MOON SHOTS PROGRAM™
ANNUAL REPORT
FISCAL YEAR 2018
Brian Pinckard knows how to confront enemies head-on. As a 10-year veteran of the U.S. Marine Corps, he returned to active duty for a second stint after September 11, 2001. Five years later, Brian was challenged by an enemy within — he was diagnosed with melanoma. He underwent surgery, but his cancer recurred in 2011. He was treated with surgery and interferon. His cancer recurred yet again in 2013 and he kept battling with immunotherapies ipilimumab and nivolumab. A third recurrence prompted him to seek treatment at The University of Texas MD Anderson Cancer Center, where the collaborative expertise and groundbreaking research of the Moon Shots Program™ helped him continue his fight against melanoma.

Hussein Tawbi, M.D., Ph.D., associate professor of Melanoma Medical Oncology and part of the Melanoma Moon Shot™ team, entered Brian in a clinical trial led by Cassian Yee, M.D., co-leader of the Moon Shot Program’s adoptive cell therapy platform. Yee’s team leveraged an emerging immunotherapy technique being advanced through the Moon Shots Program — he took T cells from Brian’s circulating blood and selected the “best” cells that would be more inclined to latch onto Brian’s melanoma tumors through a technology called endogenous T-cell therapy. The adoptive cell therapy platform harvested the T cells into tens of billions. In December 2016, along with a dose of ipilimumab, Brian received his harvested T cells. His first scan following the infusion showed his tumors shrinking. He has been in remission since February 2017, which Yee attributes to the modified T cells that were still circulating in Brian’s blood long after his infusion.

The Moon Shots Program is committed to improving patients’ lives, and patients like Brian, who come to MD Anderson from all over the world, are benefiting from the program’s team-science, impact-driven approach. The adoptive cell therapy platform — one of the nine research engines driving the Moon Shots Program — generated the successful treatment. Brian’s incredible response, however, could not occur without his team of doctors having access to the right data, technologies and available clinical trials — all under one roof, working with each other. The collaboration between Drs. Tawbi and Yee represents just one example of dozens of ongoing cooperative efforts made possible by the Moon Shots Program. You’ll find these efforts within this report wherever you see the icon.

Now past the five-year mark, the Moon Shots Program has achieved remarkable progress for patients and their families, from repurposing a drug that targets a specific mutation in certain lung cancers to engineering a viral therapy that kills brain tumor cells. Moon Shots researchers continue to advance innovative therapies to battle one of the most complex foes that exists in nature. This report details much of the exciting accomplishments of the past year resulting from this collaborative approach.

The Moon Shots Program is a collaborative effort designed to accelerate the development of scientific discoveries into clinical advances that save patients’ lives.
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Targeted Therapies

Chemotherapy is the standard treatment for those with B-cell lymphoma, but it can be especially difficult for these patients, leading to harsh side effects and, occasionally, secondary cancers. Many elderly patients cannot endure the treatment and must rely on less toxic, less effective therapies.

Our multidisciplinary team of clinicians and researchers is attempting to change the standard of care by conducting a targeted therapy “window” trial in newly diagnosed mantle cell lymphoma patients. The trial, in which patients delay standard-of-care to first receive a novel treatment regimen, combines ibutrinib, a drug that inhibits a B-cell receptor, with rituximab, which destroys malignant B cells. The drug combination flushes cancer cells out of hard-to-target areas, like the bone marrow and lymph nodes, into the bloodstream where anticancer drugs can more easily target them.

Alongside this pivotal trial, we have developed a molecular assay to detect minimal residual disease from a few drops of blood earlier than any PET/CT scan, allowing us to better monitor for disease relapse.

Cell- and Immune-Based Therapies

In the body’s immune system, T cells serve as the infantry to destroy pathogens or damaged cells, while natural killer (NK) cells act as immune defenders to eliminate a variety of abnormal or distressed cells. We are utilizing revolutionary science to engineer these cells with chimeric antigen receptors (CARs) to effectively target B-cell malignancies.

Leveraging the adoptive cell therapy platform, the B-Cell Lymphoma Moon Shot™ is employing CAR NK cells in a clinical trial. The NK cells are collected from donated umbilical cord blood and designed to seek out CD19, an antigen present on some types of lymphomas and leukemias.

These CAR NK cells can be used off-the-shelf, meaning they are prepared in advance and promptly administered to patients. NK cells need not be matched between the donor and recipient tissue type and do not instigate dangerous transplant rejection complications. Since the trial opened in 2017, these CD19 CAR NK cells have generated complete responses in five of seven patients, with no toxicities.

Another promising approach is CAR T-cell therapy, which involves extracting cells directly from a patient before outfitting them with the CAR. The modified T cells, now able to recognize and attack malignant cells, are then multiplied and infused back into the patient a few weeks later. CAR T cells remain long after the infusion to guard against any recurrent cancer cells.

An MD Anderson study showed that 42% of patients with aggressive large B-cell lymphoma remained in remission at 15 months after CAR T-cell therapy, representing an unprecedented response. Median overall survival in these patients is less than six months with available therapies. The study also demonstrated measurable responses in 82% of patients and complete responses in 54% of those treated. This therapy is expected to cure about 40% of patients and save approximately 4,000 lives each year in the U.S. alone.
The Breast Cancer Moon Shot™ is improving the outlook for breast cancer patients by pursuing new therapeutic approaches that revolutionize the way we treat this disease.

Each year, **approximately 230,000 patients in the U.S. face a diagnosis of invasive breast cancer**. While survival rates are improving, more than 40,000 patients will die from the disease annually. Our team of leading scientists and physicians is driven to make a difference for those patients and their families.

**Triple-Negative Breast Cancer**

The Moon Shot™ is committed to developing more effective, personalized treatments that lead to cures for patients with triple-negative breast cancer (TNBC) — so called because it lacks the estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2. However, TNBC is not a single cancer type, but really a “catch-all” term that encompasses many different subtypes, each requiring different treatments.

Approximately 30 to 40% of these tumors do not respond to chemotherapy, so we are working to provide alternatives. Our ARTEMIS trial leverages the unique capabilities of the Moon Shots Program™ — the longitudinal sample collection capabilities of the APOLO platform and the sequencing expertise of the Cancer Genomics Laboratory — to ask if personalized decision-making for pre-surgical treatment of TNBC is superior to standard chemotherapy.

We start with imaging and biopsies to identify patients unlikely to respond to chemotherapy, directing them to therapeutics strategies most compatible with their tumor type. More than 260 patients have enrolled in the study. For those with tumors deemed resistant to chemotherapy, over 80% have enrolled in targeted-therapy trials matched to their disease’s unique characteristics.

To broaden access to this promising approach, we worked with MD Anderson’s Cancer Network® to expand the trial to our Houston-area locations in League City, Katy, Sugar Land and The Woodlands. Patients from these local institutions accounted for 30% of ARTEMIS enrollment over the last fiscal year.

**BRCA1/2 Mutant Breast Cancer**

Because we see a high volume of breast cancer patients at MD Anderson, our clinicians offer expertise in a number of rare breast cancer types. Our team is ensuring patients with these rarer forms of breast cancer have equally effective treatment options.

We have several studies exploring poly (ADP-ribose) polymerase (PARP) inhibitors as single, front-line therapy for patients with BRCA1/2 mutations. Moon Shot researchers led studies showing impactful results for patients with both metastatic and localized breast cancer.

