Finding Answers in Blood

A published study suggests that TARDIS, a liquid biopsy test, is as much as 100 times more sensitive than other blood-based cancer-monitoring tests.
Dear Friends,

This edition of TGen Today highlights some of the ways TGen researchers remain ahead of the pack, featuring innovative techniques and lines of scientific pursuit in their quest for new treatments and, eventually, cures.

One of TGen’s advantages is our powerful alliance with researchers and clinicians at Southern California’s City of Hope.

Our cover story shows how TGen’s Dr. Muhammed Murtaza teamed with City of Hope Dr. Thomas Slavin and others to develop a remarkable new blood test for early detection and monitoring of breast cancer; a blood test that someday could substantially reduce the number of women who undergo mastectomies.

You’ll also learn how a pair of TGen scientists — Drs. Laura Goetz and Nicholas Schork — are looking for ways to prevent cancer from occurring in the first place, or at least detecting cancer in its very earliest stages when chances of successful treatment are best. Work, again, in collaboration with City of Hope.

Blending Western and Eastern medicine, we feature Dr. Winnie Liang, who is attempting to make inroads against ALS, what many know as Lou Gehrig’s disease, by culling potential genetic targets, called biomarkers, using the ancient practice of acupuncture.

In addition, you’ll see more stories about innovations in pancreatic cancer, Alzheimer’s disease and other medical advances that are working to help patients — today.

Please join us on our voyage of discovery!

With gratitude,

Erin Massey
Chief Development Officer, TGen Foundation
Vice President of Philanthropy, City of Hope
Is There an App for That?
Mobile application software plays an increasing role in research, health, and wellness.

TGen Distinguished Professor Dr. Nicholas Schork has no intention of practicing New Age medicine. He doesn’t even meditate. But as Deputy Director for Quantitative Sciences, he knows good data when he sees it.

“Working with TGen’s many abilities to probe and analyze the human genome, we want to use all these new technologies to understand why people get cancer,” she said. “The goal is getting to a better understanding of the majority of people who are going to get cancer.”

INTEGRATING DIGITAL TECHNOLOGIES INTO LIFE

An initiative by the U.S. Food and Drug Administration (FDA) aims to review internet-based devices and therapies, giving them an official government seal of approval to show they actually have a medically valid use.

Dr. Schork believes a mental health app called Stop, Breathe & Think is an example of one new digital technology worthy of FDA approval. In fact, he was the senior author of a scientific paper published in May in the Journal of Medical Internet Research (JMIR), which provides peer-reviewed research about cyber-medicine and electronic health.

“Our results suggested that the long-term use resulted in an improvement in mood,” said Dr. Schork, who examined data from more than 1 million users of the app. When the app is engaged, users record their mood at the beginning of each session. Then, they are given a menu of meditations to choose. They are asked to close their eyes and think about what is being described, such as a bubbling brook coursing through a forest. Then they record their mood at the end of the session.

“The app is one that can combat stress and promote mindfulness,” said Dr. Schork. “I’m not a meditator, but there’s a lot of data out there that suggests that practicing mindfulness and meditation could relieve stress.”

SEEING THE BIG PICTURE FOR EACH PATIENT

And stress can lead to a weakened immune system, which in turn can increase the possibilities of developing cancer, said Dr. Goetz.

“I really want to be on the front lines of bringing -omic technologies into the clinic to prevent cancer,” Dr. Goetz said. “We want to use new technologies; to find ways to quantify them so we can actually make a better assessment of someone’s health risks.”

These new apps are part of a growing body of digital therapeutics and health-data gathering devices that will play key roles in evaluating and improving patient health in the future. The challenge will be how to integrate these with other new and existing technologies into unique comprehensive care plans for each patient.

In early 2020, TGen’s parent organization in southern California, City of Hope, will open its first clinical location in Newport, California. “This site in Orange County will have a focus on integrated preventive care. Prevention is much broader than treating a particular disease,” explained Dr. Schork, who also is Director of TGen’s Quantitative Medicine and Systems Biology Division.

“We’d like the clinic to be focused on a healthy environment, wellness, and having it really well-grounded in science. It wouldn’t be a ‘New Age spa.’ It would be a bona fide medical clinic, designed in a way that is consistent with promoting health,” he said.

