improve the overall safety of indoor UV tanning devices to protect adult consumers. As of July 31, 2016, legislation banning the use of indoor UV tanning devices by people younger than age 18 is already in place in numerous countries and several U.S. states:

- **Banned all indoor tanning—** Brazil and Australia.
- **Banned indoor tanning for all people younger than 18—** Austria, Belgium, Finland, France, Germany, Iceland, Italy, Norway, Portugal, Spain, and the United Kingdom, as well as California, Delaware, the District of Columbia, Hawaii, Illinois, Louisiana, Minnesota, Nevada, New Hampshire, North Carolina, Texas, and Vermont.
- **Banned indoor tanning for people younger than 18 unless they have a doctor's prescription—** Oregon and Washington.

A number of other U.S. states have legislation that imposes less stringent restrictions on the use of indoor UV tanning devices, but eight states have no legislation restricting the use of such devices: Alaska, Colorado, Iowa, Kansas, Montana, New Mexico, Oklahoma, and South Dakota.

TABLE 4 CANCER-CAUSING PATHOGENS

Bacteria

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Helicobacter pylori	Stomach cancers	32.5

Parasites

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Clonorchis sinensis	Biliary, gallbladder, and pancreatic cancers	0.1
Opisthorchis viverrini	Biliary, gallbladder, and pancreatic cancers	unknown
Schistosoma haematobium	Bladder cancer	0.3

Viruses

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Epstein-Barr Virus (EBV)	Hodgkin and certain non-Hodgkin lymphomas,and stomach and nasopharyngeal cancers	5.4
Hepatitis B/C Virus (HBV and HCV)	Hepatocellular carcinoma	29.5
Human Herpes Virus type -8 (HHV-8; also known as Kaposi sarcoma herpes virus)	Kaposi sarcoma and certain forms of lymphoma	2.1
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	unknown
Human Papillomavirus (HPV)	Anal, cervical, head and neck, oral, penile, vaginal, and vulvar cancers	30
Human T-cell Lymphotrophic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma	0.1
Merkel Cell Polyomavirus (MCV)	Skin cancer	unknown

* where known

Data from Ref. (76)

Despite the knowledge that the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—can be prevented, fewer than 15 percent of men and 30 percent of women use sunscreen regularly on their faces and other exposed skin when outside for more than 1 hour (67), and one in three adults in the United States reports experiencing at least one sunburn in the past 12 months (68). In addition, 6 percent of U.S. adults report using an indoor UV tanning device at least once in the past 12 months (69). The most recent data show that use of indoor UV tanning devices has declined among high school students, from 13 percent in 2013 to 7 percent in 2015, although more needs to be done to reduce this number even further (53, 70).

Continued exposures to UV radiation have fueled a rise in melanoma incidence rates over the past 3 decades (3), and researchers anticipate that the number of new U.S. melanoma cases diagnosed each year will rise dramatically in the coming decades if current trends continue, increasing from 65,647 in 2011 to 112,000 in 2030 (71). Thus, it is vital that individuals, families, communities, schools, workplaces, institutions, health care professionals, media, industry, government, and multinational bodies work together to develop and implement more effective policy changes and public education campaigns to reduce exposure to UV radiation. One policy change currently being considered by the FDA is a ban on the use of indoor UV tanning devices by individuals younger than age 18 (see sidebar on **Indoor Tanning Legislation**, p. 32). This measure could be particularly effective at reducing exposure to UV radiation given that recent research showed that placing age restrictions on the use of indoor UV tanning devices reduces the use of these devices by female high school students (72).

PREVENT INFECTION WITH CANCER-CAUSING PATHOGENS

Persistent infection with a number of pathogens—bacteria, viruses, and parasites that cause disease—increases a person's risk for several types of cancer (see **Table 4**) (74-76). It is estimated to have been responsible for about 2 million of the 12.7 million new cases of cancer diagnosed

worldwide in 2008, with more than 90 percent of these cases attributable to just four pathogens: *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) (76). Therefore, individuals can significantly lower their risk for certain types of cancer by protecting themselves from infection with cancer-associated pathogens or by obtaining treatment, if available, to eliminate an infection (see sidebar on **Preventing or Eliminating Infection With the Four Main Cancer-causing Pathogens**).

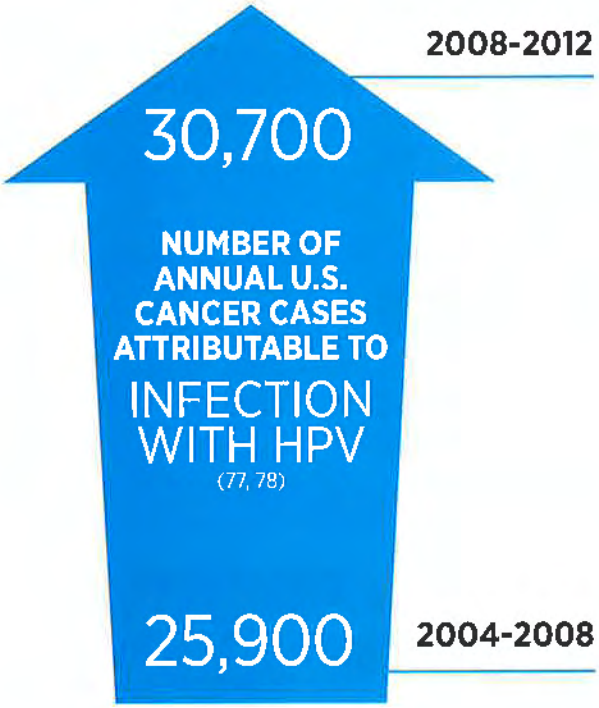
PREVENTING OR ELIMINATING INFECTION WITH THE FOUR MAIN CANCER-CAUSING PATHOGENS

PATHOGEN	WAYS TO PREVENT INFECTION	WAYS TO ELIMINATE OR TREAT INFECTION	U.S. RECOMMENDATIONS
Helicobacter pylori 	None available	Treatment with a combination of antibiotics and a proton-pump inhibitor can eliminate infection.	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.
HBV 	• HBV vaccination. • Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex).	Treatment of those chronically infected with antiviral drugs rarely eliminates infection but does slow virus multiplication; this slows the pace at which liver damage occurs and thereby reduces risk for liver cancer.	• Vaccination part of childhood immunization schedule since 1991. • USPSTF 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.
HCV 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex).	Treatment with any of several antiviral drugs can eliminate infection.	CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection.
HPV 	• Three FDA-approved vaccines. • Practice safe sex, although this may not fully protect against infection.	None available.	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.

CDC, Centers for Disease Control and Prevention; HPV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force. Adapted from (1).

Although there are strategies available to eliminate, treat, or prevent infection with *Helicobacter pylori*, HBV, HCV, and HPV, it is clear that these strategies are not being used optimally. For example, even though the CDC recommends screening all U.S. adults born from 1945 to 1965 for HCV infection and there are several therapeutics that can eliminate HCV infection, it is estimated that there are at least 3.5 million people in the United States currently infected with HCV (79). Given that infection with HCV is estimated to be responsible for 22 percent of cases of hepatocellular carcinoma (HCC)—the most common form of liver cancer—in U.S. adults age 68 or older (80), the burden of HCC could be significantly reduced through more effective implementation of HCV screening and treatment.