The international EMBRACA trial studied the PARP inhibitor talazoparib as a treatment for women with metastatic disease and found noticeable tumor reduction in more than 62% of trial participants. Inspired by that success, we initiated a small pilot study in the neoadjuvant setting — in which we administer a therapy prior to the main treatment. Driven by the Breast Cancer Moon Shot, the trial consisted of 13 patients whose tumors showed BRCA1/2 mutations. After just two months of treatment with talazoparib followed by standard-of-care chemotherapy, participants saw an average reduction in tumor volume of 88%. These results were so substantial that the trial was expanded to include an additional 20 patients on single-agent talazoparib to determine if the PARP inhibitor alone could induce excellent pathologic response. Of the 19 evaluable patients, talazoparib induced pathologic complete response/minimal residual cancer burden in 58% of patients, the highest reported response to neoadjuvant therapy ever seen in breast cancer. Building upon this data, we are expanding the trial of single-agent talazoparib in patients with BRCA-associated tumors.
The Adaptive Patient-Oriented Longitudinal Learning and Optimization (APOLLO) platform supports the Moon Shots Program™ by enabling patients to contribute to our leading-edge research so that we better understand cancer and how to treat it.

**Learning From Patients**

APOLLO is designed to make advanced cancers more predictable and easier to defeat by focusing MD Anderson’s clinical and research infrastructure to address and overcome a malignancy’s relentless ability to resist and survive treatment. We accomplish this by asking patients enrolled in clinical trials under the APOLLO research protocol to consent to biopsies and biospecimen (tissue, blood, stool, plasma, bone marrow, urine, etc.) draws before, during and after treatment.

Since cancer evolves during disease progression and treatment, it’s important to link clinical information with longitudinal molecular data, which is taken over the course of treatment. APOLLO is designed to provide the backbone for our efforts to integrate this critical molecular data with patient clinical data across cancer types. We collect high-quality longitudinal biospecimens for genomic and molecular analyses.

Coupling this research data with the patients’ clinical data is helpful for identifying suitable therapeutic targets and predictive and prognostic biomarkers, thereby supporting new clinical trials and decisions for new treatment options. Such an undertaking is critical to realizing the concept of molecularly informed, research-driven patient care.

**Expansive Analysis**

We expanded our biospecimen collection beyond the original leukemia pilot project and have now successfully collected, in total, longitudinal patient samples from 32 clinical trials within various disease sites, including breast, pancreatic, colorectal, melanoma, lymphoma, myeloma, sarcoma, leukemia, renal and rare solid tumors such as appendiceal adenocarcinoma, HPV- and Epstein-Barr virus-associated cancers, Merkel cell carcinoma, mesothelioma and neuroendocrine tumors.

**More than 800 patients** have consented to the APOLLO protocol and enrolled through various clinical studies, and we’ve completed **more than 1,000 biopsies/surgical resections** and **1,500 blood collections** through the platform. Our scientists are now collecting tissue from more patients with a broad array of cancers.

APOLLO is leveraging a new understanding of cancer — that it can behave differently before, during and after treatment — to find the best course for MD Anderson patients. In the past year, for example, APOLLO delivered approximately 350 samples to MD Anderson’s Translational Molecular Pathology - Immunoprofiling Lab, as well as approximately 200 samples to the Cancer Genomics Laboratory for RNA/DNA sequencing.
Novel Therapies

MD Anderson set the international standard of care for CLL when the Moon Shot™ leaders developed the fludarabine/cyclophosphamide/rituximab (FCR) chemotherapy regimen.

While effective, FCR is becoming obsolete as first-line therapy for most CLL patients due to the introduction of non-chemotoxic agents such as ibrutinib and venetoclax. The CLL Moon Shot has been instrumental not only in the development and FDA approval of ibrutinib for first-line treatment of CLL, but also for revealing its limitations, including cardiotoxicity and price. To this end, we examined the effect of the initial dosing schedule on the CLL cancer cells and the rest of the body and determined that there was excess in patients’ systems, which leads to off-target effects like atrial fibrillation (irregular heartbeat). We piloted a dose reduction study and found that we can effectively treat the CLL cells with less ibrutinib and, in turn, reduce off-target effects and lower the cost to patients.

These efforts were confirmed with the Center for Co-Clinical Trials, with whom we continue our fruitful partnership to better understand the effects of the latest agents in CLL cells and to identify potentially successful combinations of therapy for immediate clinical impact.

A second novel targeted approach to treating CLL uses chimeric antigen receptor (CAR)-modified natural killer (NK) cells targeting CD19. This unique approach uses allogeneic NK cells, which come from a matched related or unrelated donor, that have been altered to target and kill CLL cells expressing CD19. It is a first-in-human study for both CLL and B-cell lymphoma in collaboration with the adoptive cellular therapy platform. We’ve already completed the Phase I portion and are moving forward with the Phase II expanded study.

Molecular Research

At a deeper level, we are analyzing genetics to identify CLL patients at risk of progressing to more aggressive disease forms that are typically resistant to therapy and associated with poorer prognoses.

One of the more unexpected discoveries in oncology during the past decade is the role of small regulatory molecules called non-coding RNAs (ncRNAs) in cancer development. MicroRNAs (miRNAs), a type of ncRNA, are believed to be involved in the development of all types of cancers, including leukemias. Researchers who now are part of the CLL Moon Shot™ were the first to make this important link between miRNAs and cancer. Viral miRNAs — miRNAs encoded by viruses — are thought to be involved in CLL development as well as a patient’s response to therapy. Our team identified a role for Epstein-Barr virus (EBV) miRNA in the progression of CLL, finding higher EBV miRNA levels in patients with CLL than healthy individuals. Moreover, these higher levels correlated with shorter survival in two independent patient cohorts.

We are using RNA sequencing to examine large cohorts of CLL cell samples from around the world to identify other viral miRNAs in CLL patients, allowing clinicians to detect the virus earlier and start treatment sooner, giving patients the best chance for success and survival.

Our team also is making strides in deciphering the roles of ncRNAs in driving CLL progression to the more dangerous Richter’s syndrome. We have found that miRNAs may cause inflammatory changes that lead to Richter’s syndrome and can influence resistance to some therapies, such as fludarabine and ibrutinib. To this end, we have aligned with the Cancer Genomics Laboratory to sequence nearly 600 unique samples using our custom-designed probe for non-coding regions. This collaboration will generate a significant amount of data that will help identify molecular signatures that may provide clinical significance in early diagnosis, outcome and therapeutics.
Improving Diagnostics

Colorectal cancer is not a single disease. It encompasses several subtypes that should be treated differently. Previously, researchers lacked a clear classification system for these subtypes, but that changed in 2015.

Co-led by our Moon Shot™ team, researchers from 15 institutions shared data and applied their knowledge of genomics, proteomics and epigenetics to 4,000 patient samples. The result: a computational consensus identifying four distinct colorectal cancer molecular subtypes.

Scientists agree that 90% of the cases fall into one of the four subtypes. By precisely defining these clearly separate subtypes, we have begun to uncover new therapeutic vulnerabilities. This has led to the development of a Colorectal Cancer Moon Shot-funded clinical assay that identifies tumor subtypes, supporting clinical studies to better identify and understand the most appropriate treatment options.

Early Detection

While the colonoscopy revolutionized early detection and cut the colorectal cancer death rate in half, the disease still remains one of the leading causes of cancer deaths worldwide.

A major problem with colonoscopy is compliance. The procedure is difficult and invasive, and many people skip screenings, even if they are within the recommended screening age and at risk for the disease.

In response, our team of clinicians and scientists is developing a blood-based early-detection test — one that is simple to use, noninvasive, less expensive and more accurate at spotting the earliest molecular clues that colon cancer may be developing. This will benefit younger patients who are not recommended for colonoscopy, as well as the underserved and those in developing nations with no access to colonoscopy.

