

2016 | WORLD MEDICAL INNOVATION FORUM



THE DISRUPTIVE DOZEN CANCER

The culture of innovation at Brigham and Women's Hospital and Massachusetts General Hospital—throughout all of Partners HealthCare and collaborating institutions such as Dana-Farber Cancer Institute—naturally fosters a good deal of discussion about new “disruptive” technologies and which ones will have the biggest impact in bringing novel complex health care products and services to greater levels of affordability and accessibility. The mission of Partners clinicians and researchers to provide the best care for patients drives a continuous dialogue on what state-of-the-art medical technologies are just over the horizon. The Disruptive Dozen was created to identify and rank the most disruptive technologies that Partners leading faculty feel will break through over the next decade in cancer care.

Disruptive Dozen | 2016

The Nomination Process

Beginning November 2015 and through January 2016, 42 30-minute in-person and telephone interviews were conducted with leading faculty from Brigham and Women's Hospital, Massachusetts General Hospital, and Dana-Farber Cancer Institute to elicit their nominations of the technologies they believe will have the greatest impact on oncological care at any point in the next decade. The interviews resulted in 34 nominated technologies that varied from the broad in scope to quite specific.

Selection Process

12-15 leading Partners faculty gathered in February to form a committee of "selectors" to jointly choose and rank the final 12 technologies. Drs. Daniel Haber and Monica Bertagnolli served as selection committee moderators and were supported by Partners Innovation staff. To receive consideration for the final Disruptive Dozen, nominated technologies had to meet the following criteria:

Criteria 1

The innovation had to have the strong potential for significant onco-related clinical impact at some point in the next decade and offer significant patient benefit in comparison to current practices. The innovation may also have had a significant benefit to the delivery/efficiency of oncologic related health care.

Criteria 2

Nominated oncologic-related innovations had to have a high probability of successful commercial deployment—e.g., payers will be expected to support it.

Criteria 3

The innovation must be on the market sometime before April 2026. Ideally, the final group selected would involve a blend of disruptive technologies coming to market in the next three to four years as well as ones that will come to market later in the decade.

The Selection Ranking Process

Round 1

The initial pass of the 34 nominations by the selection committee eliminated all technologies that didn't meet the criteria or didn't have a realistic potential of being ranked in the top 15.

The moderators named each technology and asked panel members to vote "yes" or "no" to move the technology to the next round. One "yes" vote is enough to advance the technology.

Round 2

The moderators described the candidate technology, pointing out salient points, and then asked for comments from committee members. After a discussion of the pros and cons of the technology, panel members voted A, B, or C with a raise of the hand. Innovation staff recorded the voting.

A. It's highly probable that the technology will significantly influence oncology care before 2026.

B. It's probable that the technology will significantly influence oncology care before 2026.

C. It's not likely that the technology will significantly influence oncology care before 2026.

Round 3

Each surviving technology earned a score with overall rank tied to the size of the score—i.e., the higher the score, the better. Innovation staff reported this initial ranking of all technologies.

Final Scores and Announcement at the World Medical Innovation Forum

Selection committee members jointly ranked the innovations from 1 to 12 using the initial scoring and further discussion. The selection committee ranking was final and will be announced April 27, 2016 in a one-hour panel at the World Medical Innovation Forum. The session will be moderated by Monica Bertagnolli, MD, and Daniel Haber, MD, PhD, and feature 12 faculty members selected to briefly comment on each technology.

Nanotechnology and Cancer Treatment

For the first time in the United States, cancer has surpassed heart disease as the number one killer of people younger than 85. This worrisome statistic has not resulted from an increase in cancer incidence, but, rather, because deaths from heart disease have dropped nearly in half while the number of cancer-related deaths has remained about the same.

This fact accentuates the need for more effective cancer therapies.

Nanotechnology—the science of engineering and controlling matter at the molecular scale to create devices with novel chemical, physical and/or biological properties—has the potential to meet that need and, in the process, radically change how cancer is diagnosed and treated.

Biological processes, including ones necessary for life and those that lead to cancer, occur at the nanoscale. Many nanomedicines currently in development for cancer are composed of nanoparticles smaller than 100 nanometers in size. Nano, which means “dwarf” in Greek, is shorthand for nanometer, which is one-billionth of a meter. For comparison, 1,000 nanoparticles placed side-by-side equals the cross-section of a strand of human hair.

The application of nanotechnology in medicine represents an exciting new frontier, because this field of bioengineering is providing many interesting structures, materials and tools that are showing promise in the development of new cancer detection and treatment procedures. In addition, nanoscience and technology are enabling fundamental discoveries in the fields of cancer biology, genetics and oncology.

Cancer therapies are currently limited to surgery, radiation, and chemotherapy, methods that risk damage to normal tissues, and, at times, incomplete eradication of the cancer. On the other hand, nanotechnology offers the means to target therapeutics directly and selectively to cancerous cells and tumors, guide in surgical resection of tumors, enhance the therapeutic efficacy of radiation-based treatments, and, more broadly, enable complimentary technologies such as gene editing and gene therapy for a myriad of cancers. All of which, can add up to novel therapeutics with decreased patient side effects and an increased probability of survival.

