JOHNS HOPKINS MEDICINE

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ON THE ROAD TO PRECISION MEDICINE:

IMMUNOTHERAPY

Johns Hopkins Medicine's new event series will bring together thought leaders from all sectors to discuss how to improve the way we tailor health care to individuals and create better ways to engage people in the health care system. In this series, our panel of experts will discuss topics such as cost, communication, research and health care delivery.

IMMUNOTHERAPY:
Precision Medicine in Action

The importance of keeping the promise and potential of immunotherapy alive

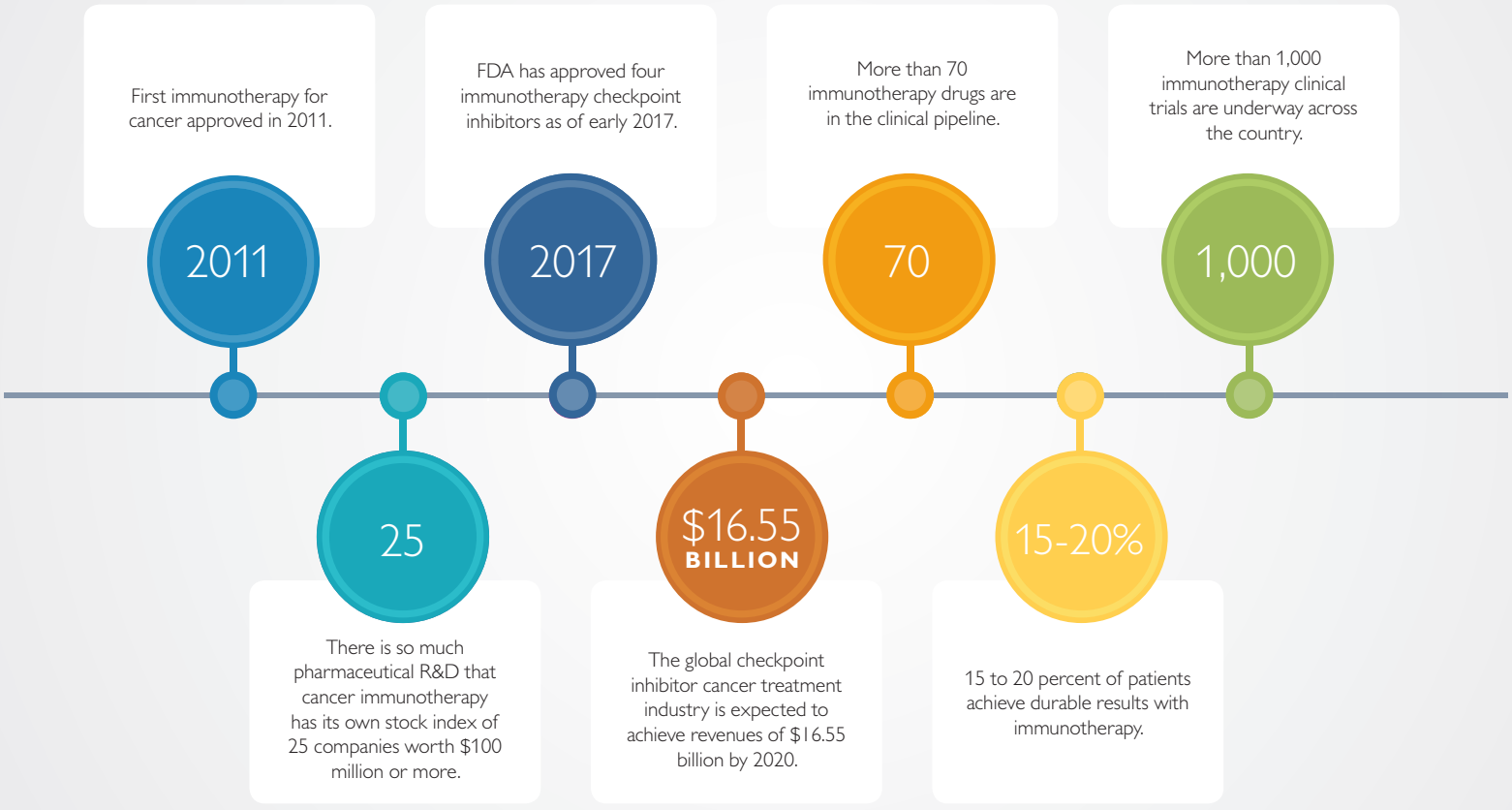
Almost 40 percent of men and women will be diagnosed with cancer during their lifetime. Thankfully, in this day of medical advancements and innovation, cancer is no longer a certain death sentence. More than 15.5 million people lived beyond a cancer diagnosis as of Jan. 1, 2016, and that number is expected to surpass 20 million by 2026.