The blood test would detect biomarkers — tiny bits of protein that are signposts of cancer — circulating in the blood. We already have received interest from numerous commercial entities who would like to partner with MD Anderson to further develop the technology.

Novel Immunotherapies

Perhaps the greatest recent advance in cancer care, along with surgery, chemotherapy and radiation, is having a fourth treatment option — immunotherapy.

Our Moon Shot scientists are collaborating with MD Anderson’s leading immunology experts to awaken the immune system against immunologically cold colorectal cancers — those subtypes that block immune cells from penetrating the tumor — either by combining approved drugs with other agents or devising new approaches. In fact, because we are able to identify specific molecular characteristics in tumors that respond to immunotherapy, these treatments are having dramatic effects on improving clinical outcomes in certain colorectal cancers.

We are working to treat subtypes that are not responsive to checkpoint immunotherapy with a therapeutic vaccine designed to trigger an attack against established cancer. The trial improves upon earlier vaccine approaches by identifying neoantigens, or targets, unique to each patient’s tumor.

Our team identifies multiple neoantigens for each patient, develops a unique patient-specific vaccine cocktail and administers the vaccine in combination with pembrolizumab, an immune checkpoint inhibitor targeting the PD-1 receptor. Already we have seen promising results and are excited to continue pioneering this personalized immunotherapy.
In-Depth Profiling
Glioblastoma is a very aggressive cancer with few treatment options. The Glioblastoma Moon Shot is working to better understand the biology of the disease with the participation of patients who are allowing their tissues to be studied. Our Prospective Assessment of Correlative Biomarkers (PROACTIVE) program seeks to more fully characterize the molecular biology of glioblastomas, with an emphasis on using high-throughput sequencing technologies to uncover mutations that drive cancer progression.

Building from MD Anderson's clinical expertise, we have recruited 381 new patients to PROACTIVE this year and, supported by the Cancer Genomics Laboratory, are moving forward with RNA capture and whole-genome sequencing to analyze their tumors. What we learn will enable our clinicians to pursue new opportunities for targeted therapy development, re-appropriate existing agents and study multidrug combinations.

Adoptive Cell Therapy
Using cutting-edge research, the Moon Shot team has launched a clinical trial with T cells, a type of immune cell, targeting cytomegalovirus (CMV) in glioblastomas. Approximately 90% of glioblastomas express CMV proteins, making them an attractive therapeutic target.

- Led by researchers from the adoptive cell therapy platform, the trial captures T cells from the blood of patients previously treated with temozolomide, a common chemotherapy for glioblastoma.

In specialized labs, our team isolates T cells that recognize CMV proteins and expands them into a much larger fighting force, up to 100 million cells. While these cells are being readied, we treat our patients with temozolomide for three weeks. We then infuse the CMV T cells back into the patient, where they should seek out glioblastoma cells expressing the CMV antigen.

We have treated 16 patients and have generated encouraging results: one complete response, two partial responses and stable disease in six others. Our ongoing work will examine how long these cells remain active and how beneficial they are for newly diagnosed patients in combination with the standard of care.

Engineered Viral Therapy
Designed from a modified cold virus, DNX-2401 (formerly Delta-24-RGD) is a novel, highly potent and tumor-selective agent invented, produced and tested entirely at MD Anderson through Moon Shot collaborations.

In a Phase I clinical trial, we treated 37 patients with DNX-2401, injecting the virus directly into the tumor through a catheter. The virus replicated, divided and killed tumor cells, leaving normal tissue unharmed.

Remarkably, DNX-2401 also activated the patient’s immune system, providing a boost to the treatment’s efficacy. As the cancer returned, DNX-2401 continued to recognize and kill malignant cells. Of the 37 participants, 20% survived more than three years, which is more than twice as long as the average survival time of glioblastoma patients following diagnosis. Additionally, three patients had greater than 95% tumor reduction.

These results spurred two other clinical trials. The first, a 15-center trial, aims to enhance DNX-2401’s immune response by pairing the virus with a PD-1 inhibitor, a type of immune checkpoint drug. The second will investigate whether stem cells can be used to deliver DNX-2401 throughout the tumor mass more efficiently with less-invasive techniques.
Multiple myeloma is unique for having two well-defined precursor states: monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Though there are several factors useful for predicting disease progression, standard of care for these precursor disease states, even for high-risk patients, is a “wait-and-see” approach.

While patients with standard disease have seen improvements in their long-term survival rates, those with high-risk disease have yet to see the same benefits from recent therapeutic breakthroughs. By bringing together MD Anderson’s world-class care and research, our Moon Shot™ team is determined to change that.

### Immune Checkpoint Therapy

About half of all patients with intermediate- and high-risk SMM progress to symptomatic myeloma within five years. Our team is running a pilot study to treat these patients with pembrolizumab, an immune checkpoint inhibitor targeting the PD-1 receptor. The results of the trial to date have been exciting.

Among 13 participants, one patient achieved complete remission, 11 patients held with stable disease and one patient experienced disease progression. Remarkably, the patient who achieved complete remission expressed multiple features of high-risk symptomatic disease, which typically progresses quickly. Instead, thanks to early intervention, this patient remains in remission 17 months later, after only three doses of pembrolizumab.

The Cancer Genomics Laboratory enables us to work diligently to characterize both myeloma and immune cells from patients on the trial. This data will contextualize the differences in responses among patients and aid in the design of future clinical trials.

### Adoptive Cell Therapy

Our Moon Shot team also is collaborating with the adoptive cell therapy platform to bring forward new natural killer (NK) cell therapies for myeloma patients. For this approach, we isolate NK cells from donated umbilical cord blood and expand them in the lab before infusing them into a patient.

Unlike other immune cells that are sometimes used to treat cancer, cord blood-derived NK cells have not produced adverse immunological reactions within our patients. Our Moon Shot team is the first to treat myeloma patients with this approach prior to stem-cell transplantation, and the results have been remarkable.

Phase I and Phase II of the trial are now complete with 42 total participants, 15 of those with high-risk disease. When we compare our high-risk participants to a historical cohort of similar patients who received standard treatment, the complete response rate quadrupled (from 5% to 20%).

These results prompted us to extend the study to 18 additional high-risk patients. Investigators are curious if the addition of elotuzumab, an immunotherapy drug, further enhances the anti-myeloma effect of NK cells. In a preclinical setting, our team also is exploring our ability to engineer NK cells in ways that improve targeting and overall effectiveness.
The Cancer Genomics Laboratory drives our discovery and understanding of how tumors grow, spread and evolve. Our complete set of DNA is called our genome. Almost every cell in the body, including a cancer cell, contains a copy of the 3 billion DNA base pairs, or letters (A, T, G and C), which, strung together, make up the genome. By sequencing the DNA in a tumor before and after treatment, researchers hope to learn how cancer adapts to treatment and potentially becomes resistant to it.

The platform generates data that clinical researchers then analyze, integrate and interpret to accelerate progress and close gaps in our understanding and treatment of cancer. This is how our team helps to uncover the underlying molecular abnormalities that drive the growth and spread of cancer. As a result, we provide valuable data that may inform new avenues for targeted treatments, with the goal of significantly improving patients’ lives. The following projects highlight the capabilities of the Cancer Genomics Laboratory at MD Anderson.

The **HPV-Related Cancers Moon Shot™** is characterizing a rare HPV-related cancer with limited treatment options, especially for advanced disease. The team believes this to be the largest whole-exome analysis of this cancer; it has the potential to uncover the involvement of multiple cancer genes contributing to tumor development.