Cancer nanomedicines work differently from conventional chemotherapy, which uses drugs that kill cancer cells effectively. Chemo, however, also kills healthy cells, leading to adverse side effects such as nausea, neuropathy, hair loss, fatigue, and compromised immune function. Nanoparticles now in clinical trials are being used as miniature drug carriers for cancer drugs to deliver medication directly to the tumor while sparing healthy tissue, and causing fewer side effects.

Nanoparticles for cancer can be made highly specific towards a particular target in the body by using ligands, the special targeting elements that allow them to bind to cancer cells. The journey of the nanoparticle begins after it is injected into the blood, when it starts to navigate its way directly to its target while carrying thousands of drugs in each single molecule.

These novel therapies are specially coated to protect the drugs from being degraded in the body before they reach their target. Upon arrival, the nanoparticles are then taken up by the cancer cells through a process called endocytosis, and they deliver the toxic contents directly inside the cells, where they can kill the cancerous cells more effectively.

Although nanotechnology has mainly been used to transport existing cancer drugs, researchers are now at work developing cancer medicine specifically for use in nanoparticles. Personalization approaches will also enable selection of patients who would maximally benefit from nanomedicines.

The pace of nanotechnology development has been brisk, and the entire field has seen a rise in innovation on a sharp slope. The expectation is that as nanoparticles begin to make their way through clinical trials, and as nanotechnology continues its impact on other medical breakthroughs—immunotherapy, gene therapy, RNA interference, and gene editing—we will begin to see the enormous power of cancer nanotechnology, as measured by improvements in patient survival and commercialized products in this field. \\\

Redefining Value in Cancer Care

When it comes to disruptive technologies in cancer, innovations in diagnostics, therapeutics and devices are certainly vital components. However, they don't tell the entire story.

Breakthrough innovations in cancer care must move forward alongside corresponding innovations in the health care delivery system, where these innovations are now taking place.

Due to technological advances and an aging population, cancer care will continue to be a primary driver of increasing health spending. Under existing health care regulations, decisions on how to treat cancer are often based on old school models of who gets paid, rather than on the true value of care. Typically, innovations that save money are regularly pitted against services that lose money.

We will need to pay for and treat cancer differently moving forward and this will become a major disruptor over the next decade.

In order to realize the full benefits of advances that are being made in cancer care, clinicians, industry leaders, insurers and policy developers are now coming together to share cancer-related data and generate performance metrics that are clinically relevant, can help guide improvements, and deliver high quality and high value in cancer care.

The ever-increasing involvement of patients and patient organizations in the decision-making process is another important step in improving value. For example, research has shown that effective patient engagement not only improves medication adherence and overall satisfaction scores, but also often leads to lower-cost treatment choices in many cases.

Cancer is an expensive disease, and with new immuno-oncology medications getting ready for approval by the Food and Drug Administration, and with many more in the pipeline, drug prices will reach highs never seen before. In the face of this country's limited health care resources and an escalating national health care budget, value is going to be front and center when making treatment decisions for patients with cancer.

Currently, however, the principal stakeholders are all at odds with each other and the health care environment remains turbulent.

When it comes to the extraordinarily high prices for drugs that patients with cancer have to pay, drug companies complain that it's the insurers who are at fault for requiring patients to absorb higher deductibles and copays. Insurers, however, often point to excessive hospital charges, doctor fees and drug pricing, while hospital systems will often note that drug companies inflate their prices and that insurers are not adequately covering the newer oncology medications.

As the various stakeholders work together, improved value in cancer care will be achieved through managing the complexity of cancer, finding alternative payment models and the assurance of guideline-conforming care that can help reduce waste—for example, better designed trials through genotyping (precision medicine)—eliminating therapies that offer little value, and avoiding inappropriate treatment.

It's this collaborative approach that will help improve cancer prevention, detection and treatment in ways that will reduce the economic and human burden of cancer, ultimately leading to pricing that reflects value and better outcomes for patients. \\\

Patient-Specific Research to Enable Efficient Drug Development

Precision medicine uses genetic information from a person's cancer to determine which treatment is best targeted to that particular genetic abnormality. Recent biotechnological advances have led to an explosion of disease-relevant molecular information, and as the range of therapeutic options for treating patients with cancer continues to expand, clinical researchers are faced with the enormous challenge of matching the right treatment, at the right dose, at the right time, with minimum side effects and maximum efficacy, all based on the unique biological underpinnings causing the patient's cancer.

In order to meet this new challenge, novel research strategies that allow individualized testing to predict treatment efficacy based on a patient's medical history, cancer stage and pathology will play an increasingly critical role in years to come. This includes interrogation of individual patient's tumors in a way that permits testing for susceptibility to drug or immune therapies.

To address the heterogeneity and complexity of treatment response, clinicians will also use computational modeling of tumor-derived parameters, including molecular genetic and proteomic data, tumor cell functional assays, drug dosing and prior treatment data.

With the costs of bringing a drug to market escalating to almost \$2 billion, experts are now conceding that the conventional approach to drug development in this era of precision medicine is outdated and that more elegant studies are needed to evaluate the targeted drugs for which the one-size-fits-all study approach would be ineffective and wasteful.