In addition, the development of strategies to increase uptake of the three FDA-approved HPV vaccines could have an immense impact on cancer prevention (see sidebar on **How Do the Three FDA-approved HPV Vaccines Differ?**). It is estimated that in the United States, more than 53,000 cases of cervical cancer and thousands of cases of other HPV-related cancers, including many anal, genital, and oral cancers, could be prevented if 80 percent of those



HOW DO THE THREE FDA-APPROVED HPV VACCINES DIFFER?

13 **strains of HPV can cause cancer:** HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66.

3 **FDA-approved 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, as well as 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, and 58.
- FDA approved in 2014.
- FDA approved for:
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of females ages 9 to 26 and males ages 9 to 15.

Information is current as of July 2016

Adapted from (24)

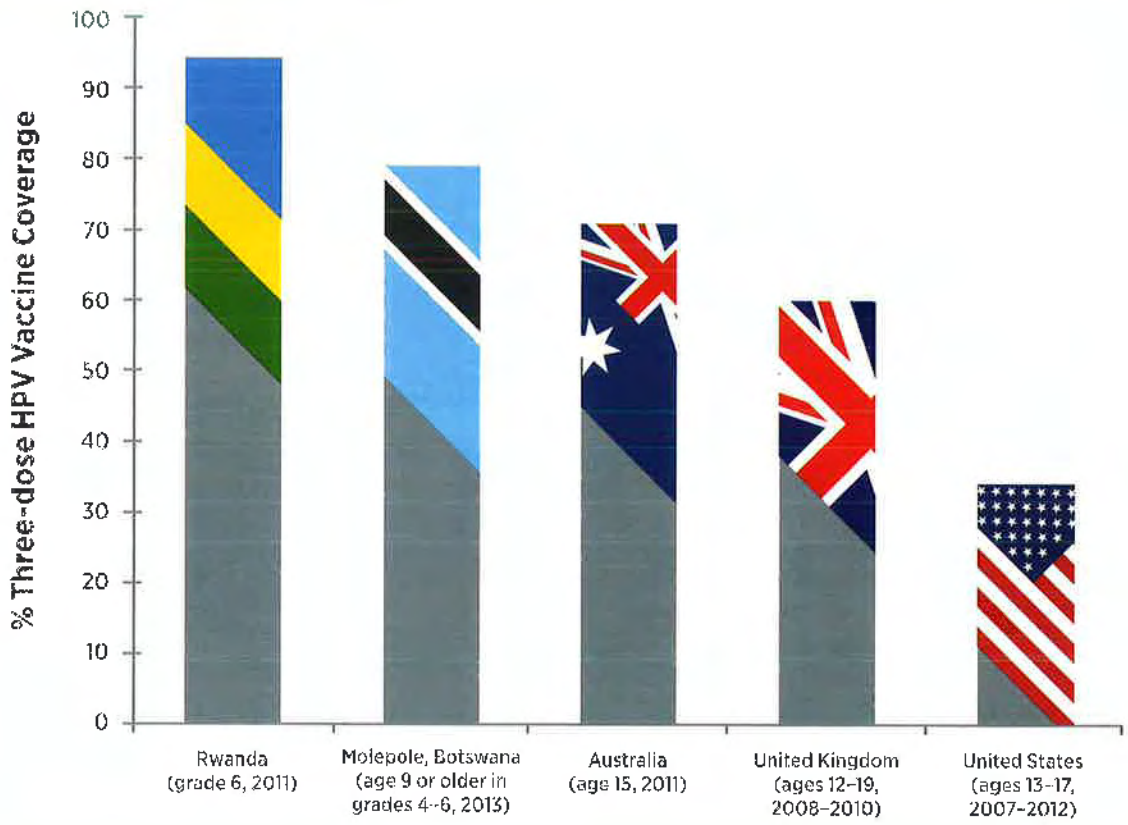
for whom HPV vaccination is recommended—girls and boys at age 11 or 12—were to be vaccinated (81). However, the most recent estimates from the CDC show that in 2014, only 40 percent of girls ages 13 to 17 and 24 percent of boys of the same age had received the full course of three or more doses of an HPV vaccine (82). This low coverage stands in stark contrast to three-dose HPV vaccine coverage in other countries (81, 83) (see **Figure 7**).

In 2011–2012,
847,000
noninstitutionalized U.S. adults were estimated to be chronically infected with HBV (79).

Several steps to address the low HPV vaccine coverage in the United States were recently recommended by the National Vaccine Advisory Committee (NVAC), a federal advisory committee that provides vaccine and immunization policy recommendations to the U.S. Department of Health and Human Services (85). Among the objectives outlined by the NVAC was the development of comprehensive communication strategies for physicians to encourage HPV vaccination at every opportunity. The need for these strategies is highlighted by recent data showing that many physicians recommend HPV vaccination inconsistently, behind schedule, or without urgency (86).

FIGURE 7

IN NEED OF A BOOST



The percentage of adolescent girls in the United States to have received the recommended three doses of the human papillomavirus (HPV) vaccine is very low compared with the percentages vaccinated in other high-income countries, such as Australia and the United Kingdom. Rwanda, a low-income country, has implemented a national, multisector, collaborative, school-based HPV vaccination program (81, 83). A trial of a school-based HPV vaccination program in Molepole, a traditional village in Botswana with a population of more than 60,000, was recently reported to have led to 79 percent of eligible girls receiving three doses of the HPV vaccine and to a nationwide rollout of the program in 2015 (84).

LIMIT EXPOSURES TO ENVIRONMENTAL RISK FACTORS

There are many other cancer risk factors in our environment, including environmental pollutants and occupational cancer-causing agents (87) (see **Figure 3**, p. 24). It can be difficult for people to avoid or reduce their exposure to many of these factors. Therefore, it is imperative that policies are put in place to ensure that everyone lives and works in a safe and healthy environment.

In the United States, some policies that help protect people from known cancer risk factors have been in place for several decades. For example, there are numerous policies to help prevent exposure to asbestos, which can cause mesothelioma, an aggressive type of cancer for which there remain few treatment options (88). There are also guidelines for reducing exposure to radon gas, which is released from rocks, soil, and building materials and is the second most common cause of lung cancer in the United States after cigarette smoking (89). That said, compliance with these guidelines is not mandatory. It is estimated that about one in every 15 U.S. homes has radon levels at or above 4 picocuries per liter of air, which is the level at which the U.S. Environmental Protection Agency (EPA) recommends taking action (89).

As we learn more about environmental and occupational cancer risk factors and identify segments of the U.S. population exposed to these, we need to develop and implement new and/or more effective policies. We also need to do more worldwide to limit exposure to well-established environmental and occupational cancer risk factors such as asbestos.