This clinical location will focus on each patient’s health risks, reducing risks, early detection of disease, and how to make healthcare more cost-effective and efficient, while at the same time making it more beneficial for the patient.

I really want to be on the front lines of bringing -omic technologies into the clinic to prevent cancer; to use new technologies; to find ways to quantify them so we can actually make a better assessment of someone’s health risks.”

— Dr. Laura Goetz
Pawsitively Good News
Treatment combating human breast cancer works for dogs with lung cancer, too!

Neratinib — a drug that has successfully been used to battle human breast cancer — might also work for many of the nearly 40,000 dogs in the U.S. that annually develop a type of canine lung cancer. The same gene — HER2 — that causes breast cancer in women also appears to cause canine pulmonary adenocarcinoma, or CPAC, according to a study of pet dogs led by TGen and The Ohio State University. CPAC is the most common lung cancer in dogs.

Neratinib inhibits a mutant cancer-causing form of the HER2, which is common to both CPAC and HER2-positive human breast cancer patients.

Published August 20 in the journal Clinical Cancer Research, this study could have significant implications for people who have never smoked. Like many humans who have never smoked, dogs still get lung cancer. "With colleagues at Ohio State, we found a novel HER2 mutation in nearly half of dogs with CPAC. We now have a candidate therapeutic opportunity for a large proportion of dogs with lung cancer," said Dr. Will Hendricks, an Assistant Professor in TGen’s Integrated Cancer Genomics Division, Director of Institutional Research Initiatives, and the study’s senior author.

Based on the results from this study, a clinical trial using neratinib is planned for dogs with naturally occurring lung cancer that have the HER2 mutation. "This is the first precision medicine clinical trial for dogs with lung cancer. That is, the selection of cancer therapy for a particular patient is based on the genomic profile of the patient’s tumor and matched with agents that are known to specially target the identified mutation," said Dr. Wendy Lorch, an Associate Professor in the Department of Veterinary Clinical Sciences at The Ohio State University College of Veterinary Medicine, who also will run the study’s clinical trial. "Our team at The Ohio State University has worked for years to find treatments for canine lung cancer. This breakthrough shows the value of these studies for dogs, as well as humans with lung cancer who never smoked," said Dr. Lorch, who also is the study’s lead author.

This clinical translation from dog to human and back is the holy grail of comparative cancer research. CPAC is an aggressive disease that clinically resembles human lung cancer among never-smokers. There is no standard-of-care treatment for CPAC and — prior to the work performed by the TGen-Ohio State team — little was known of the disease’s genetic underpinnings.

While the sequencing of hundreds of thousands of human cancer genomes has driven the transformational development of precise targeted cancer treatments for humans over the past decade, relatively few canine cancer genomes have undergone similar profiling. The canine cancer genomic discovery and drug development efforts of the TGen-Ohio State team are pieces of a larger puzzle that could similarly transform veterinary oncology, while creating bridges between canine and human cancer drug development.

"This study is groundbreaking because it not only identified a recurring mutation in a canine cancer that had never been found before, but it actually led directly to a clinical trial," said Dr. Jeff Trent, TGen President and Research Director, and one of the study’s contributing authors. "This clinical translation from dog to human and back is the holy grail of comparative cancer research."

Lung cancer is the leading cause of cancer death in the U.S., annually taking the lives of more than 154,000 Americans. "This study is really exciting to us because, not only have we found a recurrent hot-spot mutation in a canine cancer that had never been found before, but it actually has direct clinical translational relevance. For humans, we already have drugs that can inhibit many dysregulated proteins. We hope to show that we can provide the same benefit for dogs with canine cancers," Dr. Hendricks added.

No dogs were harmed in this study. Only pet dogs with naturally occurring cancer were examined. This study — Identification of recurrent activating HER2 mutations in primary canine pulmonary adenocarcinoma — lays the foundation for potential rapid translational development.

▼ MORE GOOD NEWS FOR BOTH ENDS OF THE LEASH
Study reveals genetic similarities of osteosarcoma between dogs and children

A bone cancer known as osteosarcoma is genetically similar in dogs and human children, according to the results of a study by TGen and Tufts University. The findings could help break the logjam in the treatment of this deadly disease, which hasn’t seen a significant medical breakthrough in nearly three decades.