Understanding this new problem, the National Cancer Institute (NCI) is currently testing a new precision medicine strategy that includes both "genotype to phenotype" trials—studies that screen for molecular features that may predict response to a drug with a given mechanism of action—and "phenotype to genotype" initiatives, which is a retrospective genomic analysis of a patient's tumor to determine the molecular factors, if any, that may explain why a patient responded particularly well to a specific treatment. The NCI-MATCH trial is examining the molecular features of tumors in approximately 3,000 patients with solid tumors or lymphoma who have progressed on standard therapy, and hopes to match at least 1,000 of those patients to a treatment with a targeted drug or drug combination. Patients will undergo a biopsy, which is used to screen for abnormalities in up to 143 genes known to be involved in cancer and/or to predict response to a particular drug or drug combination.

In the Exceptional Responders Initiative, the NCI's phenotype to genotype study, researchers are investigating the molecular factors of tumors associated with exceptional treatment responses of cancer patients to drug therapies. Their goal is to identify the molecular features of tumors that may predict whether a particular drug—or class of drugs—will be beneficial. The researchers are examining tumor specimens from patients in clinical trials who achieved an exceptional response relative to other trial participants, or other patients who achieved an exceptional and unexpected response to a non-investigational therapy.

Significant challenges still lie ahead, but using information from these studies and other novel clinical trial designs could help capitalize on the growing knowledge of patient subpopulations for which a therapy may be effective and not compromise the FDA's rigorous safety standards. Many are optimistic that these designs could also improve regulatory success rates and ensure the more rapid and cost-effective delivery of innovative medications to those cancer patients who are predisposed to respond favorably. \\\

mHealth and Cancer Care

With the advent of digital technology and smartphones, mobile health, or mHealth as it's also called, is something that can significantly change the way health care is viewed, managed, and delivered in the future, especially when cancer is concerned.

mHealth technology, defined by the World Health Organization as the "medical and public health practices supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices," is gaining in popularity and has the potential to transform health care delivery. Doctors and other health care providers will be able to track and care for their patients outside the four walls of hospitals and doctors' offices, alerting them to changes in their patients' condition and medication adherence.

By 2020, it's estimated that more than 20 billion everyday objects are expected to capture, receive, and share all types of data via sensors, GPS and the cloud network of servers.

Increasingly, evidence is showing that various health technologies can make health care more effective and efficient by electronically connecting patients to their doctors, patients to other patients and doctors to doctors. Patients are currently driving health by using online technologies and intelligent devices to take charge of their health and manage chronic conditions, including cancer.

The ability to use technology-enabled care with patients with cancer allows providers to reach into patients' homes and their daily lives, not only capturing patient-generated health information, but also doing it in real time.

With close to 200 million Americans now owning smartphones, experts are now predicting that mHealth has the potential for linking cancer patients, their caregivers, and health care professionals, and that this will enable increased monitoring and intervention, for both care and research. Ultimately, this will help lower health care costs and achieve better quality of life for patients with cancer.

The entry of Google, Apple and Microsoft and other major players into the mHealth field and the greater use of smart devices and bio-sensing wearable technologies, will prove to be an important and cost-effective way to provide immediate access to health records, patient education, care coordination and follow-up for patients with cancer and those providing their care.

This supportive care can help provide accurate information for patients and their providers and caregivers so they can understand the side effects of chemotherapy, for example, and also give them the opportunity to participate in the treatment decision-making along the pathway of care in the months and years following a cancer diagnosis.

The emerging field of novel cancer-care apps may also offer new, relatively inexpensive routes to supportive cancer care that can improve patient quality of life, patient education, navigation through complex medical systems and personalized social support.

For example, in an ongoing drug trial, one drug company has incorporated a mobile app that gathers information about side effects of an experimental combination therapy for ovarian cancer. The app, which is designed to help physicians monitoring the clinical trials to quickly treat and address two specific side effects for these patients, may also reduce the time it takes for patients to describe side effects to care teams. In another available app, patients set the app up to remind them when to take their medications for complex regimens and it helps them to keep tabs on their schedule and related side effects. \\\

Single-Cell Molecular Profiling

The human body is composed of approximately 37 trillion cells that live harmoniously among their neighbors. When cancer develops, however, a single rogue cell can eventually lead to the downfall of an entire organism.

As a single cell begins its journey to evolve into a malignant mass of tumor cells, the lineages diverge and form distinct subpopulations that result in a collection of related but heterogeneous cells that make up a tumor.

Cancer is inherently a complex medical problem that involves many different cell types. If scientists are really to understand what's unique about each individual cell type, they will have to measure them one at a time. Different cells in different tissue have varied functions and it has been a challenge to study that. Moreover, it's been especially difficult to understand what's happening in unusual and sometimes very rare cell types.

It's for these reasons that scientists have become very interested in studying how to measure, catalog, describe and categorize individual cells. Some techniques being used amplify material from one cell at a time, while others allow them to multiplex many cells together, which is a very powerful technique.

In order to study a single cancer cell, the cell must first be isolated from the population. Researchers can use varied approaches to do this. In one approach, a flow cytometer, which is a fluidics device that incorporates many lasers, allows a scientist to sort an individual cell into a test tube to be studied. Typically, antibodies are bound to proteins present on the outer membrane of the cell. Using a computer, scientists can then direct the cytometer to collect a very specific profile of cells based on the combination of antibodies bound to a particular cell of interest.

Another method uses a microfluidics device in which cells pass single file through channels in a chip before being deposited into a test tube where they can be studied. In still another approach, cells can be robotically picked from a solid surface—such as a glass slide or a filtration membrane—and mechanically deposited into a test tube to be studied.

