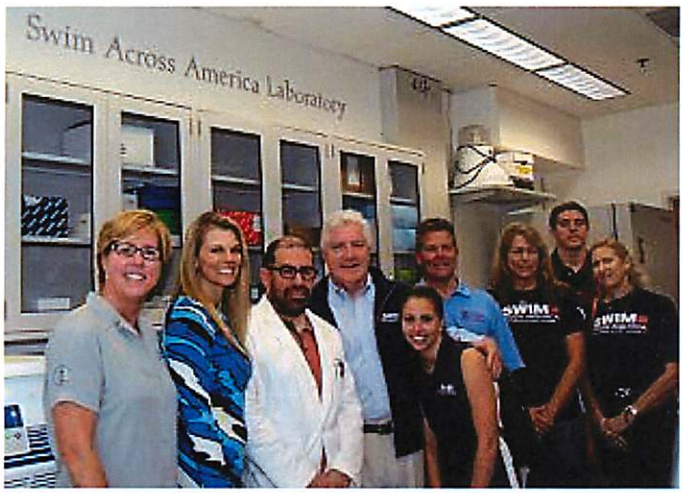
JOHNS HOPKINS MEDICINE

The Swim Across America Baltimore Lab

What Swim Across America Baltimore Supports at Johns Hopkins



Swim Across America Laboratory, Johns Hopkins Kimmel Cancer Center

Swim Across America Research Laboratory

Among the promising new discoveries we're working on in the Swim Across America laboratory is a personalized test that can tell, with 100 percent sensitivity and specificity, if a person is cured with surgery or if there are cancer cells left behind that will require additional treatment. It also will monitor the progression of each person's cancer and the response to treatment, alerting clinicians to a recurrence of disease. Continued support from Swim Across America allows us to be on the forefront of applying innovative personalized cancer medicine to benefit

Since its inception at Hopkins, the laboratory has been part of two major publications in Science and Clinical Cancer Research: The discovery of key mutations in a rare pancreatic tumor, and investigations studying the tumor margins of colorectal cancer metastases. A major study of circulating tumor DNA now underway should affect how we monitor and detect more than a dozen tumor types. In addition, this will have implications for using circulating tumor DNA as a personalized biomarker for early detection and determining if a patient is cured after surgery. A clinical trial using tumor necrosis factor (TNF) and nanoparticles, is in development. Continued support from Swim Across America allows us to be on the forefront of applying innovative personalized cancer medicine to benefit patients and their families.

Watch a video tour of the Swim Across America laboratory.

Listen to Dr. Diaz discuss the importance of Swim Across America's funds.

Swimathon to Be Held to Support The Swim Across America Laboratory

Get Involved: Donate, Swim or Volunteer

Find out how you can help support this year's Swim Across America Baltimore event. Swim, volunteer, donate or give to help raise funds to support the Swim Across America Laboratory at Johns Hopkins. You can make a difference.

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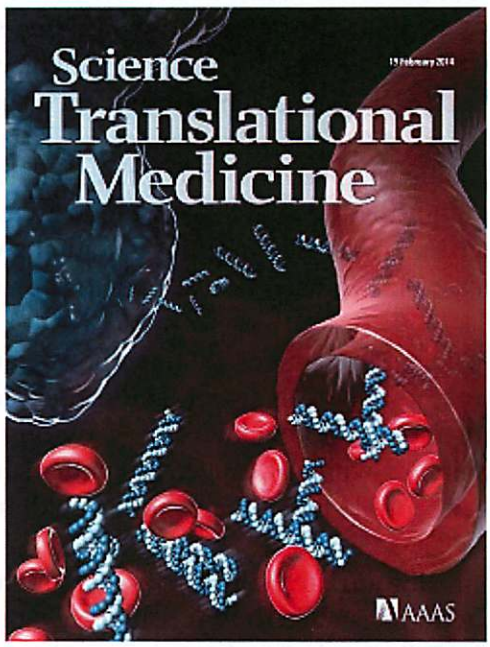
DNA Shed By Tumors Shows Promise for Non-Invasive Screening and Prognosis

Release Date: 02/20/2014

Certain fragments of DNA shed by tumors into the bloodstream can potentially be used to non-invasively screen for early-stage cancers, monitor responses to treatment and help explain why some cancers are resistant to therapies, according to results of an international study led by Johns Hopkins Kimmel Cancer Center investigators.