One environmental pollutant that was recently classified by the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, as having the ability to cause cancer in humans, is outdoor air pollution (90). Outdoor air pollution is a complex cancer risk factor because it is a mixture of pollutants that vary over space and time as a result of differences in climate and sources of outdoor air pollution. We do know, however, the sources of much outdoor air pollution—emissions from motor vehicles, industrial processes, power generation, and the burning of solid fuels for domestic heating and cooking—and it is clear that new policy efforts to reduce the release of pollutants into the atmosphere are needed if we are to reduce the burden of cancer.

Growing knowledge of the environmental pollutants to which different segments of the U.S. population are exposed highlights new opportunities for education and policy initiatives to improve public health. For example, arsenic exposure is a well-established cause of bladder cancer. A recent study identified drinking water containing low-to-moderate levels of arsenic, obtained from shallow-dug private wells, as a potential contributor to the elevated incidence of bladder cancer that has been documented in New England for more than 5 decades (91).

In other cases, increasing knowledge of the presence of environmental pollutants in certain geographic regions emphasizes the need for more research to inform the future development and implementation of education and policy initiatives. For example, researchers recently found elevated levels of uranium and other heavy metals in abandoned mines in northeastern Arizona and are now investigating how this might affect nearby Native American communities (92).

5,000

U.S. lung cancer deaths could be prevented each year if radon levels in every home were reduced below the level at which the U.S. Environmental Protection Agency (EPA) recommends taking action (4 picocuries per liter of air) (89).

Five new research centers

to improve health in U.S. communities overburdened by pollution and other environmental factors that contribute to health disparities are being funded by a partnership between the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (EPA).

For more information go to: https://www.nih.gov/news-events/news-releases/new-nih-epa-research-centers-study-environmental-health-disparities

FINDING CANCER

In this section you will learn:

- Understanding of the biology of cancer initiation and development has led to screening tests that can be used for cancer prevention and early detection.
- There are five types of cancer for which screening tests have been developed and used in the clinic to screen generally healthy individuals.
- Independent groups of experts rigorously evaluate data on the benefits and potential risks of cancer screening tests before putting forth recommendations about the use of the test; these recommendations are updated periodically to incorporate new evidence.
- Areas of disagreement among different recommendations highlight areas in which more research is needed.
- Some people are at increased risks for certain types of cancer and may need to take measures to reduce the risks.

The primary cause of cancer initiation and development is the accumulation of genetic mutations that disrupt the orderly processes controlling the multiplication and life span of normal cells. There are numerous factors that cause genetic mutation acquisition (see **Figure 3**, p. 24), and the identity, order, and speed at which a cell acquires genetic mutations determine whether a given cancer will develop and, if a cancer does develop, the length of time it takes to happen.

Knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development provides us with opportunities to develop screening strategies that allow us to detect, if present, precancerous lesions or cancer at an early stage of development (see **Figure 8**, p. 39). Precancerous lesions can be removed before they develop into cancer, something that is sometimes referred to as cancer interception. Finding cancer early, before it has spread to other parts of the body, makes it more likely that a cancer can be intercepted and the patient treated successfully.

CANCER SCREENING

There are five types of cancer for which screening tests have been developed and used in the clinic to screen generally healthy individuals (see sidebar on **Cancers for Which Screening Tests Exist**, p. 40). Some of these tests can be used to prevent cancer from developing because they detect precancerous changes in a tissue that can be removed before they have a chance to develop into cancer. Others can detect cancer at an early stage of development, when it is more likely that a patient can be treated successfully. Recommendations on how best to use these tests are discussed in the information to follow.

One area of intensive research investigation aims to gain a deeper understanding of the biology of precancerous lesions (93, 94). The goal is that as we learn more about the genetic, molecular, and cellular characteristics of precancerous lesions, we can develop new screening tests and cancer prevention therapeutics, as well as more precisely identify those for whom cancer screening and cancer prevention therapeutics would be beneficial.

WHO SHOULD BE SCREENED?

Screening to detect cancer before an individual shows signs or symptoms of the disease for which he or she is being screened has many benefits, but it can also result in unintended adverse consequences (see sidebar on **Cancer Screening**, p. 41). Thus, population-level use of a cancer screening test must not only decrease deaths from the screened cancer, but it must also provide benefits that outweigh the potential risks. Determining whether broad implementation of a screening test across the population can achieve these two goals requires extensive research and careful analysis of the data generated.

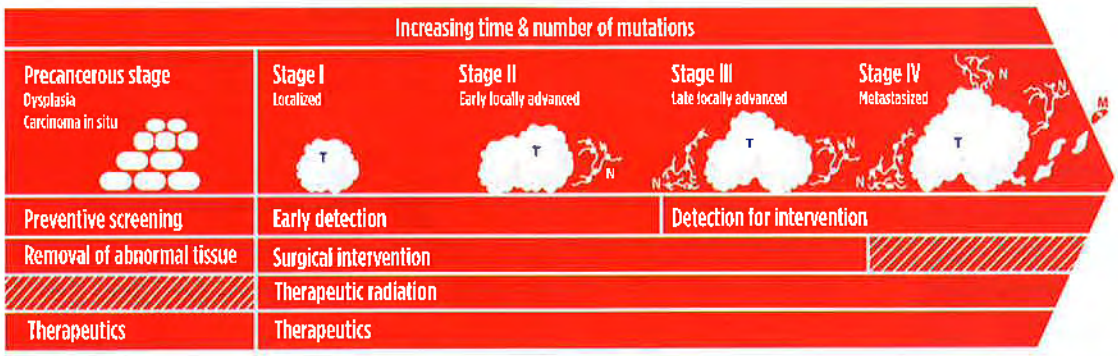
In the United States, an independent group of experts convened by the Agency Healthcare Research and Quality of the US Department of Health and Human Services rigorously evaluates data regarding the benefits and potential risks of cancer screening tests to make evidence-based recommendations about the routine use of these tests. These volunteer experts form the U.S. Preventive Services Task Force (USPSTF). In addition to considering evidence regarding potential new screening programs, the USPSTF re-evaluates existing recommendations as new research becomes available and can revise them if deemed necessary.

Many professional societies also convene panels of experts to meticulously evaluate data regarding the benefits and potential risks of cancer screening tests, and each society makes its own evidence-based recommendations about the use of these tests. Because the representatives on each panel weighing the benefits and potential risks of a given cancer screening test are often different, and different groups give more weighting to certain benefits and potential risks than other groups do, this can result in differences in recommendations from distinct groups of experts.

The existence of different cancer screening recommendations can make it challenging for individuals to ascertain when and for which cancers they should be screened. Nevertheless, there is more consensus among recommendations than disagreement (see sidebar on **Consensus Among Cancer Screening Recommendations**, p. 42). The differences among the recommendations of different groups of experts highlight the areas in which more research is needed to determine more clearly the relative benefits and potential risks of screening, to develop new screening tests that have clearer benefits and/or lower potential risks, or to better identify people for whom the benefits of screening outweigh the potential risks.