Once a cell is “singulated,” it can be amplified and examined away from other cells—or populations of single cells—to meet the demands of whatever experiment is being conducted.

Recently developed single-cell mRNA-sequencing methods enable unbiased, high-throughput and high-resolution of all the genes expressed within individual cells. Not only are tumor cells different from each other in many ways, but also the normal cells that surround a tumor are very important mediators of tumor behavior, and include immune cells that attack the cancer or other cells that support its growth.

Already, single-cell RNA-sequencing methods have revealed new biology in terms of the composition of tissues, the dynamics of transcription and the regulatory relationships between genes. Rapid technological developments at the level of cell capture, phenotyping, molecular biology and bioinformatics promise an exciting future with numerous biological and medical applications.

By separating individual tumor cells from neighboring normal cells, these single-cell analysis methods can also allow precise definition of a tumor's microenvironment. These tools will also have direct translational applications in the clinic, in areas such as early cancer detection, noninvasive monitoring and guiding targeted therapy.

In the coming years, single-cell profiling promises to answer key issues in cancer research, including resolving intratumor heterogeneity, tracing cell lineages, understanding rare tumor cell populations and measuring mutation rates.

There has already been extraordinary progress made in technological developments and research applications and the future bodes well, especially when it comes to guiding targeted therapy towards tumor cells. In the next few years, single-cell profiling is expected to greatly improve the understanding of invasion, metastasis and therapy resistance during cancer progression and this will have significant clinical application in cancer management. \\\

CRISPR: Genome Editing and Cancer

Being able to read, study, compare and edit DNA sequences for humans, plants and animals has always been the focus of researchers around the globe since chemist Francis Crick and biologist James Watson revealed DNA's double helix structure back in 1953. Scientists understand that being able to tweak or correct any damaged or missing 20,000 to 25,000 human genes would help banish so many of the common and not-so-common ailments that afflict humans, and this includes cancer.

While Watson and Crick won the Nobel Prize for their work, the process of altering genes has remained somewhat crude, laborious and yes, inexact. For example, engineering a laboratory mouse with a single mutation used to take a dedicated lab almost two years. That was then.

CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, a revolutionary new technology in the research arena, is sweeping the world with excitement due to the unprecedented ease and speed with which it allows scientists to change the genetic code of DNA.

Much like a word processing program that can edit or replace words in a text with a simple keystroke, CRISPR (pronounced "crisper"), which acts as molecular "scissors" to precisely snip and manipulate multiple genes at once, has changed the playing field, transforming almost every aspect of molecular biology and biomedical research with it. In the future, it may be possible to rewrite the human genome at will.

To edit a gene with CRISPR, a researcher only has to take a strand of guide genetic ribonucleic acid, or RNA, a nucleic acid present in all living cells. The researcher then includes an address on that guide RNA, a short string of letters corresponding to a particular location on the gene that is to be altered. The guide RNA then helps direct the Cas9 enzyme, a protein which effectively slices open the target DNA, and thereby enables modifications to the genetic code by exploiting DNA repair pathways operative in essentially all living cells.

Some say CRISPR gene editing may prove to be one of the most important biologic tools invented in the past 100 years.

Researchers have already used this technology to edit the DNA of plants to make them resistant to bacteria or fungi, build stronger immune cells, fight muscular dystrophy in lab mice and alter genes in pig embryos, creating animals that could potentially grow human organs for transplant.

Researchers are using CRISPR to develop therapies for various ailments, from muscular dystrophy and Alzheimer's to arthritis and heart disease. The technology holds great promise for discovering therapeutic targets in cancer.

By placing cancer-hunting genes into a patient's immune system, CRISPR has the potential to lead to new approaches in oncology. This genetic engineering technique allows scientists to manipulate specific genes within cells, turning them off or changing their function.

From replacement gene editing to targeting of immune cells against cancer, the technology is enabling an entire new world of possibilities for cancer treatment.

Human trials for a rare eye disorder using CRISPR-based gene therapy may begin as early as 2017, and the hope is that this technology can ultimately be used to tackle a wide variety of genetic disorders. \\\

The Microbiome and Cancer

Complex and highly diverse communities of microbes, collectively known as the microbiome, inhabit the human gut and other body surfaces. Our microbiomes contain more than 100 trillion microbes. This complex and highly diverse population of fungi, bacteria, protozoa and viruses plays an important role in our physiology, including maturation of the immune system, digestion, synthesis of vitamins, and metabolism of host factors, including bile acids and sterols, all of which influence our health and susceptibility to disease.

The gene-sequencing platforms that brought us the human genome have also opened up the world of the microbiome to researchers the world over. In fact, we now know that the gene content of the microbiota exceeds our own gene content by a factor of at least ten.

Also contributing to ongoing microbiome research efforts has been the advent of improved computational methods evaluating high-throughput sequencing, microbiologic and metabolic data, each of which has helped scientists parse out the many complexities of our microbial communities.

The gut microbiome, which is mainly found in the intestines, may help us in many ways, especially in governing normal functions in the immune system. As scientists have discovered, this three-pound mass of microbes—the same weight as the human brain—acts as an internal metabolic organ and may be holding secrets pertaining to cancer.