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Analyzing blood samples from 640 patients with various cancers, the researchers used digital polymerase chain reaction-based technology (a sophisticated method of multiplying and measuring the number DNA molecules) to evaluate how well the DNA fragments predicted the presence of tumors in the patients.

The fragments, known as cell-free circulating tumor DNA (ctDNA), were detected in the blood of more than 75 percent of patients with advanced cancers and in at least half of patients with localized, smaller tumors that had not spread outside of the organ where the cancer originated and still had the potential for cure.

Investigators say the work, published Feb. 19 in the journal Science Translational Medicine, provides strong evidence that ctDNA could be used as a "personalized biomarker" test and cancer screening tool.

"We're already very good at treating and curing cancer when it is localized," says lead study author Chetan Bettegowda, M.D., Ph.D., an assistant professor of oncology and neurological surgery. "But we wanted to develop a non-invasive technology to enhance detection of cancer at an early stage, and we feel this is an exciting starting point for further work using this method."

"The most promising aspect is that ctDNA can identify early-stage cancers," adds one of the study's senior authors, Luis Diaz, M.D., associate professor of oncology and director of the Swim Across America Laboratory at Johns Hopkins.

Among study participants with metastatic cancers, researchers detected ctDNA in 82 percent of patients with solid tumors outside the brain (112 of 136 patients), including more than 75 percent of patients with advanced ovarian, colorectal, bladder, gastroesophageal, pancreatic, breast, hepatocellular, and head and neck cancers, as well as melanomas. Fewer than 50 percent of patients with medulloblastomas or metastatic cancers of the kidney, prostate or thyroid, and less than 10 percent of patients with gliomas, had detectable ctDNA.

Among 223 patients with localized tumors, researchers detected ctDNA in 55 percent of all patient samples, and in 73 percent of those with colorectal cancer, 57 percent of those with gastroesophageal cancer, 48 percent of those with pancreatic cancer and 50 percent of those with breast adenocarcinoma. Increasing levels of ctDNA correlated with the stage of cancer: 47 percent of patients with Stage I cancers of any type had detectable ctDNA, as did 55 percent of patients with Stage II cancers, 69 percent of patients with Stage III cancers, and 82 percent of patients with Stage IV cancers.

Comparing ctDNA with circulating tumor cells (CTCs), intact cells shed from a primary tumor that circulate in the bloodstream and may lead to metastasis, researchers found that ctDNA was often present in patients without detectable CTCs. They did not identify any cases in which CTCs were detected and ctDNA was absent.

The researchers also studied how accurately the test identified mutations in patients' tumors. They analyzed tumors and blood samples in a separate group of 206 patients with metastatic colorectal cancers, finding that ctDNA correctly identified 87 percent of patients with KRAS gene mutations, meaning that these patients' tumors may be susceptible to a therapy called epidermal growth factor receptor (EGFR) blockade.

In addition, investigators assessed whether ctDNA could provide clues to how cancers build resistance to EGFR blockade therapy in 24 patients who responded to therapy initially but later relapsed. They found that 23 (96 percent) of patients developed one or more mutations in genes involved in a signaling pathway called MAPK, which regulates gene expression and cell survival, among other tasks, and may help cancer cells thrive.

The study "provides a wealth of information on the potential utility and limitations of ctDNA measurements to assess patients with various cancers," the study authors wrote.

Scientists involved in the study were from the Ludwig Center at Johns Hopkins and Boston University; the Institute for Cancer Research at Candiolo, the University of Torino, Italy; Life Technologies, Foster City, Calif.; Indiana University; the Ludwig Institute for Cancer Research at Royal Melbourne Hospital, Australia; the Children's Hospital of Philadelphia; Indivumed GmbH, Hamburg, Germany; the University of Sao Paulo, Brazil; Amgen Inc., Thousand Oaks, Calif.; Lund University Hospital, Sweden; the University of Colorado Comprehensive Cancer Center; Memorial Sloan-Kettering Cancer Center, New York; and the University of Texas Southwestern Medical Center.