"While osteosarcoma (OS) is rare in children, it is all too common in many dog breeds, which makes it a prime candidate for the kind of comparative cancer biology studies that could enhance drug development for both children and our canine friends," said Dr. Will Hendricks, an Assistant Professor in TGen’s Integrated Cancer Genomics Division, and one of the study’s senior authors.

Using multiple molecular- level testing platforms, TGen and Tufts researchers sequenced the genomes of 59 dogs, finding that canine OS shares many of the genomic features of human OS, including low mutation rates, structural complexity, altered cellular pathways, and unique genetic features of metastatic tumors that spread to other parts of the body. "Study results appeared July 19 in the Nature publication, Communications Biology. OS is an aggressive disease and the most commonly-diagnosed primary bone tumor in dogs and children. Though a relatively rare cancer in humans — with fewer than 1,000 cases each year — OS strikes a more than 25,000 dogs annually. Although surgery and chemotherapy can extend survival, about 30 percent of pediatric OS patients die from metastatic tumors within 5 years. The cancer moves much faster in dogs, with more than 90 percent succumbing to metastatic disease within 2 years.

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"No dogs were harmed in this study. Only pet dogs with naturally occurring cancer were examined. This study — Identification of recurrent activating HER2 mutations in primary canine pulmonary adenocarcinoma — lays the foundation for potential rapid translational development.

Will Hendricks, Ph.D. Assistant Professor, Integrated Cancer Genomics Division, Director, Institutional Research Initiatives
Molecular biology and a constantly evolving healthcare environment have led to multiple research breakthroughs and clinical advances in recent years. The convergence of new technologies with genomic investigations and medicine create opportunities beyond drug development for integrating clinical science with clinical care and improving the way we diagnose and treat disease.

Case in point: TARDIS, a new, highly sensitive blood test developed at TGen and City of Hope that could help thousands of patients avoid unnecessary lumpectomies and mastectomies.

TARDIS, short for Targeted Digital Sequencing, is a type of blood test known as a liquid biopsy that in the initial testing phase accurately verified that early stage breast cancer patients had responded well to pre-operative drug therapy. Results of the study led by TGen’s Dr. Muhammed Murtaza and published recently in Science Translational Medicine suggest that TARDIS is as much as 100 times more sensitive than other blood-based cancer-monitoring tests.

The TARDIS study was the first pilot project executed following TGen’s affiliation with City of Hope in late 2016.

HOW IT WORKS

TARDIS identifies and quantifies small fragments of cancer DNA — known as circulating tumor DNA, or ctDNA— coursing through a patient’s bloodstream in as little as two parts per 100,000 of patient blood.

Unlike many tests that focus on a single mutation, TARDIS integrates the results of dozens of mutations. This overcomes the issue of low levels of ctDNA available in non-metastatic cancer patients and in the residual disease setting, when there is no obvious tumor left during or after treatment.

“By precisely measuring ctDNA, this test can detect the presence of residual cancer, and inform physicians if cancer has been successfully eradicated,” said Dr. Murtaza, adding that TARDIS is precise enough to tell if early-stage breast cancer patients have responded well to pre-operative drug therapy.

WHY IT'S IMPORTANT

Today, nearly 30 percent of resected breast tissue shows no evidence of a tumor. Oncologists, however, don’t know if the pre-operative therapy is successful until after surgery and full examination of the removed tissue. Because TARDIS requires a simple blood draw — unlike traditional biopsies that extract tumor samples from the body and produce a point-in-place-and-time result—it’s possible to run multiple tests over a period of weeks, months, or years in a much less invasive manner.

“This test could help plan the timing and extent of surgical resection and radiation therapy after patients have received pre-operative therapy,” said Dr. Barbara A. Pockaj, a surgical oncologist at Mayo Clinic in Arizona, and the study’s other senior author.

When fully tested and verified, TARDIS appears sensitive enough to determine whether preoperative therapies have cleared the cancer from the patient, news that would allow treating physicians to let patients know surgery might be unnecessary.