Some scientists now suspect that select groups of microbes metabolize many medications used to treat cancer, altering their potency and increasing risks for side effects. Research into the identification and manipulation of this inner microbial ecosystem has shown a meteoric rise, and enhanced knowledge, regarding the role of our colonizing microflora in cancer development and progression.

It's the oncobiome, the interplay between the human microbiome and cancer development, which researchers feel may be an important factor to consider in response to therapy, including immunotherapies and existing anti-neoplastic agents.

As the exploration of the human microbiome increases, a better understanding of the role of the gut microbiota in cancer may lead to the development of targeted individualized interventions affecting the microbiota that prevent or ameliorate microbial imbalance, thereby reducing symptoms.

Early research had reported that the introduction of a particular strain of bacteria into the digestive tracts of mice with melanoma boosted the ability of the animals' immune systems to attack tumor cells. When combined with anti-PD-L1, an investigational anti-cancer antibody in the drug class known as checkpoint inhibitors, the therapy nearly eradicated the tumors.

Many companies have recently been launched to develop and commercialize microbiome-based cancer immunotherapies that employ select gut microbes to boost the immune system's attack on cancer cells and improve the efficacy of anti-cancer drugs.

Of course, outstanding questions still remain in understanding the unique interplay between the microbiota and cancer. For example, can alteration of the microbiota of people at high risk of cancer eventually lessen those risks, including use of modifications such as diets or existing medications? For inflammatory contributions to cancer, could microbiota-focused therapies suppress or encourage the growth of essential communities to limit or outright prevent these adverse events?

The human microbiome is highly complex. Though still in its infancy, this dynamic field of research continues to evolve as scientists learn more about the microbiome and how causative its role is in carcinogenesis, disease progression and response to treatment. The opportunity to exploit the microbiome for therapeutic benefit offers an exciting new approach with limitless possibilities. \\\

Epigenetics and Cancer Treatment

For decades, scientists and oncologists assumed that cancer was caused only by damage to the DNA sequence of critical genes within cancer cells; the genes became abnormal and cancer then developed.

But recently, a more complex picture has emerged, and it is one that shows that some cancers are also caused by epigenetic changes, which are alterations in the environment around the DNA that impact DNA packaging, gene expression and genome stability.

If you think of the genome as the body manual of cellular genetics, then think of the epigenome as the multitude of chemical compounds and proteins that tells the cell how to read that manual and, in turn, regulate gene expression and genome stability.

Unlike genetic damage to DNA, which can lead to cancer, epigenetic changes—which are a normal part of many biological functions—take place on both the DNA and proteins packaging the DNA. These changes result in proper cell growth, cell division, cell fates and proper immune responses. Should alterations to epigenetic states occur, they could promote uncontrolled cell growth and the initiation, development and progression of some cancers. In fact, the misregulation of epigenetics in the immune system could also be contributing to tumor progression.

The good news is that unlike genetic mutations, researchers are now finding that epigenetic changes that lead to some cancers can be reversed with novel treatments. In some cases, these drugs are less toxic than conventional chemotherapy.

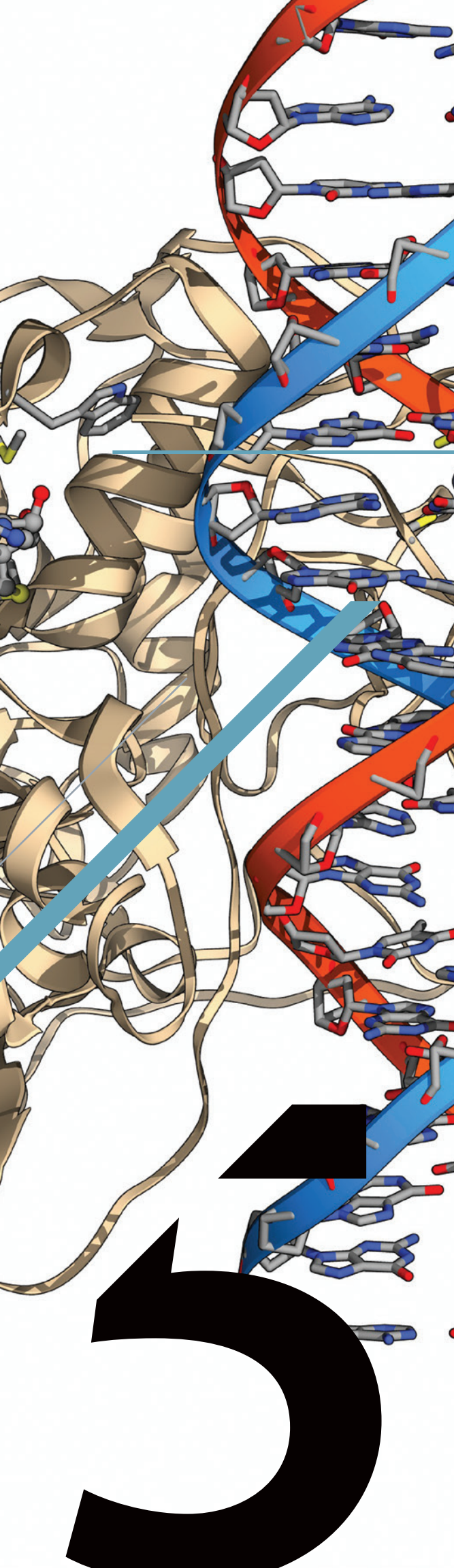
The ability to modulate epigenetics is a critical way to reset cellular states and plasticity in cancer. These drugs also open the possibility of more optimal therapeutic combinations for more durable responses. It's for these reasons that drugs that can restore epigenetic balance in the body now represent an exciting new area of research and drug development.