The **MDS and AML Moon Shot™** is studying clonal hematopoiesis of indeterminate potential (CHIP) — a premalignant condition in which somatic mutations are found in one or more leukemia-associated genes. Work from this team and others has shown that individuals with CHIP carry a higher risk of developing hematological malignancies and an increased risk of developing therapy-related myeloid neoplasms (t-MNs).

The next step is to use these findings to identify the patients at particularly high risk of developing t-MNs and create a strategy to mitigate their risks. The team is proposing a 10,000-patient study in 2019 to understand the prevalence and prognostic significance of CHIP.

To date, we have sequenced **more than 8,000 samples** across all **13 Moon Shot disease sites** to help our teams better understand cancer and how to treat it.
The immunotherapy platform integrates MD Anderson’s expertise in basic immunology with novel clinical trials to understand how a patient’s immune system and disease changes over time in response to therapy, improving treatment options for our patients.

**Broad Collaboration**

Working across the Moon Shots Program™, we collect samples over time from patients, regardless of tumor type, before they start therapy, while they’re treated and when they develop resistance. We learn from the patients who respond to immune checkpoint therapies and use that knowledge to provide effective therapy for patients who do not.

We have enrolled more than 3,500 patients in clinical trials under the platform’s umbrella since 2013, encompassing more than 120 associated clinical trials across 18 departments.

Our group has collected and analyzed more than 8,600 blood samples, 2,400 fresh solid tumor samples and 1,700 hematologic tumor samples in the past five years. We have analyzed more than 42,000 slides for immune infiltration since the program’s deployment.

Our integration with the Moon Shots Program is reflected in more than 30 trials and projects this past year across nine Moon Shots™.

**Innovative Clinical Trials**

- Working with the HPV-Related Cancers Moon Shot™ team, the immunotherapy platform helped complete a Phase II study in patients with previously treated, unresectable metastatic anal cancer, for which no consensus treatment approach exists. Of the 37 patients enrolled, 24% had responses.

  Our team was able to show that treatment response was associated with an inflammatory tumor microenvironment in patients’ pre-treatment samples. Patients who responded also had higher baseline readings of the PD-1 and PD-L1 proteins, two immune checkpoints. The results from this study led to the expansion of the combination trial for nivolumab and ipilimumab immune checkpoint therapies.

- We work incessantly to tackle the problems posed by tumor types where integrative cancer therapies have so far shown minimal or no clinical benefit. By collaborating with the Prostate Cancer Moon Shot™, our team found that a new immune checkpoint, VISTA, acts to block an immune response in prostate cancer patients treated with ipilimumab, an immune checkpoint inhibitor targeting CTLA-4. Our next steps are to perform additional studies in larger cohorts of patients and other model systems to develop novel combination trials for prostate cancer.

- With the Melanoma Moon Shot™, we analyzed the oral and gut microbiome (bacteria in the digestive tract) of 112 melanoma patients being treated with an immune checkpoint inhibitor targeting PD-1. Comparing patients who responded to therapy with those who did not, we found the two groups had different gut microbiomes, both in composition and diversity.

  Patients who responded also had a higher density of CD8+ T cells, soldiers of the immune system, and an enhanced immune-response signal in their blood, correlated with specific bacterial species. This study led us to launch a new clinical trial investigating anti-PD-1 therapy in combination with microbiome transplant.

Through integrated analyses of patient samples, we have explored the mechanisms that regulate immune responses and how responses change over time. We’ve designed novel, innovative treatment strategies, and we’ve witnessed the ability of integrative therapies to completely eliminate cancer in some patients.

We have identified biomarkers that may be used to predict which patients respond to these treatment plans. Looking ahead, we expect to translate discoveries into new treatment options to further unleash the immune system and create meaningful clinical responses for a much broader group of cancer patients.
The proteomics platform enables Moon Shots Program™ discoveries by sifting through thousands of cancer-related proteins to help investigators identify those useful for meaningful clinical advances for our patients.

Our collaborations with Moon Shot™ teams bring forward new discoveries for diagnostics and early detection, cancer imaging and targets for various types of treatments, from immunotherapies to small molecules. Our team also helps determine biologically relevant doses, identify biomarkers of sensitivity and resistance, and characterize adaptive responses to combination therapies.

**Predictive Biomarkers**
For patients with early-stage prostate cancer, it is difficult for doctors to predict which patients will progress to advanced, aggressive disease. In a study initially funded by the Moon Shots Program, we developed a panel of biomarkers that can identify patients with a higher risk of developing aggressive prostate cancer. This promising data helped to secure additional funding from the National Cancer Institute. Our long-term strategy is to understand the tumor biology that leads to more aggressive disease and transformation.

**Early Cancer Detection**
Better diagnostics in lung cancer is a major unmet need in the United States and around the world. We have collaborated extensively with the Lung Cancer Moon Shot™ for an international, multisite clinical trial to validate blood-based biomarkers for the early detection of lung cancer (please see page 31).

Diabetes, a family history or certain hereditary conditions can increase risk of developing pancreatic cancer. To preempt this cancer risk, using our latest platform technology, our team discovered new blood biomarkers that may help detect pancreatic cancer in its early stages. These new biomarkers had outstanding performance when used in combination with biomarkers already in the clinic. Our team’s success in this area led to additional grant funding by Stand Up to Cancer and the National Pancreas Foundation. Our next steps include using the biomarker panel to prospectively screen people who are at high risk for developing pancreatic cancer.

Approximately 50 million lives worldwide can be saved this decade by implementing known and effective prevention strategies. The cancer prevention and control platform is a comprehensive hub built to advance evidence-based, scalable and impactful programs in cancer prevention.

**EndTobacco**
The EndTobacco® Program calls for an unprecedented and sustained institutional commitment to leadership, investment and collaboration to further evidence-based tobacco control actions as a core element of MD Anderson’s mission. Working closely with the Lung Cancer Moon Shot™, our team has seen significant progress in the past year.

EndTobacco helped launch The University of Texas (UT) System’s Eliminate Tobacco Use initiative in 2016. As a result, all 14 system institutions adopted tobacco-free campus policies as of June 1, 2017. The initiative hosted its third summit in April 2018 to share best practices and discuss next steps, as well as plan for expansion efforts beyond the UT System.

In collaboration with MD Anderson’s Office of Government Relations, our team served as an educational resource and provided coalition-building expertise for local policy efforts, including Fort Worth’s adoption of a comprehensive smoke-free policy, San Antonio’s adoption of Tobacco21 and Houston’s proposed ordinance to make sports facilities tobacco-free.

Additionally, working with MD Anderson tobacco cessation experts, we established the Certified Tobacco Treatment Training Program, which gives health care providers access to MD Anderson expertise. As one of only 19 training sites in the U.S., MD Anderson trained 146 health care providers this year, potentially helping tens of thousands of people.

**Melanoma Prevention**
We are working together with the Melanoma Moon Shot™ to reduce untimely deaths from melanoma. This year, the platform embarked on a collaboration with Scholastic, a nationally recognized leader in education, to extend the impact of Ray and the Sunbeatable®: A Sun Safety Curriculum, originally developed by MD Anderson for preschool, kindergarten and first-grade students. As a result of the collaboration, we launched the Be Sunbeatable™ sun safety program in March 2018, expanding our programming through fifth grade and reaching over 50,000 classrooms, as well as school nurses and parents nationwide.

The Melanoma Moon Shot and the platform also are training providers through telementoring sessions to improve melanoma early detection (please see page 43).
Health Systems Strengthening
Population-health initiatives are best deployed in large health systems with patients treated across a wide range of clinical needs. Recognizing the MD Anderson Cancer Network® as a valuable partner for improving population health, we launched an initiative to improve the rates of genetic counseling and BRCA1/2 testing at three health care systems. This past year, we introduced quality improvement interventions at these three sites and began recruiting additional sites. Next year, we plan to evaluate and deploy additional initiatives, such as a project focused on breast cancer preventive therapy.