Evidence-based cancer screening recommendations are only one consideration when a person makes decisions about which cancers he or she should be screened for and when. A consideration for some people is whether a screening test is covered by his or her health insurance. The enactment of the Patient Protection and Affordable Care Act of 2010, also known as "Obamacare," increased the number of people covered by health insurance. It also includes a provision that requires qualified health insurance plans offered through health insurance exchanges, health insurance plans not designated as grandfathered, and Medicare to cover the costs of cancer screening tests recommended as grade A or B by the USPSTF. Individuals should check their own plans to see if they are covered. A consequence of this legislation is broader access to recommended screening tests for more people. For example, one recent study estimates that the enactment of this legislation enabled 6.8 million low-income women to gain access to health insurance, which should lead to increases in levels of cancer screening among this population (95). Further research is needed to confirm this result.

FIGURE 8 POINTS OF INTERVENTION

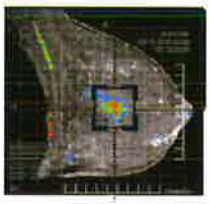


Many cancers are progressive in nature. In the example depicted here, an initial genetic mutation can lead to normal cells taking on precancerous characteristics. As these cells multiply and acquire more genetic mutations, the precancerous lesion becomes increasingly dysplastic, or abnormal. Over time, as additional genetic mutations accumulate, the dysplastic precancerous lesion may evolve into a cancerous lesion, then spread to nearby lymph nodes and, as it becomes more advanced, ultimately metastasize. Screening tests—such as the Pap test and colonoscopy—can be used to prevent cancer because they can find precancerous lesions, which can then be removed before they develop into cancerous lesions either through surgery or with the use of certain therapeutics (see **Supplemental Table 1**, p. 130). Use of other screening tests, such as mammography, aims to find cancer at an early stage, when it is more likely that the patient can be treated successfully. The treatment a patient receives depends on numerous factors, including the type of cancer and the stage of disease at which diagnosis occurred, but it can include surgery, radiotherapy, chemotherapy (both cytotoxic and molecularly targeted), and/or immunotherapy. Treating a precancerous lesion or early stage cancer detected by screening is sometimes called cancer interception.

CANCERS FOR WHICH SCREENING TESTS EXIST

Highlighted here are cancer screening tests that have been used in the clinic to screen generally healthy individuals. When to use these tests and in whom is discussed elsewhere (see Who Should Be Screened?, p. 38).

BREAST CANCER



Screening mammogram: Uses X-rays to image the breast.

The information generated by the procedure can be stored on film (a conventional mammogram) or electronically (a digital mammogram).

In most cases, the image is two-dimensional, but some machines generate three-dimensional images in a process called breast tomosynthesis.

Can detect breast cancers that cannot be felt. These cancers can be at any stage of development, but the aim of screening is to find them at the earliest possible stage.

CERVICAL CANCER

Pap test: Samples cervical cells, which are analyzed under a microscope to look for abnormalities.

Can detect precancerous or cancerous cervical lesions, but the aim of screening is to find them at the earliest possible stage.

HPV test: Detects the presence of certain cervical cancer-causing types of human papillomavirus (HPV).

Does not directly detect precancerous or cancerous cervical lesions, but identifies people for whom follow-up is recommended.

LUNG CANCER

Low-dose computed tomography (CT) scan: Uses low doses of X-rays to image the lungs.

Can detect lung cancers that are not causing symptoms. These cancers can be at any stage of development, but the aim of screening is to find them at the earliest possible stage.

PROSTATE CANCER

PSA test: Measures the level of the protein prostate-specific antigen (PSA) in blood.

Does not directly detect prostate cancer, but the blood level of PSA is often elevated in men with prostate cancer.

COLORECTAL CANCER

Stool tests: Some test for the presence of red blood cells in stool samples. Others test for both red blood cells and certain genetic mutations linked to colorectal cancer.

Do not directly detect colorectal precancerous lesions or cancers, but rather identify people for whom further testing is recommended.

Flexible sigmoidoscopy and colonoscopy: Both use a thin, flexible, lighted tube with a small video camera on the end to allow physicians to look at the lining of certain parts of the colon and rectum.

Can detect colorectal precancerous lesions or cancers, but the aim of screening is to find them at the earliest possible stage so that they can be removed.

Computed tomography (CT) colonography (virtual colonoscopy) and double-contrast barium enema: Use X-rays to image the colon and rectum.

Can detect colorectal precancerous lesions or cancers, but the aim of screening is to find them at the earliest possible stage so that they can be removed.

Blood test: Detects epigenetic abnormalities linked to colorectal cancer in blood (see **Increasing Options for Colorectal Cancer Screening, p. 57**).

Does not directly detect colorectal precancerous lesions or cancers, but rather identifies people for whom further testing is recommended.

CANCER SCREENING

BENEFITS OF SCREENING

Reduced cancer incidence. Screening tests can detect precancerous lesions. Removal of the lesions can reduce, or even eliminate, an individual's risk of developing the screened cancer at that spot (see **Figure 8**, p. 39).

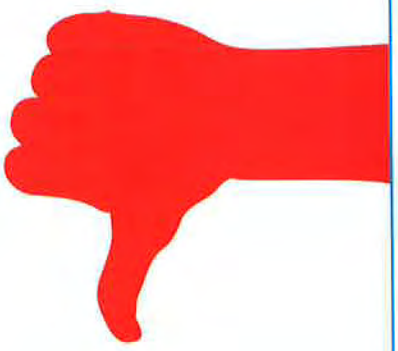
Reduced incidence of advanced disease. Screening tests that detect developing cancers can reduce the individual's risk of being diagnosed with the screened cancer at a stage when it has spread to other parts of the body (see **Figure 8**, p. 39).

Reduced cancer mortality. Diagnosis at an early stage of disease can increase the likelihood that a patient can be successfully treated, which thereby reduces the individual's risk of dying from the screened cancer.

POTENTIAL RISKS OF SCREENING

Adverse events. Screening tests are medical procedures; thus, they carry some risk. However, the chance that an adverse event will occur during a screening test recommended by the U.S. Preventive Services Task Force (USPSTF) or a professional society 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 test results. Not all individuals who have a positive screening test result have the screened cancer. The rates of false-positive test results vary depending on the test but are generally low; a false-positive screen can result in additional unnecessary medical procedures, treatments, and anxiety.

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

Overdiagnosis and overtreatment. Not all precancers or cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, can lead to overtreatment, which may carry its own risks and costs. The rates of overdiagnosis and overtreatment vary among screening tests and are difficult to quantify.

Adapted from (1)

CONSENSUS AMONG CANCER SCREENING RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) and many professional societies have evidence-based recommendations about the use of cancer screening tests. Here, we highlight consensus, as of July 31, 2016, among cancer screening recommendations from the USPSTF, the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), the American College of Physicians (ACP), the American College of Obstetrics and Gynecology (ACOG), and the American Urological Association (AUA). Not all of the professional societies have recommendations for every cancer screening test.

