Blood Test Identifies More Treatable Cancer Mutations Than Biopsy

In one of the largest clinical studies to ever examine the impact of using a blood test to detect treatable mutations in non-small cell lung cancer (NSCLC), researchers from the Abramson Cancer Center of the University of Pennsylvania found that they could identify significantly more mutations through liquid biopsy instead of a solid tissue biopsy alone. The findings also show that patients whose actionable mutations were detected by the blood based liquid biopsy responded favorably to targeted therapies. Overall, the addition of liquid biopsy nearly doubled the number of mutations detected compared to what solid tissue testing alone would have found. Importantly, 86 percent of patients with targetable mutations identified via liquid biopsy achieved either a complete response, partial response, or stable disease. Researchers published their findings in JAMA Oncology last week.

"Most previous studies have analyzed the impact of liquid biopsy in the setting of a specific clinical trial or for a single therapeutic agent, but our goal here was to quantify the effect of using liquid biopsy in the real-world clinical setting," said the study’s senior author Erica L. Carpenter, MBA, PhD, a research assistant professor of Medicine and director of the Abramson Cancer Center’s Circulating Tumor Material Center. “To our knowledge, this is the largest study to date aiming to answer this simple, and as of yet, unanswered question as to whether non-invasive biopsies increase the number of potentially effective therapeutic options for our patients. Importantly, we found patients whose therapies were selected based on the liquid biopsy results generally achieved a positive clinical response.”

Therapies that target specific mutations have changed the face of cancer treatment, and screening for such mutations – which can be drivers of both disease growth and treatment resistance – is standard of care. This can often be done with a biopsy of tumor tissue, but sometimes that tissue is hard to obtain or doesn’t have sufficient DNA for analysis. Also, mutations may change over the course of treatment, meaning patients are sometimes subjected to multiple invasive biopsies. Instead, liquid biopsies use circulating tumor DNA (ctDNA) – shed by tumors and circulating in the blood – to test for mutations using next-generation sequencing. Since ctDNA can be obtained through a simple blood test in the physician’s office, this ultimately gives patients more therapeutic options and helps them avoid the discomfort and inconvenience of an invasive biopsy procedure.

Researchers wanted to know if the addition of liquid biopsy could improve detection of actionable mutations in genes such as EGFR, ALK, ROS1, and BRAF, among others – all of which are pertinent to managing the care of patients with NSCLC. Their study included 323 patients treated between April 2016 and January 2018, 35 percent (113) of whom were determined to have targetable mutations. Overall, among 229 patients who had both liquid and solid biopsy, and including patients for whom solid biopsy was not possible, the addition of liquid biopsy nearly doubled the number of mutations detected from 47 (20.5 percent) to 82 (36 percent).

Sixty-seven patients received a targeted therapy indicated by liquid biopsy alone or liquid and solid biopsy together. Of those, 42 were evaluated for their response, and 36 (86 percent) achieved either a complete response (1), partial response (19), or stable disease (16).

“These findings show that liquid biopsy is increasing the detection of mutations we can target and improving patient outcomes, and when you combine that with the reality that liquid biopsy is less invasive for patients and, in some cases, may be the only option for patients, the clinical impact is very clear,” said the study’s co-lead author Charu Aggarwal, MD, MPH, an assistant professor of Hematology-Oncology and member of the ACC’s Cancer Therapeutics Program.

The researchers note the findings do not indicate liquid biopsy should replace tissue biopsy.

“Solid tissue biopsy is still essential for accurate diagnosis, but we’ve now shown liquid biopsy can..."
Blood Test for NSCLC

(Continued from page 1)

add value when it’s used additionally, and also that it can serve as a viable alternative when solid biopsies aren’t feasible,” Carpenter said. “Given how rapidly targeted therapies are evolving, this is something that should be routinely incorporated into standard of care.”

The study was supported by the Penn Center for Precision Medicine’s Accelerator Fund Projects. The center is led by Director David B. Roth, MD, PhD, the Simon Flexner Professor of Pathology and Laboratory Medicine.

“This work represents the best of Penn’s collaborative and multidisciplinary approach, and it’s gratifying to see it make a real difference in the management of non-small cell lung cancer for patients,” Roth said.