Solid and hematological malignancies in children and adults are being linked to epigenetics. For example, glioblastoma is the most aggressive primary brain tumor and despite available therapies, prognosis is extremely poor. The majority of patients don't survive for more than two years following diagnosis, and the average survival is generally less than a year. The average five-year survival rate is less than 3 percent. However, scientists are now identifying key epigenetic pathways that could aid in the treatment process. Emerging research suggests that proteins affecting epigenetic states are critical biomarkers and drug targets for this aggressive type of brain cancer as well as many other malignancies.

A major challenge for glioblastoma and many other tumor types is the ability to eradicate the cancer cells. The data is clear that epigenetics is influencing this process. Understanding how to leverage epigenetics to block resistance and increase drug response will have a profound impact in the future.

The epigenetic approach to treating cancer is going to be truly disruptive because it not only changes the way that researchers will look at cancer but also the way that they will treat it: Instead of killing cancer cells, these new epigenetic cancer treatments will instead transform them from diseased cells to healthy ones or increase their sensitivity to new or existing therapies.

Such knowledge of wiring differences in the packaging of DNA within cancer cells could help doctors one day prescribe more potent and precise drugs that home in on specific epigenetic targets within tumors, leading to durable remissions and, quite possibly, cures. \\\



Machine Learning and Computational Biology to Transform Cancer Care

The accelerating field of precision medicine includes all of those diagnostics and treatments targeted to the needs of individual patients on the basis of their genetic, biomarker or physical characteristics that distinguish one patient from another with similar clinical presentations.

In recent years, great progress has been made in recording an individual's state of health, right down to the molecular level of gene activity. However, the ultimate goal of using this information for precision medicine has remained largely unfulfilled when it comes to cancer care.

With all of the reams of data available from a patient's full genome sequencing, the thousands of pages of critically important background information from medical journals and with the doubling of overall medical information every five years, most cancer researchers and clinicians can't keep up with this avalanche of information and derive maximum value from it. Unfortunately, it's the patient with cancer who ultimately misses out on crucial information that may be pertinent to their care and, many times, has to then settle for a one-size-fits-all cancer treatment and hope for the best.

This is where computational biology, which involves the development and using of tools to analyze and model biological data and systems, along with machine learning, which is the ability of computers to learn without being explicitly programmed, can revolutionize personalized medicine and make cancer diagnoses more accurate.

To understand the cause of cancer and to develop more effective methods of prevention, detection and treatment, clinicians and researchers need access to rich molecular and clinical data sets. The good news is that over the next few years, technology will be revolutionizing the understanding and treatment of diseases, especially cancer. By gathering the latest information from the patient's biology, and combining that with trillions of data points from tens of thousands of other cancer patients, individualized patient-specific cancer treatment options can then be created in days, and sometimes in just a matter of minutes.

Thanks to the latest machine learning algorithms and bioscience advancements, future advances in cancer diagnosis and treatment will be based on DNA mutations, not simply the location of the cancer in a person's body. Using supercomputers, researchers will be able to quickly examine specific genes in pathology samples, note the type and location of the cancer, the grade and size of the tumor, review all of the proteins, metabolites, and lipids, and then compare them all, taking into account demographics, age and gender. After subjecting this to a mathematic algorithm that uses machine learning to compare the many associations and correlations, a more precise and targeted treatment plan can then be developed.

In just a few years, experts envision that these targeted cancer treatment plans will be available within the span of 24 hours. This, of course, will represent the true value of machine learning and computational biology. Human intelligence and medical experience is not being replaced by the gathering and distillation of this statistical data, but rather it's being augmented and enhanced by it, which allows researchers and clinicians to be better at what they do.

Leading U.S. and European research institutes in machine learning and statistical genetics are now working together to develop techniques for robust biomarker discovery and elucidation of the causal mechanisms governing cancer and its progression. Ultimately, this treasure trove of information will be added to data banks and help cancer researchers from across the world mine and glean insights from the gigantic amounts of data in order to truly progress in the fight against cancer. //

Liquid Biopsy for Oncology

A new type of blood test has the potential to transform cancer diagnosis and treatment while sparing patients the surgical and needle biopsies long needed to guide their care and enabling repeated sampling of patients through the course of their disease.

Instead of taking tissue from the tumor itself, these experimental tests called liquid biopsies rely on the capture of cancer cells in the blood (called circulating tumor cells, or CTCs), and isolation of cell fragments called exosomes or free circulating tumor DNA that tumors shed into the blood. Molecular analysis of these blood-borne, tumor-derived entities is then used for diagnosis and to inform treatment options.

Diagnosing and monitoring cancer the traditional way with biopsies of primary and metastatic tumors is a rigorous, expensive process that often causes pain to the patient and sometimes leads to dangerous complications.

By contrast, liquid biopsies currently in testing phases entail a simple blood draw, taking a test tube of a patient's blood, which contains free-floating DNA from dead cancer cells, CTCs and exosomes, and then analyzing it for mutations and abnormalities.