The goal in cancer treatment now is to target care more precisely to patients through individualized health care. This is called precision medicine, and it is an especially welcome change for cancer patients who traditionally have been exposed to treatment such as chemotherapy and radiation that attacks their cancer but often damages healthy tissue in the process.

Precision medicine is at the heart of immunotherapy, currently one of the hottest areas of cancer research. Immunotherapy is a new approach that harnesses the power of our immune systems to identify and control diseases such as cancer.

Immunotherapy is being studied in just about every type of cancer. The number of cancers successfully treated by immunotherapy stands at 15 and growing and includes skin, lung, kidney and bladder cancers.

IMMUNOTHERAPY
BY THE NUMBERS



THE BASIC SCIENCE

A decade ago, Suzanne Topalian, M.D., associate director of The Bloomberg~Kimmel Institute for Cancer Immunotherapy, led a team that contributed to the astonishing discovery that many cancers "put the brakes" on the body's immune cells that would normally attack a tumor and destroy it.

Topalian and others developed a class of drugs called immune checkpoint blockers that take the brakes off the immune system and give it a chance to fight back against the cancer.

But while men and women are 99.9 percent identical genetically, there are still as many as a million differences between people, and that makes it unlikely any two of us will respond the same way to diseases and treatment.

That's where immunotherapy comes into play — helping retrain a persons own cells to attack their cancer. So who will respond best to immunotherapy? That is one of the top questions facing researchers in the field today.

The fact that some patients treated with immunotherapy have a durable response to cancer shows this treatment's potential. But despite response rates between 20 and 50 percent in certain groups, scientists still don't know why the majority of people with cancer do not respond to immunotherapy drugs.

CTLA4, for example, is an immune checkpoint. Blocking it with as few as four doses of immunotherapy can give rise to 10-year survival rates in patients who otherwise had melanoma—skin cancer. But current agents only do that in a small fraction of patients.

"There is an enormous amount of work that needs to be done to improve outcomes for most cancer patients," says Glenn Dranoff, M.D., global head of immuno-oncology at Novartis Institues for Biomedical Research.

THE FUTURE OF RESEARCH: MAKING THE POSSIBLE PREDICTABLE

Scientists are now hunting for biomarkers to better understand who will and who won't respond to immunotherapy treatments. These can be genetic mutations or proteins from tissue or blood that will help them figure out which patients will benefit most from immunotherapies. Some cancer treatments target single genetic mutations, but immunotherapy biomarkers are more complex and could involve a number of genes and proteins.

"We are early in this journey. I think we are identifying a lot of cancers that are responsive but there is a lot of work to be done," explains Roy Baynes, M.D., Ph.D., chief medical officer of Merck Research Laboratories.

Johns Hopkins researchers have played a leading role in this search. In 2015, for example, a team of Johns Hopkins oncologists found genetic biomarkers that identified a small group of patients with a variety of cancers who responded well to a checkpoint blocker.

But while much progress has been made in immunotherapy research, "We still only know a small fraction of the rules that guide these immune reactions," Dranoff says.

Researchers are working to answer many questions.

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CAN WE COMBINE IMMUNOTHERAPY WITH OTHER TREATMENTS?

Lab studies have shown that some checkpoint blocker therapies, while potent, are even more powerful when combined with other drugs. Clinical trials are underway at Johns Hopkins and elsewhere to test combinations that can involve the addition of standard therapies such as radiation, chemotherapy or other medications to a checkpoint blocker to rev up the immune system.