Project ECHO Superhub
Recognizing a critical need to address disparities in cancer care, the Project Extension for Community Healthcare Outcomes (ECHO) Institute at the University of New Mexico designated MD Anderson as the first “superhub” for oncology in January 2017. The MD Anderson Project ECHO programs are teleconsulting and telementoring partnerships between MD Anderson specialists and health care providers in rural and underserved communities. As one of only nine superhubs worldwide, MD Anderson extends best practices domestically and globally by providing technical expertise and direction to other institutions. To date, the team has trained 31 specialty centers, organizations and societies to become ECHO hubs with a focus on mentorship and partnering to improve outcomes in the community.

Be Well Communities™ unite individuals, schools, workplaces, government agencies, health care providers and policymakers to plan and execute community-led solutions that will make positive, long-lasting change in people’s lives.

Through this initiative, we engage communities in ongoing dialogues about the importance of health behaviors; create and advance community-based strategies to improve cancer prevention and control policies; and increase behaviors that lower cancer risk, including diet, physical activity, preventive care, tobacco control and limited ultraviolet radiation exposure.

Our inaugural initiative is Be Well™ Baytown in Baytown, Texas, the third largest city in Harris County. In collaboration with a community-based steering committee of more than 25 stakeholders, our team led the implementation of an action plan affecting 80% of Baytown’s population, or nearly 60,000 individuals.

The Pasadena Vibrant Community initiative aims to mobilize Pasadena, Texas, to promote health and wellness, with a focus on maintaining a healthy weight, being physically active and consuming a balanced diet as key ways to reduce the risk for chronic disease. Working with a community-based steering committee, we implemented an action plan focused on diet and physical activity interventions. Over the next three years of programming, approximately 33% of the Pasadena community, or more than 50,000 individuals, will be affected.
Recognizing that cancers caused by the human papillomavirus (HPV) are increasing at epidemic rates, the HPV-Related Cancers Moon Shot™ brings together broad teams from multiple clinical specialties to **improve screening and prevention, to advance personalized therapies** and to validate emerging treatments for our patients.

**HPV-Related Cancer Prevention**

Cancer-causing forms of HPV account for virtually all cervical cancers, most oropharyngeal and anal cancers, and a major proportion of penile, vaginal and vulvar cancers. HPV-related cancers are now estimated to account for roughly 40,000 new cancer cases each year.

Fortunately, there is a safe and effective vaccine available to prevent the majority of these infections and related cancers. Unfortunately, it is sorely underutilized in the United States.

We partnered with community health systems throughout Texas to train health care providers to increase vaccination rates in their clinics. After early results showed vaccination rates increased by as much as 17% in some clinics, we expanded the program beyond Texas through the National Comprehensive Cancer Network (NCCN), an alliance of 27 cancer centers across the country. We also cultivated a team-based learning program for students at the John P. and Kathrine G. McGovern Medical School at The University of Texas Health Science Center at Houston.

Our investigators contributed to the Texas HPV Strategic Plan, called for by the 2015 Texas Legislature, to provide rational approaches to improving vaccination rates in Texas. We were instrumental in drafting consensus statements, including all National Cancer Institute (NCI)-designated cancer centers, supporting HPV vaccination for cancer prevention. We also launched an advocacy project to engage and train survivors in the vaccination effort.

**Personalized Therapies**

Working with MD Anderson’s clinical and research experts, the Moon Shot is advancing novel targets and biomarkers that will enable us to give personalized care to our patients with HPV-related cancers.

Through genomic analysis, we identified a biomarker signature for HPV-positive disease that could lead to personalized therapy, a critical clinical need for patients with refractory, or treatment-resistant, HPV-positive head and neck squamous cell carcinoma.

We also performed the largest high-throughput drug screen in HPV-positive cell lines to date and identified Aurora kinases as an effective drug class that scientists should study as potentially new therapeutic targets.

**Changing Standard of Care**

Two studies led by our Moon Shot team also have changed treatment guidelines set by the NCCN for patients with HPV-related metastatic anal cancers.

In the first clinical trial to evaluate an immune checkpoint inhibitor in patients with refractory metastatic anal cancer, our investigators found positive results from the use of nivolumab, which targets PD-1. Results from this trial prompted revisions in the NCCN 2018 treatment guidelines, which now recommend nivolumab as a potential therapeutic option for patients with treatment-resistant disease.

Another clinical trial involving Moon Shot investigators — the International Rare Cancers Initiative randomized Phase II study — led to another change in the NCCN 2018 guidelines. Based on results from the study, the guidelines now advise clinicians to consider combination chemotherapy with carboplatin/paclitaxel as a treatment in patients whose prior therapies have failed.
Patient-Guided Treatments

The Moon Shot™ team is committed to learning from our patients to better treat them going forward. Our Genomic Marker-Guided Therapy Initiative (GEMINI) captures clinical and molecular data on all lung cancer patients treated at MD Anderson. Likely the world’s largest database of its kind — GEMINI enables us to correlate treatment with molecular alterations to understand why certain patients are responsive or resistant to treatment.

Through mining the GEMINI database, cell line screenings and preclinical studies using novel lung cancer models, we have systematically screened existing drugs to find new, effective treatments faster and cheaper. This innovative research approach revealed the potential impact of a drug called poziotinib.

Originally developed for another use and abandoned, poziotinib has shown promise against non-small-cell lung cancers with a specific alteration in either the EGFR or HER2 genes. To date, we’ve had no effective treatments for these patients. These results magnify our hope for this groundbreaking line of research, which also may treat other cancers with the same mutations.

Early results of the Phase II clinical trial to test poziotinib in this subset of patients showed confirmed responses in 64% of patients, with tumor shrinkage of at least 30%.

Based on these data, we opened an international Phase III trial, under a licensing agreement with Spectrum Pharmaceuticals Inc., to bring this drug forward in the lung cancer setting.

Lung Cancer Early Detection

MD Anderson also seeks FDA approval to validate a biomarker panel developed in collaboration with the proteomics platform, which includes a pioneering international trial that grew to 9,000-plus participants last year. FDA approval will allow us to move closer to being the first to bring a blood-based biomarker test to market for lung cancer screening in current and former smokers.

This tool has the potential not only to reduce the cost of screening (which currently relies on CT scans), but also to broaden the screening population beyond current U.S. Preventive Services Task Force recommendations. We are in discussions with potential industry partners to facilitate domestic and international market development for the panel, which also is expected to help clinicians better distinguish between benign nodules revealed on CT scans and actual lung cancer.

Tobacco Cessation

In addition to our extensive collaboration with EndTobacco (page 25), we are working to develop personalized cessation therapies to help more smokers quit. We have advanced through three groundbreaking clinical trials and an extensive, retrospective analysis of genetic information from previous trials. We used these data to develop an algorithm, which integrates molecular, behavioral and neurophysiological markers, to guide personalized cessation treatments. We plan to launch a pivotal clinical trial testing the algorithm this year.

Through these and other projects — from clinical trials to increase the effectiveness of immunotherapies for more patients to a certification program set to train health care providers nationwide in MD Anderson’s evidence-based smoking cessation methods — the Moon Shot is well positioned for future progress against lung cancer.
The Institute for Applied Cancer Science (IACS) delivers innovative new drugs to precisely defined patient populations. This past year, IACS continued to partner with clinicians and other Moon Shots™ teams to advance multiple programs toward the clinic to benefit patients.