Journal Article: Aggarwal C, Thompson JC, Black TA et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non–Small Cell Lung Cancer. JAMA Oncol. Published online 10/11/2018
Source: Penn Medicine Communications

Three ACC Researchers Receive NIH Director’s Awards

Seven University of Pennsylvania researchers, including three members of the Abramson Cancer Center, have been selected to receive highly competitive National Institutes of Health (NIH) Director’s Awards from the NIH Common Fund’s High-Risk, High-Reward Research Program. The Common Fund supports biomedical research that will be conducted over a five-year period and that requires trans-NIH collaboration to succeed, while the High-Risk, High-Reward Research program supports innovative research proposals that might not prove successful in the conventional peer-review process despite their potential to advance medicine.

The 2018 ACC recipients, among 97 awardees nationally, are:

New Innovator Award
Michael Mitchell, PhD, the Skirkanich Assistant Professor of Innovation in Penn’s School of Engineering and Applied Science’s Department of Bioengineering and member of the ACC’s Cancer Therapeutics Program, will receive $2.4 million to further his lab’s work employing tools and concepts from cellular engineering, biomaterials science, and drug delivery to understand and therapeutically target complex biological barriers in the body. His lab applies their research findings — and the drug delivery technologies developed — to a range of human health applications, including cancer metastasis, immunotherapy, and gene editing. Among his research interests, Mitchell designs drug delivery technologies to engineer cells in the bone marrow and blood vessels as a way of gaining control over how and why cancer disseminates throughout the body, as well as to engineer immune cells for immunotherapy and vaccination.

Transformative Research Award
Nicola J. Mason, BVetMed, PhD is an associate professor of Medicine and Pathobiology at Penn’s School of Veterinary Medicine, and holds Immunology and Cell and Molecular Biology graduate-group affiliations at the Perelman School of Medicine; she is also a member of the ACC’s Immunobiology Program. Dr. Mason will receive $727,277 for the first year of a five-year grant (shared with co-PI Aimee S. Payne, MD, PhD). Dr. Mason’s work focuses on the translation of basic scientific immunological principles that govern the generation of immune responses into therapeutically-relevant hypotheses and immunotherapies that can be tested for safety and efficacy in canine patients. Funding is commensurate to project needs. Mason’s work with Payne aims to expand the scope of translational immunotherapy beyond comparative immunoncology to encompass companion animals with spontaneous autoimmune and infectious disease.

Early Independence Award
Mark A. Selwyn, MD, PhD, an assistant professor of Radiology with a secondary appointment in Biochemistry and Biophysics, and a member of the ACC’s Radiobiology and Imaging Program, will receive $393,349 for the first year of a five-year grant for his work on developing small molecule tools and converting molecular-imaging technologies into clinical use in order to address problems in such areas as cancer biology, immunology, and infectious disease. Most recently, he developed new positron emission tomography (PET) probes to detect bacterial infections in patients.

Source: Penn Medicine Communications
New, Rare Mechanism for ALL Relapse after CAR T Cell

A single leukemia cell, unknowingly engineered with the leukemia-targeting chimeric antigen receptor (CAR) lentivirus and infused back into a patient, was able to reproduce and cause a deadly recurrence of pediatric B-cell acute lymphoblastic leukemia (ALL). New research from the Abramson Cancer Center of the University of Pennsylvania found that in one patient, the CAR lentivirus that would usually enter a T cell to teach it to hunt cancer also ended up binding with a leukemic cell. The presence of the CAR on the leukemic cell may have given that cell the ability to hide from the therapy by masking CD19, the protein that CARs target to kill cancer. Leukemic cells without CD19 are resistant to CAR T therapy, so this single cell led to the patient’s relapse. Nature Medicine published the findings earlier this month.

The treatment, developed by researchers in Penn’s Perelman School of Medicine and at Children’s Hospital of Philadelphia (CHOP), modifies patients’ own immune T cells, which are collected and reprogrammed to potentially seek and destroy the patients’ cancer cells. Once they are infused back into patients’ bodies, these newly built cells both multiply and attack, targeting cells that express CD19.