Additional benefits might include avoiding the emotional aspects associated with surgery and recovery and early detection of recurrence.

“Reliably identifying often multiple circulating tumor mutations in the plasma of patients with non-metastatic breast cancer also holds promise that ctDNA may one day be a great tool for early breast cancer detection,” said Dr. Thomas Slavin, assistant clinical professor at City of Hope and a contributing author of the study.

GRANT FUNDS CLINICAL TRIAL

In October, TGen received a $2.1 million grant from the National Cancer Institute to refine TARDIS, including testing with a planned 180-patient clinical trial. If successful, this would mark another step toward making TARDIS widely available to patients. Also contributing to the initial TARDIS study were The Cancer Research UK Cambridge Institute at Cambridge University, and the Biodesign Institute at Arizona State University.
The combination of nab-paclitaxel and gemcitabine as a treatment regimen for pancreatic cancer gained FDA approval in 2013 following extensive testing that demonstrated the combination enabled longer survival for patients with advanced pancreatic cancer.

Following that success, continuing laboratory investigations showed that adding a third ingredient — platinum in the form of a drug called cisplatin — inhibited the ability of pancreatic cancer cells to repair their DNA, causing them to self-destruct. Adding this third drug — coined the TGen Triple — to the previously approved duo of nab-paclitaxel and gemcitabine targeted that molecular vulnerability, providing even more benefit to patients.

Published October 3 in the Journal of the American Medical Association (JAMA) Oncology, researchers found that among a clinical trial of 25 patients, the TGen Triple resulted in substantial tumor shrinkage for 71 percent of those patients, and dramatically increased survival beyond one year.

40 Percent of Patients Survive More Than Two Years

One year after entering the trial, 64 percent were still alive, far greater than the average one-year survival, which is only 26 percent for advanced pancreatic cancer patients. After two years, 40 percent were alive, a survival rate not previously seen for patients with stage IV pancreatic cancer, said Dr. Daniel Von Hoff, the study’s senior author.

“The results of this triple-drug regimen are very encouraging for these patients,” said Dr. Von Hoff.

Considering the rapid disease response, acceptable safety profile, and encouraging anti-tumor activity, further study of this triple-drug combination and additional tumor molecular analysis is needed to correlate these molecular findings with patient response to treatment.”

In the quest for even greater patient benefit, Dr. Von Hoff and his multi-institutional teams are now studying the TGen Triple in combination with super-enhancer modifying drugs such as entinostat, minnelide, high-dose pharmaceutical vitamin C, ketogenic diet and AXL inhibitors.

The results of this triple-drug regimen are very encouraging for these patients.

Substantial Improvement Seen in First Three Weeks

Because some patients showed substantial improvement in the first three weeks of the TGen Triple pilot clinical trial, this three-drug combination is being considered for early management of pancreatic cancer patients, and also as a pre-surgical treatment, according to the study.

Nearly two-thirds of patients in the TGen Triple clinical trial completed at least three 21-day, full-dose therapy cycles, said HonorHealth’s Gayle Jameson, N.P., the principal investigator in this clinical trial and one of the study’s co-lead authors. Toxicity levels were minimized by using a relatively low dose of cisplatin and providing patients with aggressive intravenous hydration.

“Many pancreatic tumors possess DNA repair deficiencies and are potentially vulnerable to new targeted therapies. We hypothesized that the addition of a platinum, in this case cisplatin, could improve treatment efficacy and patient outcomes,” said Dr. Erkut Borazanci, a clinical oncology investigator at HonorHealth Research Institute, and clinical associate professor at TGen. Dr. Borazanci also is a co-lead author of the paper.

This TGen Triple is being further studied at the HonorHealth Research Institute. The clinical trial is available to patients with untreated advanced pancreatic cancer. For more information, please go to HonorHealth.com/research or call 480-323-1339.

Contributing to the study — Response rate to albumin-bound paclitaxel plus gemcitabine plus cisplatin treatment among patients with advanced pancreatic cancer: A phase Ib/II pilot clinical trial — were: University of Arizona Comprehensive Cancer Center, Rutgers Cancer Institute, Vita Medical Associates, Mayo Clinic in Arizona, Imaging Endpoints Research and Core Lab and Cancer Research And Biostatistics, as the operations office and statistics and data management center for the Pancreatic Cancer Research Team.