It's this novel testing technique—a molecular stethoscope, some experts are calling it—that can provide a snapshot of key genetic irregularities and reveal the particular genetic fingerprints of a cancer. And it can do so without having the patient undergo a traditional invasive biopsy procedure and can be repeated many times over the course of the disease to monitor how the cancer evolves as it becomes resistant to therapies.

Moreover, liquid biopsies would actually provide a more accurate picture of cancer in the body, since genetic sequencing of free-floating tumor DNA, CTCs and exosomes may better capture the diversity of genetic alterations found in cancer cells residing in various parts of the body including the lung, liver, bone and brain, often long after the primary tumor has been surgically removed.

Although there is still much unknown about the value of these early tests, many doctors think liquid biopsies will be the transformative advance that could make personalized medicine possible for far more people. That's because this testing procedure could provide the first noninvasive way to repeatedly sample a cancer so doctors can profile its genes, identify those patients who can benefit from drugs targeting specific mutations, tell quickly whether treatment is working, and provide guidance in adjusting therapies as the cancer evolves.

Liquid biopsies offer another advantage in cancer clinical trials: Rapid results. In a recent study of non-small cell lung cancer, liquid biopsy results were returned within three days, on average, while tissue biopsies took 12 days for newly diagnosed patients and almost a month for drug-resistant patients.

The so-called "Holy Grail" in oncology has been the search for biomarkers that will reliably point out the presence of cancer at the earliest stages in asymptomatic patients. In the near future, some experts are predicting that super-fast genetic sequencing technology will be able to reliably uncover genetic material from a patient's blood sample long before he or she has any evidence of cancer. These tests would look for cancer markers typically found in tumors, and do so when the disease may still be at a highly curable stage.

Although anti-virus and anti-malware programs are readily available for computers, we don't yet have this protection for our bodies. Ten years from now, however, we should have this special blood test for cancer. Capitalizing on advances in gene sequencing and the falling costs of performing genetic analyses, more than a dozen companies currently have liquid biopsy tests in development. //

Immune Modulators (Checkpoint Inhibitors) and Vaccines

Cancer is difficult to treat, let alone cure. Instead of treating cancer by just targeting the tumor for elimination with radiation and chemotherapy, researchers have spent years exploring ways to harness the immune system and prompt it to recognize, fight, destroy, and remember cancer cells in the same way that it does with infectious agents.

More than a century ago, doctors suspected that the immune system had a powerful effect on certain cancers but research in this area soon fell out of favor as surgery, radiotherapy, and chemotherapy became the backbone of oncology.

Recently, however, interest in using the body's immune system in the war on cancer has been heightened by the remarkable results achieved by the class of drugs called immune checkpoint inhibitors.

"Checkpoint" refers to the encounter between immune system T-cells—which patrol the body relentlessly for signs of infection or other disease—and the PD-L1 protein on tumor cells. T-cells use a protein on their own surface, called PD-1, to probe cancer cells for PD-L1, as well as a closely related protein called PD-L2. When they find it, they simply pass by, leaving the tumor cells free to go about their cancerous business.

However, when an experimental checkpoint-inhibitor drug blocks that signal, the T-cells are no longer misled by PD-L1 and PD-L2. They quickly mount an all-out immune system attack on the once invisible cancer.

Checkpoint inhibitor drugs that target the PD-1/PD-L1 pathway have made a lasting impression on cancer outcomes during a rapid rise from benchtop to FDA approval. Beginning with melanoma, these inhibitors have demonstrated activity across a wide range of malignancies, leading to an unprecedented number of market approvals since late 2014.

The use of checkpoint inhibitors for non-small cell lung cancer, for example, now represents a totally new and exciting cancer treatment strategy. Instead of poisoning the cancer cells with chemotherapy, oncologists are now letting the immune system loose to do its job and wipe out the cancerous cells.

These intravenous immunomodulators are stirring excitement not only because of significant long-term cancer remissions—cures, in some cases—but because of the novel way the drugs work by removing an immune system brake that cancer cells have cleverly exploited. It's this unique approach of boosting the body's own defenses that is producing stunning results, especially when checkpoint inhibitors are combined with standard anticancer therapies.

Researchers are now combining checkpoint inhibitors with either chemotherapy or radiation in treating lung, gastric, pancreatic, kidney and breast cancers. By directly killing cancer cells with radiation or chemotherapy, it's hypothesized that the addition of immunotherapy will help create special T-cells that will remain and will be able to recognize and kill any returning cancer cells long after the initial treatment has stopped.

With two drugs already approved for metastatic melanoma by the Food and Drug Administration (FDA), one of them two months earlier than expected, there is now increasing evidence that checkpoint inhibitors can also work on other cancers. Multiple pharmaceutical companies are expecting approval of their drugs by the FDA, while several others have clinical trials already in advanced testing stages.

In addition to the checkpoint inhibitors, novel vaccines are also being developed that can generate anti-tumor responses by expanding the population of immune cells capable of fighting cancer. Vaccines are now being tested in a variety of malignancies and, once approved, will allow doctors to make significantly more progress against advanced cancer than they had been able to achieve in decades. \

Cellular Immunotherapy

CARs, or chimeric antigen receptors, are proteins that allow certain immune cells, called T-cells, to recognize a specific target on tumor cells. While CAR T-cells are being tested first as cancer monotherapies and have been shown to achieve long-term durable remissions in B cell malignancies in clinical trials, researchers are also giving thought to how best to use CAR T-cells with other immunotherapies in the future. Combining checkpoint inhibitors, such as PD-1 inhibitors and anti-CTLA4 drugs, with CAR T-cells are strong possibilities.