“In this case, we found that 100 percent of relapsed leukemic cells carried the CAR that we use to genetically modify T cells,” said the study’s lead author Marco Ruella, MD, an assistant professor of Hematology-Oncology at Penn. “This is the first time in hundreds of patients treated at Penn and other institutions that we’ve observed this mechanism of relapse, and it provides important evidence that steps in the delicate and complex process of engineering personalized cells can play a role in patient outcomes.”

The patient, a 20-year-old who received CAR-T cell therapy manufactured by Penn as part of a Penn-sponsored clinical trial which was completed in 2016, entered the trial with very advanced leukemia that had relapsed three times previously. After receiving the modified T cells, the patient had a complete remission for nine months before relapsing. In about 60 percent of ALL relapses, testing shows cancer cells that do not express CD19. CD19 was also not detectable at relapse in this patient. But in this case, analysis showed the leukemia cells were positive for the CAR protein.

This study comes on the heels of another case which showed essentially the opposite situation—a patient went into remission thanks to a single CAR T cell that reproduced and fought off chronic lymphocytic leukemia (CLL).

“We learn so much from each patient, in both success or failure of this new therapy, that helps us improve these still-developing treatments so they can benefit more patients,” said J. Joseph Melenhorst, PhD, an associate professor of Pathology and Laboratory Medicine and a member of Penn’s Center for Cellular Immunotherapies. Melenhorst was the senior author on this study as well as the research showing remission from a single cell. “This is a single case, but is still incredibly important and can help us refine the intricate processes required for manufacturing CAR-T cell therapy to ensure the best chance of long-term remissions.”

Further development of this type of T-cell therapy, including improvements to the manufacturing process to remove and limit the risk of B-cell presence, led to the approval of Kymriah (tisagenlecleucel, formerly CTL 019), the first therapy based on gene transfer approved by the U.S. Food and Drug Administration, in August 2017 for the treatment of relapsed or refractory pediatric and young adult patients with B-cell precursor ALL. It is also approved for treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) – the most common form of non-Hodgkin’s lymphoma – as well as high grade B-cell lymphoma and DLBCL arising from follicular lymphoma. Journal Article: Ruella M, et al. Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell. Nature Medicine 24, 499–1503 (2018)

Source: Penn Medicine Communications

2018-2019 Penn Medicine Employee Flu Campaign

The 2018-2019 Employee Flu Campaign is underway. Penn Medicine requires influenza immunization on an annual basis for all personnel. Immunizations are being offered at various Penn Medicine sites throughout October. Personnel may also be immunized elsewhere, as long as they provide appropriate documentation to Occupational Health.

Complete information, including the campaign calendar and links to personalized bar-coded consent forms, is available at the Penn Medicine Flu Campaign UPHS intranet page.
OncoLink Receives 2018 CPEN Excellence in Patient Education Award

The Cancer Patient Education Network (CPEN) honored the Patient Education Team from Penn Medicine’s OncoLink with the 2018 Excellence in Patient Education Award. The award recognizes individuals or programs that use creative approaches to develop and circulate cancer education to patients and health care professionals. The OncoLink team received the award last week Friday during the CPEN annual meeting in Atlanta.

Launched in 1994, OncoLink was the first cancer information website on the internet and remains one of the largest, with a mission to support patients, caregivers, and practitioners with up-to-date information on all aspects of cancer diagnosis, treatment, and recovery.

The award honors the OncoLink educational content team, which includes managing editor Carolyn Vachani, MSN, RN, oncology content specialist Karen Arnold-Korzeniowski, BSN, RN, and psychosocial oncology content editor Christina Bach, MBE, MSW, LCSW, OSW-C.

OncoLink’s information covers all types of cancer, treatment options, risk factors, prevention strategies, and survivorship concerns, with the intent to help patients and families make educated treatment decisions and become active participants in their care. Other features include a section to help newly diagnosed patients navigate their cancer experience.

OncoLink also provides tools and educational materials to support the practice of busy practitioners, including on treatment education, psychosocial support and survivorship care plans. These create a one-stop shop for patient education, enabling more impactful patient interactions, improving patient-provider communication and satisfaction.

Among its accomplishments, the team has produced a survivorship care-plan builder. The resulting care plans aim to ease common concerns expressed by cancer survivors. This tool has been used to create over 80,000 individualized care plans, which have received overwhelmingly positive feedback. The team continues to refine the tool based on the needs of cancer survivors and care providers. The team also regularly expands and updates OncoLink’s library of resources, including articles, videos, and blogs. Its work reaches millions of patients via the website as well as syndication and licensing partners.