The research was supported by a SU2C-CRIUK-Lustgarten Pancreatic Cancer Dream Team research grant (SU2C-AACR-DT20-16). Additional funding was provided by: Roger E. Magowitz and the Seena Magowitz Foundation, the TGen Foundation, the HonorHealth Foundation and Mattress Firm.
It's modern science with a nod to the past. By combining the very new with the very old, a team of TGen led researchers hopes to advance research into Amyotrophic Lateral Sclerosis (ALS) by adding an ancient twist to existing therapeutic strategies.

TGen's Dr. Winnie Liang is spearheading a clinical research study to determine if acupuncture adds value when treating newly diagnosed ALS patients. Acupuncture, a form of traditional Chinese medicine whose roots date back nearly 3,500 years, most often involves the insertion of needles into specific locations on the body to reduce chronic pain.

TGen — in partnership with Barrow Neurological Institute, and the Phoenix Institute of Herbal Medicine & Acupuncture — will evaluate the impact of therapeutic acupuncture for its effects on the immune system as it relates to improved patient outcome.

"The goal of this study is to determine if acupuncture treatments in newly diagnosed ALS patients are associated with changes in blood-based biomarkers of inflammation," said Dr. Liang, Associate Professor of TGen's Neurogenomics Division.

Biomarkers are measurable indicators associated with a particular state. Body temperature, for example, is a common biomarker for fever; elevated blood pressure is a biomarker for increased risk of stroke.

The effect of acupuncture on modulating immune responses — a critical component of successful therapeutic strategies — will be measured over time in the blood. If effective, this ancient therapy could be incorporated into future therapeutic strategies.

"As inflammatory biomarkers are easily accessible in blood, respond rapidly to changes in the body, and give insight into immune system responses, their assessment will provide key information about the biological impact of treatment," said Dr. Liang.

A number of studies have looked at acupuncture's benefits for various aches and pains, but this study will integrate the practice into a genomic study.

ALS, also known as Lou Gehrig's disease, is a progressive and deadly neuromuscular disorder characterized by degeneration of motor neurons in the brain and nervous system, resulting in progressively weak muscles, especially in the arms, legs and face.

ALS patients gradually lose voluntary movement and eventually are unable to breathe. It has no cure, and currently the only available treatments are designed to slow, but not to stop, the physical decline. ALS patients generally live 3-5 years following diagnosis.

Individuals diagnosed with ALS that meet study entrance criteria will be enrolled. Participants will undergo 8 weeks of acupuncture treatments and donate blood samples, which will be analyzed at the molecular level through targeted assays and next generation sequencing.

Study participants also will use a mobile phone app to evaluate subtle speech changes indicative of neurological health to better assess acupuncture's overall benefits.

For more information, please contact a TGen Clinical Research Coordinator at: ALS@tgen.org or 602-343-8653.
TGen Today - November 2019

The run-walk-dash is a community and family-friendly morning of races, music, games and activities, celebrating TGen’s 10th Anniversary, 12th Anniversary of the annual event is helping fund clinical trials and support the development of a quicker and more accurate way to detect and monitor breast cancer. SmartPractice’s donation supports work on a simple blood test, or liquid biopsy, that could provide early warning of cancer’s progression and continuous, non-invasive disease monitoring during treatment.

“We have donated to TGen for five years now because we believe TGen is making a unique contribution to advancing state-of-the-art treatments for breast cancer,” said Dr. Curt Hamann, CEO of SmartPractice.

Early detection of breast cancer — and identifying the exact type of breast cancer — is essential to effectively treat the disease and give patients the best chance of recovery. In addition, early detection may help limit unnecessary or ineffective therapies in some breast cancer patients.

“By supporting this remarkable research at TGen, we at SmartPractice believe we can help make a real difference in the lives of breast cancer patients,” said Michelle Shaw, Vice President of Human Resources at SmartPractice.