Our commitment to stringent go/no-go decisions early in drug development is being rewarded as our latest-stage programs progress rapidly toward the clinic. We also maintain an ambitious portfolio of earlier-stage projects and are identifying novel targets to enter the drug discovery pipeline in collaboration with the Center for Co-Clinical Trials (CCCT).

**Targeting Cancer Metabolism**

IACS-10759 is a first-in-class metabolism-targeting drug that inhibits a cellular process called oxidative phosphorylation to cut off the fuel supply in certain cancer cells. Based on extensive preclinical evaluation, we anticipate IACS-10759 may have therapeutic benefit in multiple contexts, including with or without additional chemotherapy or radiation.

We’ve begun evaluating IACS-10759 in two clinical studies: one in patients with relapsed/refractory acute myeloid leukemia (AML) and a second in patients with solid tumors or lymphoma. Both trials are in the early stages of determining a safe and effective dosage for patients. Analyses of blood samples from patients with AML are encouraging, indicating that IACS-10759 is engaging the intended molecular target — valuable information the team will use to monitor the efficacy of the drug as studies advance.

A second cancer metabolism drug candidate, IACS-6274, stems from a collaboration with the CCCT, the Lung Cancer Moon Shot™ and the Ovarian Cancer Moon Shot™. Over the past year, our teams conducted vigorous preclinical testing and toxicology studies. Currently, we are manufacturing clinical supplies in accordance with FDA regulations.

Our results support using IACS-6274 for a specific subset of patients with lung or ovarian cancers and, most notably, helped develop diagnostic tests to identify the patients. We anticipate enrolling the first patient to receive IACS-6274 in early 2019, pending FDA approval.

**Chemotherapy Side Effects**

There is an immense need for therapies that improve the quality of life for cancer patients, and drugs that help patients tolerate chemotherapy can have far-reaching impact. Peripheral neuropathy is a common side effect of chemotherapy that results in tingling in the fingers and toes, loss of touch and mild cognitive deficits referred to as “chemo brain.” These impairments can cause hardships for survivors and their loved ones and often lead to dose reductions or even breaks in treatment.

Working with the Neurodegeneration Consortium — a multidisciplinary team working to better understand the underlying biology of Alzheimer’s disease and translate this knowledge into therapeutic interventions — we developed a novel neuroprotective therapy, IACS-8287, to prevent side effects. To accelerate the development of IACS-8287, MD Anderson licensed the project to Magnolia Neurosciences, with additional funding secured from venture capital and the Cancer Prevention and Research Institute of Texas. We expect clinical trials to begin in early spring 2019.

IACS and CCCT have several other projects in progress, including innovative therapies for patients with lung, colorectal, prostate, head and neck, pancreatic and renal cancers, as well as lymphomas and leukemias. Our team is particularly passionate about our programs focused on rarer and most difficult-to-treat tumor types, such as glioblastoma and sarcoma, as these diseases are often passed over by the biopharmaceutical industry.
The Center for Co-Clinical Trials (CCCT) integrates expertise from industry and academia to accelerate the discovery and translation of novel therapeutics, leveraging cutting-edge technologies and platforms to identify and evaluate the biological and clinical relevance of drug targets.

This past year, CCCT and IACS advanced several drug discovery programs, expanded relationships with Moon Shot™ teams and formalized new alliances with biopharmaceutical partners. Our collaborative efforts resulted in two clinical studies now underway, with multiple others scheduled to begin in the coming year and an expansion of our work to encompass additional cancer indications.

Identifying New Targets
To more rapidly help patients who urgently need new treatments, we developed an industrialized platform that enables us to systematically identify and validate new oncology targets in patient-derived tumor tissues. Over the past year, we collaborated with the Colorectal Cancer Moon Shot™ and Pancreatic Cancer Moon Shot™ to learn about tumor dependencies in specific subtypes of gastrointestinal cancers.

We also expanded our continued work with the Lung Cancer Moon Shot™ to identify and validate drug targets that may improve patient responses to immunotherapy, with several positioned for clinical testing in 2019. Through these and other cooperative efforts, we validated a number of promising drug targets that are advancing through the IACS/CCCT discovery and development pipeline.

Evaluating New Therapies
Our team continues to work with multiple Moon Shot teams to broaden our disease-modeling capabilities and boost our translational biology platforms to rapidly evaluate approved and investigational drugs.

Together with the IACS platform, we advanced a robust portfolio of small molecule drugs toward clinical development — including IACS-10759, a cancer metabolism inhibitor now in clinical testing for relapsed/refractory acute myeloid leukemia and solid tumors, described in depth on page 32. To guide the future clinical development of this drug, our team engaged with the clinical study teams to investigate the biology of response in patient samples. We also are pursuing efforts to stratify patients based on genetic biomarkers.

Additionally, we are working closely with the Lung Cancer Moon Shot and Ovarian Cancer Moon Shot™ teams to advance a second metabolic drug called IACS-6274. We generated valuable data to define the clinical trial design and developed clinical assays to inform patient selection, which will best position the drug for success in specific patient groups. To accelerate clinical development of the compound, we partnered with the pharmaceutical company, Ipsen, and expect first-in-human studies to begin in January 2019.

Industry Collaborations
Our investment in translational biology has helped to forge partnerships with biopharmaceutical companies that complement and enhance our drug portfolio. Our alliance with Taiho Pharmaceutical Co. is enabling us to evaluate an array of compounds that may benefit patients whose cancers have spread to the brain. Our discovery partnership with Boehringer Ingelheim is focused on a novel drug candidate in colorectal and pancreatic cancers and, by coordinating with disease-site experts, we are expediting this research into clinical development.
The Oncology Research for Biologics and Immunotherapy Translation (ORBIT) platform is dedicated to the discovery and development of innovative anti-cancer monoclonal antibodies (mAbs). Our goal is to combine scientific excellence with industry-standard expertise to effectively guide, accelerate and execute the translation of novel discoveries into therapies for our patients.

Advancing New Therapies
We have delivered on our initial objectives of accelerating the development of promising mAb programs. ORBIT collaborated with GlaxoSmithKline to bring one antibody to clinical trial, testing it alone and in combination with an immune checkpoint inhibitor.

In addition, MD Anderson and Astellas Pharma US, Inc. are collaborating on h8F4, a humanized antibody invented at MD Anderson to specifically target and kill acute myeloid leukemia (AML) cells. This represents the first ORBIT-Astellas collaboration on a T-cell receptor-like antibody.

This year, we received a safe-to-proceed letter from the FDA for Phase I clinical testing of h8F4. We hope that patients with AML will benefit from development of this first-in-class mAb.

Revolutionizing Antibody Discovery
We also are developing a revolutionary approach for antibody discovery, through cloning individual B cells, a type of immune cell that produces antibodies. With this approach, researchers first sort individual B cells, then clone their antibody genes into cell lines for reproduction.

This method not only expedites the process of antibody generation, but also overcomes certain drawbacks of old technology, such as low efficacy of antibody production. Our researchers have successfully established a single B-cell cloning method, which allows us to identify high-quality antibody candidates for multiple new therapeutic considerations.

Industry Partnerships
We collaborate extensively with external contract research organizations (CROs) for antibody development to avoid redundancy and accelerate project development. The team has established long-term contract agreements with selected CROs to manage all activities required to generate investigational new drug-enabling data in an efficient and cost-effective manner.

We have established strategic alliances with antibody companies that have advanced proprietary technologies that generate high-quality antibodies, including next-generation multi-specific mAbs that can engage multiple targets. Among these are Kymab Limited, a platform and mAb discovery biotechnology company; MorphoSys AG, a German biotechnology company that is providing access to the most advanced phage-display platform technology for mAb research and development; and Adimab, a company with yeast-display technology for the library of synthetic human antibodies.