CAR therapy begins by removing some of a patient's T-cells in an apheresis process similar to kidney dialysis. These cells are then specially engineered in a laboratory in a week-long process using a special viral vector that programs the cells to recognize cancer cells expressing specific targets. These genetically-altered cells are then infused back into the patient. When the CAR T-cells recognize the target on tumor cells, the signaling domain built into the CAR is activated to promote CAR T-cell-mediated killing of the tumor and proliferation of these special cells as cancer-fighting weapons.

When all goes as planned, this personalized immune therapy redirects the special hunter cells to recognize, zero in on and kill cancer cells that harbor a specific antigen on their surfaces. Additionally, the CARs may reactivate other immune cells that had been affected by the inhibitor signals from the cancer, and they join in the hunt as well.

Think of this analogy: Each cancer cell has a piece of Velcro attached to it, but the T-cells are initially lacking the necessary piece of complementary Velcro to stick to the cells. By genetically changing the T-cells in the laboratory, however, a new piece of Velcro has been placed on the outside of the cells, which now allows them to recognize the cancer cell, stick to it, and kill it.

The first CAR T-cells were developed in the late 1980s in Israel and helped pave the way for current CAR technology. Researchers are now working on next-generation CAR technologies that incorporate mechanisms to further amplify T-cell activation or to dampen it, in the case of adverse reactions. CAR T-cells are a platform technology, and can be further amplified to make it more potent for solid tumors, whose microenvironment and potent immunosuppressive mechanisms have made them especially difficult to treat.

In addition to altering the components of the CAR T-cells themselves, researchers are also experimenting with different methods to introduce the receptors into the patients' cells.

The significant successes that CAR T-cell therapy has registered in treating some chemotherapy-resistant leukemias—complete response in many patients—has led to a surge of investment in CAR T-cell research. Many pharmaceutical companies have now made substantial investments in biotech companies specializing in this therapy, and companies large and small have signed lucrative licensing deals with major cancer treatment centers for access to their proprietary CAR T-cell technologies.

While the field is early in its development, the response rate to many of these CAR T-cell therapies has been unprecedented for patients who had stopped responding to all other cancer treatments. Going forward, cancer experts predict that CAR Ts have the potential to become frontline cancer therapies by engineering the patient's own immune system to fight their cancer and defeat it. \\\

2016 Disruptive Dozen | C A N C E R

Below is our Disruptive Dozen for 2016, guided through the nomination and selection-ranking process by our committee, each earning scores along the way.

We present them to you in order of their rank after the final voting was completed.

The medical professionals listed below, experts in oncology, were each paired with a specific disruptive innovation.

At the Forum presentation, each expert explained its potential impact on cancer in the decade ahead.

1 | Cellular Immunotherapy

Marcela Maus, MD, PhD
Director of Cellular Immunotherapy, MGH,
Assistant Professor, Harvard Medical School

2 | Immune Modulators
(Checkpoint Inhibitors)
and Vaccines

Antonio Chiocca, MD, PhD
Chairman, Neurosurgery, BWH, Professor
of Surgery, Harvard Medical School

3 | Liquid Biopsy for Oncology

Shyamala Maheswaran, PhD
Associate in Molecular Biology, Surgery, MGH,
Associate Professor, Surgery, Harvard Medical School

4 | Machine Learning and Computational
Biology to Transform Cancer Care

James Brink, MD
Radiologist-in-Chief, MGH, Juan M. Taveras Professor
of Radiology, Harvard Medical School

5 | Epigenetics and Cancer Treatment

Johnathan Whetstine, PhD
Tepper Family MGH Research Scholar, Associate
Professor of Medicine, Harvard Medical School

6 | The Microbiome and Cancer

Lynn Bry, MD, PhD
Associate Professor of Pathology, Director,
Massachusetts Host-Microbiome Center and
Crimson Core, Dept. Pathology, BWH

7 | CRISPR: Genome Editing and Cancer

Keith Joung, MD, PhD
Associate Pathologist, Associate Chief for Research,
The Jim and Ann Orr MGH Research Scholar, MGH,
Professor of Pathology, Harvard Medical School

8 | Single-Cell Molecular Profiling

Carl Novina, MD, PhD
Cancer Immunology, DFCI, Associate Professor,
Microbiology and Immunobiology, Harvard
Medical School

9 | mHealth and Cancer Care

Ann Partridge, MD
Director, Adult Survivorship Program, Program for
Young Women with Breast Cancer, DFCI, Associate
Professor of Medicine, Harvard Medical School

10 | Patient-Specific Research
to Enable Efficient Drug Development

Jeffrey Engelman, MD, PhD
Director, Center for Thoracic Cancers, MGH Cancer
Center, Associate Professor of Medicine, Harvard
Medical School

11 | Redefining Value in Cancer Care

Tim Ferris, MD
Senior Vice President of Population Health
Management, PHS

12 | Nanotechnology and Cancer
Treatment

Omid Farokhzad, MD
Physician-scientist, Anesthesiology, BWH,
Associate Professor,
Harvard Medical School

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