Source: Penn Medicine Communications

Analysis Reveals Genomic Effects of a New Cancer Treatment

A twist on the molecular mechanism of how a new cancer drug works could aid in better identifying the best treatments for patients for an array of cancers. The finding is described in Molecular Cell in a study led by Eric J. Brown, PhD, an associate professor of Cancer Biology in the Perelman School of Medicine at the University of Pennsylvania and a member of the ACC’s Breast Cancer Program.

Using mouse and human cells, Brown’s team, including co-first authors Nishita Shastri and Yuchen Tsai, identified over 500 sites in DNA that require an enzyme called ATR checkpoint kinase to not break when they are replicated. These sites are characterized by stretches of repeating DNA building blocks, which impede the normal replication of DNA. The harmful impact of these “genomic potholes” are lessened when the ATR kinase goes to work as a virtual “shock absorber” to smooth over the bumpy parts of replication. Importantly, inhibitors of ATR cause DNA to break, which is key to the anti-cancer effects of this drug.

ATRs and PARP enzymes are part of the DNA Damage Response (DDR), which is used by cancer cells to survive high levels of replication stress and defects in DNA repair. Because cancers rely on the DDR for survival, stopping this process with ATR inhibitors is more toxic to cancer cells than normal cells. As such, DDR drugs such as ATR and PARP inhibitors may be more effective than standard therapies.

“Customized clinical use of DDR inhibitors is frequently based on changes in the level or function of specific proteins in cancer cells and this approach aims to improve treatment efficacy,” Brown said. “However, it is possible that the effects of ATR inhibitors may not be solely based on lethal interactions with defective gene expression in cancer cells, but also on the state of the repetitive DNA that relies on the ATR enzyme for stability.”

ATR inhibitors are in clinical trials for a variety of cancers, including lung, colon, pancreatic, lymphoma, leukemia and others. Penn recently opened a clinical trial, led by Fiona Simpkins, MD, an associate professor of Obstetrics and Gynecology and member of the ACC’s Cancer Therapeutics Program, to investigate the benefit.

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Seminars and So Forth

Monday 10/15/18  12:00 pm
Path & Lab Grand Rounds Seminar Series
“Discovering RNA biology with informatics.” Manolis Maragkakis, PhD, Research Associate, Pathology and Laboratory Medicine, PSOM
CRB Austrian Auditorium

Tuesday 10/16/18  12:00 pm
Distinguished Lecture in Cancer Research
“Squamous Epithelial Cell Biology and Oncogenesis.” Anil Rustgi, MD, T. Grier Miller Professor of Medicine (Gastroenterology), PSOM
Wistar Institute, Caplan Auditorium

Tuesday 10/16/18  4:00 pm
Immunology Colloquium
Harvey Cantor, MD, Dana-Farber Cancer Institute, Baruj Benacerraf Professor, Division of Immunology, Microbiology and Immunobiology, Harvard Medical School
CRB Austrian Auditorium

Wednesday 10/17/18  12:00 pm
CRRWH Seminar
“A surprising role of long non-coding RNA in breast cancer metastasis: Important lessons from studying IncRNA functions in vivo.” Li Ma, PhD, Associate Professor of Experimental Radiation Oncology, MD Anderson Cancer Center
252 BRB Seminar Room

Wednesday 10/17/18  12:00 pm
CT3N Seminar Series
“Synthetic Virology: Reprogramming Viruses into Controllable Nanodevices.” Junghae Suh, PhD, Associate Professor of Bioengineering and BioSciences, Rice University
SCTR 10-146AB

Wednesday 10/17/18  3:00 pm
Cancer Biology Recruitment Seminar
“Regenerative Origin of Metastasis Stem Cells.” Karuna Ganesh, MD, PhD, Memorial Sloan Kettering Cancer Center
CRB Austrian Auditorium

Thursday 10/18/18  12:00 pm
RadOnc Invited Speaker Seminar Series
Arta M. Monjazeb, MD, PhD, Associate Professor, Radiation Oncology; CCGS Staff Investigator for Cancer Immunotherapy, UC Davis
SCTR 8-146AB