AS YOU COMBINE MORE THERAPIES ARE SIDE EFFECTS INCREASING?

There can be increased side effects including the onset of diabetes, inflammatory arthritis and other serious conditions, even death. Steroids and other treatments usually help avoid serious consequences and the hope is that as researchers learn more, they can inhibit signals on cells that cause damage.

QUESTIONS OF COST

When you combine therapies, rising prices can be an issue. But immunotherapy also presents opportunities for savings.

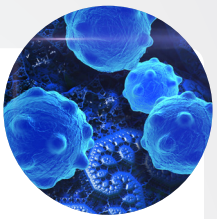
"The better we understand who benefits, the more judicious we can be and the more cost-effective it will become," explains William Nelson, M.D., Ph.D., director of Johns Hopkins' Sidney Kimmel Comprehensive Cancer Center. "If we understand clearly that a new immunotherapy agent might not work for a person then we won't indiscriminately use it and waste those resources."

The cost of four immunotherapy infusions may seem high on its own, but much is saved when it works and cancer is adequately treated. Nelson says that is true both in quantifiable terms — such as hospital visits and missed work — as well as priceless ways, like being there to coach your daughter's soccer game.

"When it comes to value in health care, I wonder whether payers aren't going to look a lot more at how effective these are at restoring people's lives and making them happy and healthy and able to work," Nelson suggests.

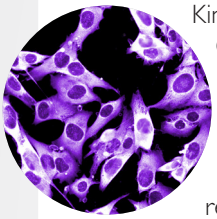
5 IMMUNOTHERAPY SUCCESS STORIES

1



Immunotherapy has shown success in 15 different types of cancers including lung cancer, head and neck cancer, bladder cancer, kidney cancer and Hodgkin's lymphoma.

2



Researchers at Johns Hopkins' Sidney Kimmel Comprehensive Cancer Center are leading the way in developing novel immunotherapies called anti-PD-1 and anti-PD-L1– a significant advance in cancer medicine offering more long-term remissions than all other cancer drugs combined.

3

A study published in November 2016 by researchers at the Bloomberg~Kimmel Institute for Cancer Immunotherapy showed that lung cancer patients taking the immunotherapy drug pembrolizumab as first-line therapy fared much better than those who got chemo.

4

A 2016 study by researchers at the Fred Hutchinson Cancer Research Center and Bloomberg~Kimmel Institute for Cancer Immunotherapy showed that with immunotherapy half of 25 patients with a rare virus-linked skin cancer had major tumor shrinkage and outperformed conventional chemo.

5

Former President Jimmy Carter—diagnosed in August 2015 with metastatic melanoma in his brain and liver—announced he was melanoma free after receiving combination therapy including immunotherapy drug pembrolizumab.

5 IMMUNOTHERAPY CHALLENGES

1

Participation in clinical trials is low. Research is key for medical advancements, but studies in humans can be difficult because there aren't enough patients in many trials. Just 3 percent of adult cancer patients participate in clinical trials and 40 percent of trials fail to get minimum patient enrollment.

2

It doesn't work for everyone.

Immunotherapy drugs work better for some cancers than others. While they can be a miracle for some patients, they fail to work for all. Overall response rates are about 15 to 20 percent.

3

We don't know who will respond best. Researchers haven't yet broken the code to figure out who will respond to immunotherapy and who won't. This remains a major focus of much research.

4

Cost: Insurance often covers the cost of these medications but they are expensive—often $100,000 a year with one costing as much as $1 million per patient per year.

5

President Donald Trump's first budget proposal threatened to take $5.8 billion from the National Institutes of Health—a 20 percent cut that would have negatively impacted potentially lifesaving research at a critical time.

POLICY IMPLICATIONS ARE PERSONAL

Researchers say the pace of immunotherapy development is "truly breathtaking," and momentum needs to be maintained with continued funding of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA).

"The moment for translating basic discoveries into practical clinical therapies to improve patients' lives has never been as compelling as it is now," Dranoff says.

Patient advocates such as Margaret Anderson, former executive director of FasterCures, agree that the urgency of this work can't be overstated. She says you have to plant the seeds for scientific discovery to reap the benefits, which for patients can be lifesaving and life extending.