The work was supported by The Lustgarten Foundation for Pancreatic Cancer Research; the Hilton Foundation; the Commonwealth Fund; Swim Across America; a Burroughs Wellcome Career Award for Medical Scientists; the Johns Hopkins Clinician Scientist Career Development Award; a Brain Science Institute Translational Research Grant; a Pediatric Brain Tumor Foundation Award; the Virginia and D.K. Ludwig Fund for Cancer Research; the National Institutes of Health; the European Community's Seventh Framework Programme; the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; the American Association for Cancer Research Stand Up to Cancer - Dream Team Translational Cancer Research Grant; the Ballanger Trust; a Clinical Innovator Award from the Flight Attendant Medical Research Institute Fund; the Victorian Cancer Agency; the Sao Paulo Research Foundation; the Michael Rolfe Foundation; Dennis Troper and Susan Wojcicki; the Sol Goldman Pancreatic Cancer Research Center; and AIRC IG grants.

Diaz and coauthors Kenneth W. Kinzler, Victor Velculescu, Bert Vogelstein and Nickolas Papadopoulos are co-founders of Personal Genome Diagnostics. They own stocks in Personal Genome Diagnostics and are members of their Scientific Advisory Board. Kinzler and Vogelstein are consultants to Inostics. Personal Genome Diagnostics and Inostics have licensed several patent applications from Johns Hopkins. These relationships are subject to certain restrictions under The Johns Hopkins University policy, and the terms of these arrangements are managed by the university in accordance with its conflict-of-interest policies.

Science Translational Medicine: DOI: 10.1126/scitranslmed.3007094

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Johns Hopkins Scientists Use Pap Test Fluid To Detect Ovarian, Endometrial Cancers

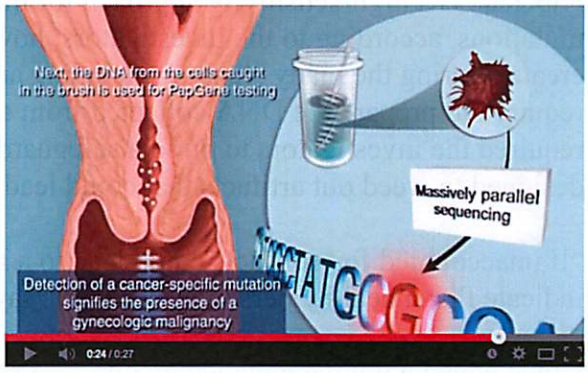
Release Date: 01/09/2013

Using cervical fluid obtained during routine Pap tests, scientists at the Johns Hopkins Kimmel Cancer Center have developed a test to detect ovarian and endometrial cancers. In a pilot study, the "PapGene" test, which relies on genomic sequencing of cancer-specific mutations, accurately detected all 24 (100 percent) endometrial cancers and nine of 22 (41 percent) ovarian cancers. Results of the experiments are published in the Jan. 9 issue of the journal *Science Translational Medicine.*

The investigators note that larger-scale studies are needed before clinical implementation can begin, but they believe the test has the potential to pioneer genomic-based cancer screening tests.

The Papanicolaou (Pap) test, during which cells collected from the cervix are examined for microscopic signs of cancer, is widely and successfully used to screen for cervical cancers. However, no routine screening method is available for ovarian or endometrial cancers.

Since the Pap test occasionally contains cells shed from the ovaries or endometrium, cancer cells arising from these organs could be present in the fluid as well, says Luis Diaz, M.D., associate professor of oncology at Johns Hopkins, as well as director of translational medicine at the Ludwig Center for Cancer Genetics and Therapeutics and director of the Swim Across America Laboratory, also at Johns Hopkins. The laboratory is sponsored by a volunteer organization that raises funds for cancer research through swim events. "Our genomic sequencing approach may offer the potential to detect these cancer cells in a scalable and cost-effective way," adds Diaz.



Hear Diaz discuss the research in this podcast, courtesy of the American Association for the Advancement of Science, and watch an animation describing the PapGene test.

Cervical fluid of patients with gynecologic cancer carries normal cellular DNA mixed together with DNA from cancer cells, according to the investigators. The investigators' task was to use genomic sequencing to distinguish cancerous from normal DNA.