BREAST CANCER

There is consensus among the ACS, NCCN, and USPSTF that: women ages 50–74 who are at average risk for breast cancer should have regular screening mammograms. However, there is variability about whether this should be done every year or every other year.

CERVICAL CANCER

There is consensus among the ACOG, ACS, ACP, and USPSTF that:

- average-risk women younger than 21 should not be screened;
- average-risk women ages 21–29 should have a Pap test every 3 years;
- average-risk women ages 30–65 should have either a Pap test every 3 years or a Pap test and HPV testing every 5 years; and
- women older than 65 should not be screened if they have previously had regular screenings with normal results and are not otherwise at high risk for cervical cancer.

COLORECTAL CANCER

There is consensus among the ACS, ACP, NCCN, and USPSTF that:

- adults ages 50–75 who are at average risk for colorectal cancer should be screened; and
- adults ages 50–75 should consult with their health care providers to choose the test that is right for them.

Some professional societies, however, recommend certain approaches over others. The overall message is that using any one of the approved tests is better than not being screened.

LUNG CANCER

There is consensus among the ACS, ACP, and USPSTF that:

- screening with low-dose computed tomography should be limited to adults ages 55–79 who are at high risk for lung cancer because they have smoked at least 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.

The USPSTF recommends annual screening for these individuals, whereas the ACS and ACP recommend these individuals talk to a physician about the benefits and potential harms of screening before deciding if it is right for them.

PROSTATE CANCER

There is little consensus among the ACS, ACP, AUA, NCCN, and USPSTF, with recommendations ranging from do not screen at all to screen regularly. That said, the ACS, ACP, and AUA all recommend that men ages 55–69 who are at average risk for prostate cancer talk to a physician about the benefits and potential harms of PSA testing before deciding if screening is right for them.

To find out more about cancer screening recommendations for people who fall outside the age groups highlighted here or for people who are at increased risks for certain cancers see: http://www.uspreventiveservicestaskforce.org/, http://www.cancer.org/, http://m.acog.org/, https://www.auanet.org/, https://www.acponline.org/, and https://www.nccn.org/.

TABLE 5 INHERITED CANCER RISK

Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	ATM
Basal cell carcinoma	Basal cell nevus syndrome	PTCH1, PTCH2, SUFU
All cancers	Bloom syndrome	BLM
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	BRCA1, BRCA2
Breast, thyroid, and endometrial cancers	Cowden syndrome	PTEN
Breast and stomach cancers	Diffuse gastric and lobular breast cancer syndrome	CDH1
Colorectal cancer	Familial adenomatous polyposis (FAP)	APC
Melanoma and pancreatic cancer	Familial atypical multiple mole-melanoma syndrome (FAMM)	CDKN2A
Retinal cancer	Familial retinoblastoma	RB1
Leukemia	Fanconi's anemia	FACC, FACA
Kidney cancer and uterine fibroids	Hereditary leiomyomatosis and renal cell cancer	FH
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	PRSS1, SPINK1
Leukemias, breast, brain, and soft tissue cancers	Li-Fraumeni syndrome	TP53
Colorectal and endometrial cancers	Lynch syndrome	EPCAM, MLH1, MSH2, MSH6, PMS2
Pancreatic cancers, pituitary adenomas, benign skin, and fat tumors	Multiple endocrine neoplasia 1	MEN1
Thyroid cancer and pheochromacytoma	Multiple endocrine neoplasia 2	RET, NTRK1
Pancreatic, liver, lung, breast, ovarian, uterine, and testicular cancers	Peutz-Jeghers syndrome	STK11/LKB1
Tumors of the spinal cord, cerebellum, retina, adrenals, and kidneys	von Hippel-Lindau syndrome	VHL
Kidney cancer	Wilms' tumor	WT1
Skin cancer	Xeroderma pigmentosum	XPD, XPB, XPA

This list is not meant to be exhaustive, but contains some of the more commonly occurring cancer syndromes.
Source: http://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq

A person's own unique risks for developing each type of cancer, his or her tolerance of the potential risks of a screening test, and his or her general health are also important considerations when deciding when and for which cancers to be screened (see sidebar on **Cancer Screening**, p. 41). A person's overall risks are determined by genetic, molecular, cellular, and tissue makeup, as well as by lifetime exposures to cancer risk factors (see **Figure 3**, p. 24). Therefore, every individual should consult with his or her health care practitioner to develop a cancer prevention and early detection plan tailored to his or her personal cancer risks and tolerance of potential screening risks, as **Congressman Donald Payne** did (see p. 44). Given that these factors can vary over a person's lifetime, it is important that individuals continually evaluate their cancer screening plans and update them if necessary.

Some individuals are at increased risk of certain cancers because they inherited a cancer-predisposing genetic mutation (see **Table 5**) (96). If an individual has a family

About 5%–10%

of new U.S. cancer cases are linked to inherited cancer-predisposing genetic mutations (22).

RAISING AWARENESS ABOUT COLORECTAL CANCER SCREENING AND CANCER HEALTH DISPARITIES

THE HONORABLE DONALD M. PAYNE, JR. // U.S. REPRESENTATIVE FOR NEW JERSEY'S 10TH CONGRESSIONAL DISTRICT // CO-CHAIR OF THE CONGRESSIONAL MEN'S HEALTH CAUCUS // AGE 57

Witnessing my father's heartbreaking battle with colorectal cancer was one of the most difficult times in my life. On the other hand, it made me passionate about increasing awareness of the benefits of colorectal cancer screening, particularly in communities disproportionately affected by the disease. It also drove me to work toward the elimination of cancer health disparities and led me to be vigilant about my own cancer screening.

My father, the late Congressman Donald M. Payne, was a member of Congress for 23 years. He was very well educated, but neither he nor I realized the importance of colorectal cancer screening. As a result, he was not tested in time to prevent his cancer or even to detect it at an early stage, when it could have been more easily treated. He ultimately lost his battle with colorectal cancer in March 2012. I have often said that had he been screened earlier, he would still be with us today.

After my father's diagnosis with colorectal cancer, I set out to educate myself about the disease. I learned that experts recommend that men and women at average risk for colorectal cancer begin screening for the disease at age 50. I also learned that colorectal cancer affects the African-American community more deeply than it does other communities and that some experts recommend African Americans start screening at age 45.

Given my father's experience and what I had learned in my own research about colorectal cancer, I decided to have my first colonoscopy in December 2012, the day I turned 54. It was a good decision because the doctor found and removed 13 polyps, or precancerous growths, during the procedure. I was shocked to learn this, but I was glad to have caught the polyps before they became cancerous.

When I went back the following year for a second colonoscopy, the doctor found and removed another three polyps. Since then, I have had a colonoscopy every year on my birthday. I tell people it is my birthday present to myself because I know routine screenings are essential for maintaining my health.

As a result of my experiences, I am dedicated to spreading the word about how colorectal cancer screening saves lives. I speak to a lot of communities—at community health centers, on neighborhood corners, and at places of worship—about the fact that colorectal cancer is highly preventable, but you have to catch it early. I tell people about the need for testing, and I try to dispel the notion that the screening process is painful and extremely unpleasant. It's a moment of discomfort, but it can save your life. By talking about colorectal cancer, I hope to remove the stigma that is attached to the disease and the screening tests.