"These discoveries didn't happen by accident," Anderson says. "I don't think we should take this for granted. The rest of the world has woken up to the power of investment in biomedical and life sciences."

Funding clinical trials is not only important for medical advancements; it can also reduce patients' costs. Nelson says about 60 percent of patients visiting Johns Hopkins medical oncologists are enrolled in clinical trials. There are often no drug costs to patients enrolled in these trials.

"WE ARE STEWARDS OF CANCER CARE. WE HAVE TO FIGURE OUT WAYS TO HELP EVERYONE."

–WILLIAM NELSON, M.D., PH.D.

Johns Hopkins has found pragmatic solutions to increase diverse participation in trials, such as offering transportation to research sites for those who need it. And to spread the benefits of immunotherapy to a geographically wider audience beyond the nation's cancer centers, the hospital has built a precision medicine consultation service to help regional physicians have access to high-end pathology imaging and understand the resulting reports.

"We are stewards of cancer care," Nelson says. "We have to figure out ways to help everyone."

PARTNERING FOR PROGRESS

Right now checkpoint blockers are given to patients intravenously every two to three weeks during an hour-long treatment. Scientists are looking at whether this is the best way or if pills or less frequent clinic visits are possible.

Moving forward, pharmaceutical companies and researchers are looking at how to block multiple immune checkpoints simultaneously. They are developing therapies that target the metabolism of the immune system and are better understanding how microorganisms such as bacteria influence tumors.

Some policy improvements have helped the process. The FDA has sped up approvals in the cancer space and is interacting with more patient organizations for education. The agency's new breakthrough designation has also been revolutionary in moving research forward quickly to get accelerated approvals for drugs, with unprecedented effect.

The biggest need now is continued funding for research, and doctors aren't the only ones who realize that. Elizabeth Jaffee, M.D., associate director at the Bloomberg~Kimmel Institute for Cancer Immunotherapy, says patients are partners in this fight. "They see progress and are motivated to make it fast," Jaffee says. "The time is right. We can really make a difference, but we need to remind Congress that money for NIH and the FDA is critical for this process."

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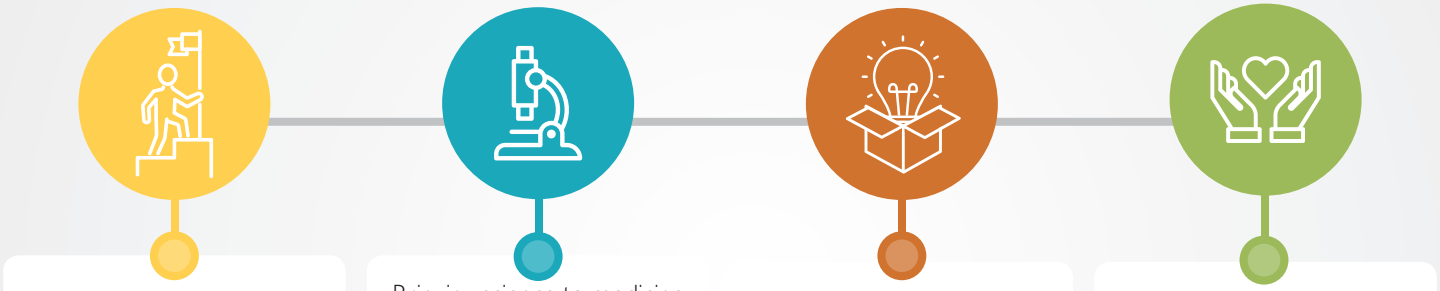

Leader in biomedical discoveries for 125 years.

Bringing science to medicine in the context of great clinical care.

The Bloomberg~Kimmel Institute for Cancer Immunotherapy was launched in 2016. It is committed to accelerating the progress of immunotherapies and developing "out-of-the-box" approaches to help patients' immune systems battle and defeat their cancers.

Johns Hopkins *in*Health brings precision medicine efforts together—uniting researchers, clinicians and others to speed the translation of knowledge to clinical practice.

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