Friday 10/19/18  9:30 am
CRRWH/OCRC Special Seminar
“Exosome-mediated tumor innervation leads to clinically more aggressive tumors.” Paola D. Vermeer, PhD, Assistant Professor of Surgery, University of South Dakota
1301 BRB II/III

Friday 10/19/18  12:00 pm
IFI-ACC Research in Progress Seminar
Yi Fan, MD, PhD, Assistant Professor of Radiation Oncology, PSOM
BRB II/III Gaulton Auditorium

Monday 10/22/18  12:00 pm
Path & Lab Grand Rounds Seminar Series
“From genomics to therapeutics: dissection and manipulation of human disease circuitry at single-cell resolution” Manolis Kellis, PhD, Professor, Computer Science, MIT
CRB Austrian Auditorium

Tuesday 10/23/18  12:00 pm
Distinguished Lecture in Cancer Research
“Gene-environment interactions in breast and prostate cancer risk.” Kara Maxwell, MD, PhD, Assistant Professor of Medicine (Hem-Onco) and Genetics, PSOM
BRB II/III Gaulton Auditorium

Tuesday 10/23/18  12:00 pm
CHOP GGPD Research Affinity Group Seminar
“Epigenetic Mechanisms in Tissue-Specific Gene Regulation and in Rare Inherited Tumors.” Rebecca Oakey, PhD, Professor of Epigenetics, Medical & Molecular Genetics, Dean for Doctoral Studies, King’s College London
Abramson Research Center 123C (CHOP)

Tuesday 10/23/18  4:00 pm
Immunology Colloquium
“Mechanistic Insights into the Immunoediting and Immunotherapy of Cancer” Robert Schreiber, PhD, AM Bursky & JM Bursky Distinguished Professor, Pathology & Immunology, Washington University School of Medicine
CRB Austrian Auditorium

Thursday 10/25/18  12:00 pm
Gastroenterology Seminar Series
“Control of the embryonic stem cell state by metabolism.” Xiaolu Yang, PhD, Professor of Cancer Biology, PSOM
901 BRB II/III

Friday 10/26/18  12:00 pm
IFI-ACC Research in Progress Seminar
Sara Cherry, PhD, Professor of Microbiology, PSOM
John Morgan Building, Reunion Auditorium
Funding Opportunities

PAR-18-947 Integrating Biospecimen Science Approaches into Clinical Assay Development (NCI U01)
LOI Due Date: 30 days before application due date
Application Due Date: November 28, 2018; March 14, 2019
This FOA will support extramural research to investigate and mitigate challenges facing clinical assay development and subsequent analytical validation due to preanalytical variability in tumor tissue biopsies and blood biospecimens utilized as “liquid biopsies.” Extramural research funded under this FOA may include investigations of preanalytical variability associated with the procurement and study of small biopsies (core biopsies, small excision samples), pleural aspirates, and blood utilized for liquid biopsies. Investigator-designed experiments will explore how different biospecimen preanalytical conditions affect emerging and clinically relevant biomarkers quantified by a variety of testing platforms. The results from this research program will improve the understanding of how analytical quantification of clinically relevant biomarkers is affected by variation in biospecimen collection, processing, and storage procedures. The overall goal is to expedite biomarker clinical assay development through evidence-based standardization of biospecimen handling practices.

LOI Due Date: 30 days before application due date
Application Due Date: March 4, 2019
This initiative will support multidisciplinary research to understand the underlying causal factors and mechanisms that result in lung cancer disparities in U.S. health disparity populations.

Analysis Reveals Genomic Effects of a New Cancer Treatment

(Continued from page 4)
of combining ATR inhibitors with PARP inhibitors for the treatment of recurrent ovarian cancer. “ATR inhibitors may help PARP inhibitors work more effectively during different clinical situations, including overcoming PARP inhibitor resistance,” Simpkins said.

“While it is too early to tell exactly how detecting specific DNA sequences that break due to ATR inhibition will be applied in the clininc, the idea that the genome itself, not just the proteins expressed from it, might influence responses to treatment is a novel concept worthy of exploration,” Brown said.

The Penn team plans to monitor these sites of repetitive DNA as part of the ATR inhibitor combination clinical trial, which seeks to identify biomarkers that will maximize treatment efficacy.