During my work to raise awareness about colorectal cancer screening, I have come to realize that men oftentimes think they are invincible. However, we need to be more proactive about our health so that we can enjoy our later years and so that we can give ourselves and our families the security we deserve.

As co-chair of the Congressional Men's Health Caucus, I have a great opportunity to raise awareness of the importance of preventive care among men and to help reduce health disparities across diseases, particularly those that touch so many lives, like cancer. Improving outcomes for communities disproportionately affected by cancer not only means spreading awareness about preventive care, but it also means educating people in these communities about the importance of participating in clinical trials.

Although clinical trials are at the heart of the process for bringing new medicines to patients, African Americans and other minorities remain significantly underrepresented in these trials. Encouraging minority participation in clinical research is important so that all communities, regardless of race, ethnicity, or socioeconomic status benefit from promising new treatments.

My role as co-chair of the Congressional Men's Health Caucus has also afforded me the chance to more effectively advocate for getting the National Institutes of Health and the Centers for Disease Control and Prevention the funding they need to push forward research and screenings to save and improve more lives. As a lawmaker, I have the responsibility to make sure that people do not experience what my family went through. We must continue to educate people about the importance of funding for research and prevention in our fight against cancer.

ADULTS AGES 50–75 ARE RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF) TO BE SCREENED FOR **COLORECTAL CANCER**, BUT ONE IN EVERY THREE IS NOT UP TO DATE WITH SCREENING

© Karen Sayre

TABLE 6

SURGERIES FOR THE PREVENTION OF CANCER

Genetic Mutation(s)	Cancer	Technique	Removes
APC	Colon Cancer	Colectomy	Colon/large intestine
BRCA1 or BRCA2	Breast Cancer	Mastectomy	Breasts
BRCA1 or BRCA2	Ovarian Cancer	Salpingo-oophorectomy	Ovaries and fallopian tubes
CDH1	Stomach Cancer	Gastrectomy	Stomach
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

or personal history of cancer and thinks that he or she is at high risk for inheriting such a mutation, he or she should consult a physician and consider genetic testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?** p. 47). There are genetic tests that individuals can use without a prescription from a physician, but there are many factors to weigh when considering whether to use one of these direct-to-consumer tests (see sidebar on **Direct-to-Consumer Genetic Testing**, p. 47).

In addition to cancer-predisposing genetic mutations, a number of medical conditions increase a person's risk for certain types of cancer. For example, ulcerative colitis and Crohn disease increase an individual's risk for colorectal cancer, and a complication of gastroesophageal reflux disease (Barrett esophagus) increases risk for esophageal adenocarcinoma (97, 98). These are all relatively rare conditions, but much more prevalent medical conditions also increase risks for certain cancers. For example, type 2 diabetes, which affects 9.5 percent of U.S. adults age 18 or over (20), increases an individual's risk of developing liver, pancreatic, and endometrial cancers (99, 100).

If a person is at increased risk for developing a certain type or types of cancer, he or she can tailor risk-reducing measures to his or her personal needs. Some people may be able to reduce their risk by modifying their behaviors, for example, by smoking cessation. Others might need to increase their use of certain cancer screening tests or use cancer screening tests that are not recommended for people who are generally healthy; for example, the American College of Gastroenterology (although not the USPSTF) recently put forth recommendations about using endoscopy to screen people diagnosed with Barrett esophagus for precancerous lesions, esophageal lesions, and/or esophageal cancer (101). Yet others may consider taking a preventive medicine or having risk-reducing surgery (see **Table 6** and **Supplemental Table 1**, p. 130).

As we learn more about the genetic, molecular, and cellular characteristics of precancerous lesions, we will be able to develop and implement new strategies that pair this increased understanding with knowledge of an individual's unique cancer risk profile, including his or her genetic makeup at birth, exposures to cancer risk factors, age, and gender. This information will allow us to better tailor cancer prevention and early detection to the individual patient, ushering in a new era of precision cancer prevention (26).

The USPSTF recently recommended that

adults ages 50–59

who have a 10% or greater 10-year risk for developing cardiovascular disease, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years, start taking low-dose aspirin to prevent cardiovascular disease as well as colorectal cancer (102).

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);

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); and

one or more members with cancers in both of a pair of organs (such as both eyes, both kidneys, or both breasts);

more than one childhood cancer in a set of siblings (such as sarcoma in both a brother and a sister);

members with a type of cancer usually occurring in the opposite sex (such as breast cancer in a man).

Adapted from: http://www.cancer.org/cancer/cancercauses/geneticsandcancer/heredity-and-cancer.

DIRECT-TO-CONSUMER GENETIC TESTING

Direct-to-consumer (DTC) genetic tests are marketed directly 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 his or her 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.

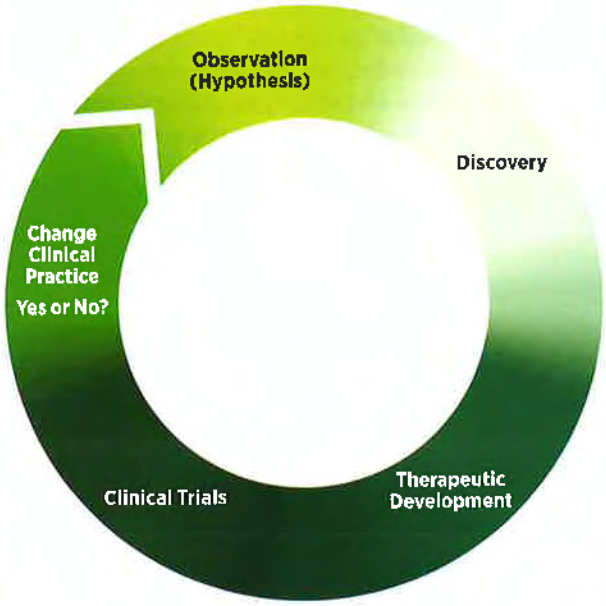
DTC Genetic Tests and the FDA
DTC tests that claim to provide only information such as a person's ancestry or genealogy are not regulated by the U.S. Food and Drug Administration (FDA). In February 2015, however, the FDA authorized marketing of the first DTC genetic test: 23andMe's Bloom Syndrome carrier 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.

FDA APPROVED

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.