The scientists had to determine the most common genetic changes in ovarian and endometrial cancers in order to prioritize which genomic regions to include in their test. They searched publicly available genome-wide studies of ovarian cancer, including those done by other Johns Hopkins investigators, to find mutations specific to ovarian cancer. Such genome-wide studies were not available for the most common type of endometrial cancer, so they conducted genome-wide sequencing studies on 22 of these endometrial cancers.

From the ovarian and endometrial cancer genome data, the Johns Hopkins-led team identified 12 of the most frequently mutated genes in both cancers and developed the PapGene test with this insight in mind.

The investigators then applied PapGene on Pap test samples from ovarian and endometrial cancer patients at The Johns Hopkins Hospital, Memorial Sloan-Kettering Cancer Center, the University of São Paulo in Brazil and ILSbio, a tissue bank. The new test detected both early- and late-stage disease in the endometrial and ovarian cancers tested. No healthy women in the control group were misclassified as having cancer.

The investigators' next steps include applying PapGene on more samples and working to increase the test's sensitivity in detecting ovarian cancer. "Performing the test at different times during the menstrual cycle, inserting the cervical brush deeper into the cervical canal, and assessing more regions of the genome may boost the sensitivity," says Chetan Bettegowda, M.D., Ph.D., assistant professor of neurosurgery at Johns Hopkins and a member of the Ludwig Center as well.

Together, ovarian and endometrial cancers are diagnosed in nearly 70,000 women in the United States each year, and about one-third of them will die from it. "Genomic-based tests could help detect ovarian and endometrial cancers early enough to cure more of them," says graduate student Yuxuan Wang, who notes that the cost of the test could be similar to current cervical fluid HPV testing, which is less than $100.

PapGene is a high-sensitivity approach for the detection of cancer-specific DNA mutations, according to the investigators; however, false mutations can be erroneously created during the many steps — including amplification, sequencing and analysis — required to prepare the DNA collected from a Pap test specimen for sequencing. This required the investigators to build a safeguard into PapGene's sequencing method, designed to weed out artifacts that could lead to misleading test results.

"If unaccounted for, artifacts could lead to a false positive test result and incorrectly indicate that a healthy person has cancer," says graduate student Isaac Kinde.

Kinde added a unique genetic barcode — a random set of 14 DNA base pairs — to each DNA fragment at an initial stage of the sample preparation process. Although each DNA fragment is copied many times before eventually being sequenced, all of the newly copied DNA can be traced back to one original DNA molecule through their genetic barcodes. If the copies originating from the same DNA molecule do not all contain the

same mutation, then an artifact is suspected and the mutation is disregarded. However, bonafide mutations, which exist in the sample before the initial barcoding step, will be present in all of the copies originating from the original DNA molecule.

Funding for the research was provided by Swim Across America, the Commonwealth Fund, the Hilton-Ludwig Cancer Prevention Initiative, the Virginia & D.K. Ludwig Fund for Cancer Research, the Experimental Therapeutics Center of the Memorial Sloan-Kettering Cancer Center, the Chia Family Foundation, The Honorable Tina Brozman Foundation, the United Negro College Fund/Merck Graduate Science Research Dissertation Fellowship, the Burroughs Wellcome Career Award for Medical Scientists, the National Colorectal Cancer Research Alliance and the National Institutes of Health's National Cancer Institute (N01-CN-43309, CA129825, CA43460).

In addition to Kinde, Bettegowda, Wang and Diaz, investigators participating in the research include Jian Wu, Nishant Agrawal, Ie-Ming Shih, Robert Kurman, Robert Giuntoli, Richard Roden and James R. Eshleman from Johns Hopkins; Nickolas Papadopoulos, Kenneth Kinzler and Bert Vogelstein from the Ludwig Center at Johns Hopkins; Fanny Dao and Douglas A. Levine from Memorial Sloan-Kettering Cancer Center; and Jesus Paula Carvalho and Suely Kazue Nagahashi Marie from the University of São Paulo.

Papadopoulos, Kinzler, Vogelstein and Diaz are co-founders of Inostics and Personal Genome Diagnostics. They own stocks in the companies and are members of their Scientific Advisory Boards. Inostics and Personal Genome Diagnostics have licensed several patent applications from Johns Hopkins. These relationships are subject to certain restrictions under The Johns Hopkins University policy, and the terms of these arrangements are managed by the university in accordance with its conflict-of-interest policies.

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