ORBIT researchers also are in the process of developing a strong drug discovery pipeline consisting of six programs per year. The platform is a testament to the quality of work and complexity of operations only possible at MD Anderson through the Moon Shots Program™.
The adoptive cell therapy (ACT) platform programs immune cells to recognize and attack cancer and helps implement these cellular therapies across the Moon Shots Program™ and MD Anderson.

Leveraging the immune system’s ability to discriminate between cancer cells and the body’s own healthy cells, cellular therapies offer the promise of minimal toxicities with the benefit of long-term immune protection.

Collaborative Approach

This past year, our platform collaborated with six of the Moon Shots™ teams and is forming new collaborations with two additional Moon Shots. We launched and conducted eight clinical trials of the most innovative cellular therapies to treat patients with cancers including acute myeloid leukemia (AML), high-risk multiple myeloma, chronic lymphocytic leukemia, B-cell lymphoma, glioblastoma and melanoma.

These patients, whose cancers had not responded to any other available treatments, were given new hope with these cutting-edge therapies. We treated approximately 50 patients last year through the ACT platform and found the outcomes of the treatments to be extremely encouraging. We continue to develop and test therapies so we can help thousands of patients moving forward. And we are working to launch new therapies to tackle some of the most challenging cancers.

Utilizing Natural Killer Cells

In high-risk AML patients, donor natural killer (NK) cell infusions have resulted in remission. However, this approach has been limited by the relatively low number of NK cells that can be collected from donors. Using technology developed through collaborations at MD Anderson, we have discovered a solution to this problem.

By multiplying NK cells in the lab, we are able to provide a far larger dose of activated tumor-killing NK cells. This system has proven to be superior to all other reported methods, yielding over 30,000-fold expansion in just three weeks. And our patients are directly benefiting with critical therapeutic options produced faster than anywhere else.

In preclinical models, we also have shown that NK cells from donated umbilical cord blood, multiplied in the lab, accelerate the rebuilding of the immune system in the recipient and kill leukemia cells when infused. This is the first time such supercharged cancer-fighting cells have been expanded in the lab for clinical use as a potent addition to a cord blood transplant.
Preventing Therapy-Related Cancers

Our team of Moon Shot™ researchers and clinicians have identified a family of mutations in the blood and bone marrow, known as clonal hematopoiesis of indeterminate potential (CHIP). CHIP is associated with an increased risk of developing secondary cancers, specifically those caused by cancer treatments, known as therapy-related myeloid neoplasms (t-MNs).

Taking advantage of the Cancer Genomics Laboratory, we have found that up to 75% of patients with therapy-related leukemias, which are very aggressive and carry a poor prognosis, harbor CHIP mutations. By identifying these mutations during treatment for the original cancer, we can take measures to try to proactively prevent the second from emerging.

Building on the clinical expertise of MD Anderson, the Moon Shot is designing clinical trials and establishing a CHIP clinic to screen for patients carrying these mutations, advising their physicians on different forms of treatment. These measures may include targeted therapy, immunotherapy and epigenetic drugs. Our goal is to treat patients with CHIP mutations effectively while preventing the emergence of secondary cancers.

Overcoming Treatment Resistance

For some patients with MDS, hypomethylating agents (HMAs) are miracle drugs. Developed at MD Anderson, HMAs can successfully treat the cancer and allow our patients to move on with their lives. The drugs have become the standard of care, used to treat 80% of patients who are eligible for therapy.

Unfortunately, for many patients, these drugs stop working and the disease returns. The prognosis for these treated individuals is dismal. In an MD Anderson study, Moon Shot researchers found that survival after HMA failure is just five months. Therefore, we have committed ourselves to address this critical issue.

We are driven to fill this treatment gap through groundbreaking research. Through the Moon Shot, we have made a discovery that could lead to effective treatments for patients with cancers resistant to HMAs. By analyzing more than 250 samples from patients with MDS, taken during different stages of disease progression, we found that HMAs effectively eliminate mature MDS cells but leave the cancer stem cells behind. This eventually leads to treatment failure and relapse.

These patients with therapy-resistant stem cells can then be divided into two groups based on the profiles of those stem cells. Each is biologically distinct and requires different approaches to overcome their resistance to HMAs. Our Moon Shot team continues to make progress in finding and testing drugs that may be able to treat these two distinct populations, improving outcomes for these patients without any treatment alternatives.
Melanoma Prevention

With the expertise of the cancer prevention and control platform, the Moon Shot™ team expanded its relationship with the American Cancer Society Cancer Action Network to serve as an educational partner and scientific resource in states considering tanning bed legislation. The partnership builds upon our success serving in a similar role for the Texas Legislature, which adopted a law in 2013 prohibiting tanning bed use by minors under 18. Studies show that starting indoor tanning as a minor is associated with higher melanoma risk. To date, 19 states and the District of Columbia have passed similar legislation.

Our efforts also focus on educating providers on the early detection and diagnosis of melanoma through the use of dermoscopy, a low-cost handheld magnifier that enables physicians to better detect melanoma at earlier, more treatable stages. Project DERM:EMD (Early Melanoma Diagnosis) educates dermatology residents in the use of dermoscopy as part of a multi-pronged vision to educate providers of varying backgrounds. This year, we launched six training sessions in eight academic dermatology programs in Texas and Missouri to train dermatology residents in proficiencies of dermoscopic use. Additionally, we developed instructional materials, a database and a robust educational dashboard to provide feedback to each program.

Moving forward, we plan to pilot test adapted curriculum for primary care residency training programs. The goal is to turn this social investment in provider training into a model by which we can spread early melanoma detection capabilities across Texas.

Improving Treatments

Treatment of metastatic melanoma has dramatically improved over the last decade, but most patients ultimately experience relapse. Our multidisciplinary team of surgeons, oncologists and researchers is working to identify predictors of response and resistance to optimize current therapies and develop new combinations.

Melanoma Moon Shot researchers demonstrated a correlation between the diversity of the gut microbiome (bacteria in the digestive tract) and clinical outcomes in metastatic melanoma treated with anti-PD-1, an immune checkpoint inhibitor. These findings will help determine whether we can change the microbiome in melanoma patients undergoing anti-PD-1 therapy to improve outcomes.

Our team also is exploring ways to use therapies approved for late-stage melanoma in treating early-stage disease. In our successful single-center randomized clinical trial, we tested a combination of targeted therapies, dabrafenib and trametinib, given before and after surgery compared to standard of care (upfront surgery) in patients with BRAF mutations.

The trial was closed early, with a more than 60-fold reduced risk of relapse in those receiving pre-surgical therapy. Initial results also showed that the pre-surgical combination achieved complete responses in approximately 60% of patients, which correlated with decreased risk of subsequent distant metastases. This study changed the way we treat certain patients with BRAF-mutated melanoma and generated new insights into determinants of resistance.

From implementing prevention and policy initiatives to enhancing current therapies and developing new combinations, the Melanoma Moon Shot is working to lower or reverse the high number of new melanoma cases and improve patient outcomes.
Improving Surgical Outcomes

One of the first projects initiated by the Moon Shot™, the Anderson Algorithm, continues to be a shining example of how we can apply current knowledge and garner dramatic results.

The Anderson Algorithm improves the rates of complete surgical resection to boost survival outcomes. Our clinicians first evaluate tumors laparoscopically, then devise a score based on the likelihood of achieving complete surgical resection. If likely, they schedule an operation. However, if complete resection is unlikely, the patient receives chemotherapy treatment first to shrink the tumors. Since the algorithm was implemented, complete surgical resection rates have jumped to nearly 90%, up from just 25%. This strategy allows for a much more personalized surgical approach, resulting in avoidance of unnecessary surgery and improvement of surgical outcomes.