Adapted from (24)

FIGURE 9 THE BIOMEDICAL RESEARCH CYCLE



Results from any type of research can fuel biomedical research by providing observations relevant to the practice of medicine, which lead to questions, or hypotheses, that are tested in experiments during the discovery phase of research (see sidebar on **Biomedical Research: What It Is and Who Conducts It**, p. 50). During the discovery phase, traits unique to a disease may be uncovered, leading to the development of a potential therapeutic (see sidebar on **Therapeutic Development**, p. 54). Before entering clinical testing, potential therapeutics are subjected to preclinical testing to identify any toxicities and help determine initial dosing. Clinical testing is a multiphase process aimed at demonstrating the safety and efficacy of a potential therapeutic (see sidebar on **Phases of Clinical Trials**, p. 55). If a therapeutic is safe and effective and is approved for use by the U.S. Food and Drug Administration (FDA), it will enter into clinical practice, where it can improve the lives of patients. Importantly, observations made during the routine use of a new therapeutic can feed back into the biomedical research cycle and further enhance the use of that therapeutic or the development of others like it. If, however, a therapeutic is not safe or effective and fails to gain FDA approval, the observations from the clinical testing still feed back into the biomedical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge, and research undertaken during any part of the cycle continually powers new observations.

Figure adapted from Ref. (24)

After a potential therapeutic target is identified, it takes several years of hard work before a candidate therapeutic is developed and ready for testing in clinical trials (see sidebar on **Therapeutic Development**, p. 54). During this time, candidate therapeutics are rigorously tested to identify an appropriate dose and schedule, as well as any potential toxicity.

Clinical trials are a central part of the biomedical research cycle that ensure that novel discoveries ultimately reach the patients who need them the most, as quickly and safely as possible. Before most potential new diagnostic, preventive, or therapeutic products can be approved by the FDA and used as part of patient care, their safety and efficacy must be rigorously tested through clinical trials. All clinical trials are reviewed and approved by institutional review boards before they can begin and are monitored throughout their duration. There are several types of cancer clinical trials, including treatment trials, prevention trials, screening trials, and supportive or palliative care trials, each designed to answer different research questions.

In oncology, treatment clinical trials often add the investigational anticancer therapeutic to the current standard of care. These types of clinical trials have traditionally been done in three successive phases, each with an increasing number of patients (see sidebar on **Phases of Clinical Trials**, p. 55).

As a result of recent, research-powered advances in our understanding of cancer biology, in particular the genetic mutations that underpin cancer initiation and growth (see **Cancer Development: Influences Inside the Cell**, p. 18), researchers, regulators, and the pharmaceutical industry have been able to develop new ways of conducting clinical trials. The new approaches aim to streamline the development of new anticancer therapeutics by matching the right therapeutics with the right patients earlier, reducing the number of patients that need to be enrolled in clinical trials before it is determined whether or not the therapeutic being evaluated is safe and effective. They can also decrease the length of time it takes for a new anticancer therapeutic to be tested and made available to patients.

At the regulatory level, the FDA has implemented several changes that have altered how clinical trials can be conducted and reviewed in an effort to reduce the length

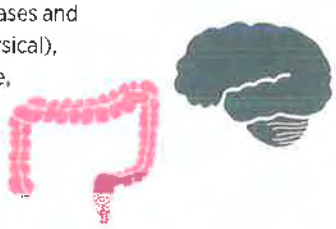
of time it takes to obtain a clear result from a clinical trial (see sidebar on **FDA's Expedited Review Strategies**, p. 56). An increasing number of anticancer therapeutics are being approved by the FDA using the most recently introduced of these review strategies—breakthrough therapy designation. A key part of this review strategy is that the FDA engages with those developing the investigational therapeutic early in the clinical trials process and provides continued guidance throughout the review period. It is sometimes used alongside other expedited review strategies, such as accelerated approval.

One of the main changes to the way in which clinical trials are conducted is the increasing use of genomics and adaptive trial designs to identify the patients most likely to benefit from an investigational anticancer therapeutic. These approaches aim to reduce the number of patients that need to be enrolled in a clinical trial to determine whether the therapeutic being evaluated is effective. They largely fall into one of two clinical trial designs: "basket" studies and "umbrella" studies (see **Figure 10**, p. 57). Basket trials test one given therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original

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, prevention, treatment, and rehabilitation of persons.



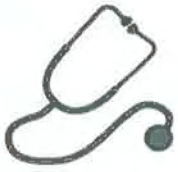
The scientific investigation required to understand the underlying life processes that affect disease and human well-being, including areas such as the cellular and molecular bases of diseases, genetics, and immunology.

The design of methods, drugs, and devices used to diagnose, support, and maintain the individual during and after treatment for specific diseases or conditions.

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 organisms, 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 also conduct research. They may perform population, clinical, or basic research.

Adapted from (1)

cancer. Umbrella trials test multiple therapeutics across multiple genetic mutations on a group of patients, all of whom have cancer arising in the same anatomic site.

As our knowledge of cancer biology grows at an ever-quickening pace, continued and increased dialogue among researchers, regulators, and the pharmaceutical industry is essential to provide the right patients access to the best anticancer therapeutics that have been proven to be safe and highly effective in well-designed, well-conducted clinical trials at the earliest possible time (105).

Dialogue among researchers, regulators, and the pharmaceutical industry is also important as physician-scientists look to use genomics to identify patients who might benefit from therapeutics not previously FDA approved for their type of cancer, an approach known as drug repositioning or drug repurposing.

One patient who is benefiting from drug repositioning is **Luke Theodosiades**, who was just 11 years old when he was diagnosed with acute lymphoblastic leukemia (ALL) (see p. 58). After his leukemia did not respond well at all to intensive standard-of-care chemotherapy, Luke's team of physicians at Children's Hospital of Philadelphia were very concerned and pursued a specialized genomic analysis of his leukemia cells performed by researchers at the University of New Mexico. This analysis found that his leukemia cells had undergone genetic recombination (see sidebar on **Genetic Mutations**, p. 20), resulting in the fusion of two genes (GOLGA5 and JAK2). The GOLGA5-JAK2 fusion gene generated a new protein that was driving the multiplication of Luke's leukemia cells and likely conferred resistance to his initial chemotherapy. Because JAK2 is a protein targeted by ruxolitinib (Jakafi), which was first approved by the FDA in 2011 for treating adults with myelofibrosis, Luke's physicians added ruxolitinib to his treatment regimen. After several months of combination therapy, no leukemia cells with the GOLGA5-JAK2 fusion protein were detectable in Luke's bone marrow, making him eligible to receive other treatments to maintain long-term remission.

As of July 31, 2016, breakthrough therapy designation has been awarded to

45

anticancer therapeutics since its introduction in 2012; 18 of these have received FDA approvals after being designated breakthrough therapies.

RECLASSIFICATION OF BRAIN TUMORS

23,770 NEW CASES

16,050 DEATHS

Researchers estimate that 23,770 new cases of brain and other nervous system cancers will be diagnosed in the United States in 2016, and that there will be 16,050 deaths from these types of cancers (3).

There are many types of brain and central nervous system tumors. Most oncologists use the World Health Organization (WHO) classification system to identify which of the many types of brain tumors a patient has. This information is vital to physicians and their patients as they understand the patient's outlook and decide which treatments are the best options.

In May 2016, the WHO updated the brain and central nervous system tumor classification system (103).

The previous classification system was based on identifying the cell type in which the tumor arose and how closely the cancer cells resemble the cell of origin (104).

The new classification system integrates molecular information about a patient's tumor with information on the cell of origin and how the cells look compared with the cell of origin (103). This reclassification was made possible by research that revealed the genetic and epigenetic variability among tumors previously thought to be of the same type.