Investing in research for pancreatic cancer: pancake and pizza power the mission

Thanks to Rick Holland, this past spring 214 Wendy’s® restaurants in ten states across the West and Midwest sold Jr. Frosty® donation coupons for 835,000 of the mini ice cream treats, helping raise funds for colon cancer research at TGen. Jr. Frosty coupon sales, combined with the proceeds from the Bernice E. Holland Foundation’s annual golf tournament raised $270,000, bringing the foundation’s total giving to more than $1.5 million in support of TGen research and drug development efforts.

Individuals with a family history of Alzheimer’s disease may demonstrate changes in memory performance in their 20s, decades before the usual onset of memory loss due to this and other dementia-related diseases.

A recent TGen-led study looked at data from 59,571 participants aged 58-85, and the effect of family history was shown across every age group, up until age 65. Researchers collected the data through the online word-pair memory and reaction-time test called MindCrowd, one of the world’s largest scientific assessments of how healthy brains function.

Published in the scientific journal eLife, study data suggests that those younger than 65, who have a family history of Alzheimer’s disease, on average do not perform as well as their peers who do not have a family history of this disease.

The family history effect is particularly pronounced among men, as well as those with lower educational attainment, diabetes, and carriers of a common genetic change in APOE, a gene long associated with Alzheimer’s disease risk.

While family history has previously been associated with the risk of Alzheimer’s, this is the first study of its kind, and in these numbers, that indicates this risk can be detected up to four decades before the typical age of onset.

In this study we show that family history is associated with reduced pared-associate learning performance as many as four decades before the typical onset of Alzheimer’s disease,” said Dr. Matt Huentelman, TGen Professor of Neurogenomics, and the study’s senior author.

Because there is no cure or proven way of slowing progressive memory-loss among those with Alzheimer’s, early indicators of the disease can help those at risk to focus on ways to help stave off dementia.

“TGen needs citizen-scientists to join the 150,000 people from all 50 states and more than 150 nations who’ve already participated. Join them at: mindcrowd.org.

Upcoming Events Benefiting TGen

January 19-19
Barrett-Jackson Auction, Scottsdale
View thousands of the world’s most sought-after automobiles, including a 1965 Shelby Cobra and a 3/4-scale Shelby Cobra tribute go-kart going across the block to benefit TGen. www.barrett-jackson.com

February 23
Fitness for the Cure, 10th Anniversary, benefiting TGen cancer research at all Village Health Clubs & Spas, DC Ranch, Gainey Village, Camelback, and Ocotillo. www.villageclubs.com.

March 6 — Runway for Research, benefiting women’s cancer research at TGen. Neiman Marcus at Scottsdale Fashion Square, 6900 E. Camelback Road, Scottsdale.

April 11 — Casey’s Cup 3v3 Charity Hockey Tournament, benefiting TGen’s Adrenocortical Carcinoma (ACC) research program. The tournament is in memory of Casey Strale, a youth hockey player whose life was cut short by ACC. Great Park Ice & FivePoint Arena, 888 Ridge Valley, Irvine, Calif.

To learn more about these and other upcoming events, please call the TGen Foundation at 602-343-8411 or visit: www.tgen.org/events
Cardinals honor Sen. John McCain, support McCain Chair endowment

On October 31, the Arizona Cardinals honored the late Sen. John McCain throughout the Cards – 49ers matchup, and helped support the John S. McCain III Endowed Chair in Brain Cancer Research at TGen through their 50/50 raffle. Thanks to the entire Cardinal’s organization and dozens of TGen volunteers, the 50/50 raffle raised more than $44,500 in support of the endowment.

The holder of the chair will be an innovative investigator who, much like the senator, embodies a “maverick” spirit to drive unconventional, outside-the-box research.

“The support from the Cardinal’s, the Senator’s friends, family and community brings us a step closer to recruiting a world-class innovative clinical investigator who will create a research program committed to pursuing effective clinical applications that set new standards of research and patient care for brain cancer,” said TGen President and Research Director Dr. Jeffrey Trent.

Those interested in supporting the John S. McCain III Endowed Chair in Brain Cancer Research are encouraged to visit: www.tgen.org/mccainchair.

Pictured: Dr. Jeffrey Trent, TGen President and Research Director turns “The Big Red Siren,” an Arizona Cardinals game day tradition.