Medical centers worldwide are recognizing MD Anderson’s expertise in this area and the success of our Moon Shot research. Faculty at Hospital Israelita Albert Einstein in Sao Paulo, Brazil, are uploading laparoscopy images for MD Anderson faculty to consult on scoring. Disseminating this information is the next step in the process, including discussions with Mexico’s National Cancer Institute equivalent. We are excited at the opportunity for these collaborations, as our goal is to improve cure rates for women globally.

We also are launching new projects through tissue collection. All patients donate tissue from at least four sites (the primary tumor, the omentum and two metastatic sites). During surgery, tissue is collected again. With expert analysis by the Cancer Genomics Laboratory, these samples have proven valuable across all Ovarian Cancer Moon Shot trials, allowing our researchers to learn from our patients and refine therapeutic approaches through a more complete understanding of the molecular and immune differences in those whose cancer responds well to therapy versus those who do not.

Treating Resistant Disease

Although 80% of patients enter remission after a combination of surgery and chemotherapy, the majority relapse and their cancer becomes resistant to available therapies. How can we incorporate novel agents to improve durable outcomes?

Through our clinical and research collaborations, we have taken an innovative approach to clinical trials, learning from our patients’ responses to incorporate new therapies and more effective combinations.

High grade serous ovarian cancers often have mutations in a DNA repair process called homologous recombination (HR). These tumors should be sensitive to treatments with poly ADP ribose polymerase (PARP) inhibitors, which also prevent cancer cells from repairing DNA damage, effectively killing the malignant cells.

PARP inhibitors have not demonstrated activity in all patients with the HR deficiency, but they may be effective when used in combination with other drugs. We have identified several drug combinations likely to increase PARP inhibitor activity and are exploring how to overcome targeted-therapy resistance by identifying patients most likely to benefit from PARP inhibitors.

Researchers also are using newly developed clinical trials to test rational combinations identified through our Combinatorial Adaptive Response Therapy (CART) platform. With the CART platform, we analyze patient samples for adaptive changes in the tumor after treatment. Identifying early changes in select proteins has allowed us to develop new combination therapies to overcome resistance, some of which have already entered clinical trials across multiple Moon Shot efforts targeting ovarian, melanoma, pancreatic, gastrointestinal and lung cancers. This approach to explore adaptive responses is key to the development of new and more effective treatments.
In 2018, more than 44,000 people were expected to die from pancreatic cancer, most within one year of diagnosis. Pivotal research advances over the last decade have not yet translated into significant progress in patient outcomes, leading to a dismal five-year survival rate of just 9%. The Moon Shot™ brought together a focused team of physicians and researchers with the singular goal of saving those patients’ lives.

Improving Treatment

Our program’s newest treatment strategy is neoadjuvant therapy, an approach that treats the patient with chemotherapy, radiation or other drugs prior to surgery. Not all institutions follow MD Anderson’s neoadjuvant approach when treating nonmetastatic patients. Standard of care is to perform surgery first when possible, but nationally the median survival of these patients is about 15 to 25 months. At MD Anderson, the median survival is 43 months — nearly double the national average. Although we lead in care for these patients, we can and must do even better.

We’ve launched an initiative to improve our neoadjuvant approach for patients with nonmetastatic pancreatic cancer. Our innovative trials will offer treatment strategies personalized for each patient. We have designed an adaptive master trial protocol, which allows ineffective or harmful treatments to be dropped and promising agents to move forward. We also plan to complete extensive blood- and tissue-based analysis to better understand tumor response and resistance to particular treatments.

Early Cancer Detection

Unlike some other cancers, there is no blood test to find pancreatic cancer at an early stage. A simple, affordable and widely available blood test for pancreatic cancer will have a transformational impact on survival rates.

To be accurate and reliable, a blood test will need to be based on several biomarkers. Through the Moon Shot, and in collaboration with the proteomics platform, we’ve built a panel of three promising proteins and are validating more markers to improve accuracy. Our unprecedented effort to find these biomarkers brings together four laboratories under the Moon Shot, as well as research teams outside of MD Anderson.

For our biomarker research, we are leveraging biospecimens obtained by Houston’s first Pancreatic Cancer High-Risk Clinic, now in its fourth year of operation. This pioneering MD Anderson clinic — which has both research and clinical arms — has screened and advised more than 200 area patients at increased risk for pancreatic cancer. These individuals do not have disease but remain at a higher lifetime risk.

Research supported by the clinic has led to important discoveries: We now know that there is a higher prevalence of genetic mutations, and therefore, a higher likelihood of developing pancreatic cancer, in “young onset” pancreatic cancer patients compared to those diagnosed at the median age population for the disease (68 years old). This underscores the importance of genetic testing and monitoring of high-risk individuals, even at younger ages. We have also discovered an association between long-term pancreatic cancer survivorship and particular types of bacteria in the pancreatic tumors, opening the door for simple interventions that have potential to increase the effectiveness of treatment. This clinic has enormous potential to impact the lives of families touched by this disease.
Predicting Cancer Progression

A variety of therapeutic options is available for our patients, but each carries the risk of serious side effects that impair sexual, urinary and bowel function. We can’t yet reliably predict which tumors will grow slowly and harmlessly and which tumors will grow rapidly, metastasize and become treatment-resistant and lethal. As a result, many men receive unnecessary treatment while others undergo therapy that isn’t aggressive enough.

The Moon Shot™ team is conducting impactful clinical research to transform the way we classify, and therefore treat, the disease — from the prevailing prognostic system to a predictive system that accounts for biologic changes that occur as the disease progresses. Other areas of focus include developing methods to monitor the evolution of prostate cancer with a simple blood test and implementing new strategies for biologically based combination therapies.

Advancing New Therapies

Driven by the presumption that precisely targeted therapies lead to better patient outcomes, our team of clinical and scientific experts led several groundbreaking studies to bring these therapies into the clinic.

We demonstrated that combining immune checkpoint inhibitors, which prevent the immune system from turning off before cancer is fully eliminated, resulted in complete remission of prostate cancer — noting for the first time that some patients have a striking and total disappearance of disease. This promising clinical finding suggests that some men with advanced and treatment-resistant disease may be cured with immunotherapy.

Researchers also completed follow-up and data analysis for the first trial of hormone therapies with curative intent for selected men with early, high-risk prostate cancer. Our team found that a combination of leuprolide and abiraterone, which reduces the levels of male hormones that drive most prostate cancers, made a significant difference in patients’ progression-free survival compared to leuprolide alone. The shorter duration of this approach spared some men the side effects of recurrent cancer and the toxicity of sustained androgen deprivation.

For patients with aggressive-variant prostate cancer, three clinical trials will link a proposed molecular signature to three unique therapeutic vulnerabilities: androgen indifference, sensitivity to poly (ADP-ribose) polymerase (PARP) and site-directed therapy. We also revealed a fourth vulnerability, called epigenetic modulation, through preclinical work, and we have detected its emergence in blood samples. To explore this new domain, we designed a clinical trial that has been approved by supporting companies and will be activated in the coming year.

Also underway is an exciting collaboration with the Cancer Genomics Laboratory to conduct a study of circulating tumor DNA over time. The project involves serial samples from 160 patients with metastatic castration-resistant prostate cancer, which is difficult to treat because it continues to grow and spread despite low levels of the hormones usually required for tumors to thrive. Patients participating in the trial will undergo blood draws, not biopsies. The results should reveal important information about the DNA that is shed by the primary tumor into the bloodstream — as well as suggest potential new targets for therapy.