The new classification system will allow physicians to more precisely diagnose and treat patients.

THERAPEUTIC DEVELOPMENT

Target validation.
Potential therapeutic targets identified in discovery research are confirmed to play a causative 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.
Cellular and 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 or "first-in-human" 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.

Adapted from (1)

Additional genomics research has identified JAK2 gene rearrangements in leukemia cells from other children with ALL (106). However, before ruxolitinib can become part of the standard treatment for children with this genomically defined form of ALL, it must be proven to be effective in well-designed, well-conducted clinical trials.

The advent of technologies that allow researchers to interrogate all of the changes in a patient's cancer at one time and to look at all of the proteins in a diseased or healthy tissue simultaneously has revolutionized cancer research and is poised to do so for other diseases as well. Physicians and researchers are beginning to apply the knowledge gained from this research and use it to benefit patients like Luke Theodosiades, as well as Zach Witt, Warren Ringrose, Rita Porterfield, and Maryann Anselmo [all of whom were featured in the *AACR Cancer Progress Report 2015* (24)].

However, as we generate more data about all aspects of a patient's cancer and look to integrate this with the patient's baseline and long-term medical information, it becomes difficult to convert all of these various data into effective treatment decisions, because physicians are literally swimming in a sea of data. The enormous amount of data is both the problem and a potential solution (see **Figure 11**, p. 60).

Recognizing this paradox, several groups have independently started different efforts to address this challenge posed by the explosion of genomic information and the ability to link it to the clinical outcomes of the patients whose tumors have been genetically sequenced. Many of these groups are in the early stages of developing these efforts.

The analysis of the treasure trove of sequencing data has also revealed that the majority of tumors carry mutations that occur very infrequently. If we are to discover which of these mutations actually fuel tumor growth and to develop precision therapeutics that target the consequences of these mutations, many more patient samples will need to be sequenced.

In fact, a comprehensive analysis estimated that to discover all mutations that generate potential therapeutic targets in a patient population would require several thousand patients each with the same host of mutations (111). This analysis underscores the need for even more and bigger data than we currently have, as well as the tools necessary to convert the data into real knowledge that could inform patient treatment.

PHASES OF CLINICAL TRIALS

Clinical trials evaluating potential new anticancer therapeutics have traditionally been done in successive phases, each with an increasing number of patients.

PHASE I

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

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

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). When successful, the results of these trials can be used by regulators to approve new therapeutics or new indications for existing therapeutics.

PHASE IV

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.

Adapted from (1)

PROGRESS ACROSS THE CLINICAL CANCER CARE CONTINUUM

The hard work of individuals throughout the biomedical research cycle constantly powers the translation of discoveries to new medical products for cancer prevention, detection, diagnosis, treatment, and care (see **Figure 9**, p. 49).

In the 12 months spanning Aug. 1, 2015 to July 31, 2016, the FDA approved 18 new medical products—13 new anticancer therapeutics, one new blood-based companion diagnostic test, one new cancer screening test, two new diagnostic imaging agents, and a new medical device (see **Table 1**, p. 10). During this period, the FDA also approved new uses for 11 previously approved anticancer therapeutics, including obinutuzumab (Gazyva).

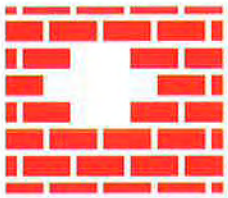
In February 2016, the FDA approved obinutuzumab for use in combination with the cytotoxic chemotherapeutic bendamustine to treat certain patients with follicular lymphoma, which is the second-most common form of non-Hodgkin lymphoma diagnosed in the United States. This approval followed its November 2013 approval for treating chronic lymphocytic leukemia (CLL), which was highlighted in the *AACR Cancer Progress Report 2014* (1). The approval

FDA'S EXPEDITED REVIEW STRATEGIES

The U.S. Food and Drug Administration (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. Atezolizumab (Tecentriq) for the treatment of advanced urothelial carcinoma (the most common form of bladder cancer) was approved under this pathway in May 2016 (see p. 87).

Fast track. This designation is given to therapeutics 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. Nivolumab (Opdivo) for the treatment of advanced renal cell carcinoma (the most common form of kidney cancer) was approved through fast track in November 2015 (see p. 83).



Breakthrough therapy. A therapeutic 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 April 2016, after receiving a breakthrough therapy designation is venetoclax (Venclexta) for the treatment of chronic lymphocytic leukemia (see p. 75).

Priority review. Therapeutics that have the potential to significantly improve safety or effectiveness may be granted priority review after all clinical trials are completed. This allows the therapeutic to be assessed within 6 months as opposed to the standard 10 months. Alectinib (Alecensa) was granted priority review and approved in December 2015 for the treatment of certain patients with lung cancer (see p. 70).

Adapted from (1)

of obinutuzumab for treating follicular lymphoma was based on the results of a phase III clinical trial, which showed that adding obinutuzumab to bendamustine more than doubled the median time to disease progression for patients whose disease had progressed despite treatment that included rituximab (Rituxan) (112).

New FDA-approved medical products are used alongside those already in the physician's armamentarium. Thus, most patients with cancer are treated with a combination of surgery, radiotherapy, chemotherapy (including both cytotoxic chemotherapeutics and molecularly targeted therapeutics), and/or immunotherapy (see **Supplemental Table 2**, p. 131, and **Supplemental Table 3**, p. 134).

The following discussion primarily highlights recent FDA approvals that are improving lives by having an effect across the continuum of clinical cancer care.

Cancer Prevention and Detection

Preventing cancer from developing and, if cancer develops, detecting it at the earliest stage possible are the most effective ways to reduce the burden of cancer. The development of new and better approaches to cancer prevention and early detection has been spurred by research that led to increasing knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development.

Increasing Options for Colorectal Cancer Screening

Colorectal cancer screening has helped reduce U.S. colorectal cancer incidence and mortality rates because it can identify precancerous colorectal abnormalities, which can be removed before they have a chance to develop into cancer, as well as early-stage cancers, which are more easily treated compared with advanced-stage cancers (see sidebar on **Consensus Among Cancer Screening Recommendations**, p. 42) (113). However, colorectal cancer remains the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths (3).

One in every three U.S. adults for whom colorectal cancer screening is recommended is not up to date with screening (113). It is clear that new ways to increase participation in colorectal cancer screening could significantly reduce the burden of this common cancer.

Research shows that people who are able to pick the colorectal cancer screening test they prefer are more likely to actually get the test done (115).

In an effort to increase the number of colorectal cancer screening options, and hopefully thereby increase the number of people who are screened, researchers built on the discovery that a specific epigenetic abnormality—

FIGURE 10 GENOMICALLY INFORMED CLINICAL TRIALS

One of the major uses of genomics in clinical research is in the design and execution of novel clinical trials. Two such types of trials are basket and umbrella trials. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, bone, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, green, blue, and red dots) in lung cancer.

Figure adapted from Ref. (1)