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Further to @pathologistmag *http://ow.ly/O0xC4* Digital First report *http://bit.ly/1cV3eJ6* … for role of pathology
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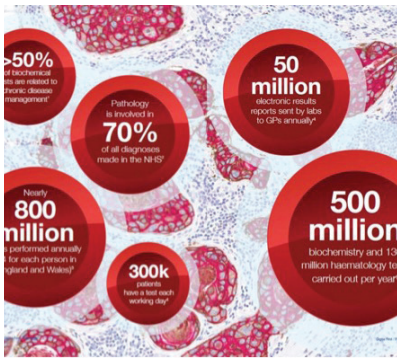


**The Pathologist** @pathologistmag
Defining #amyloid #pathology in persons with and without #dementia syndromes - making the right diagnosis
*http://bit.ly/1IcvRmt*
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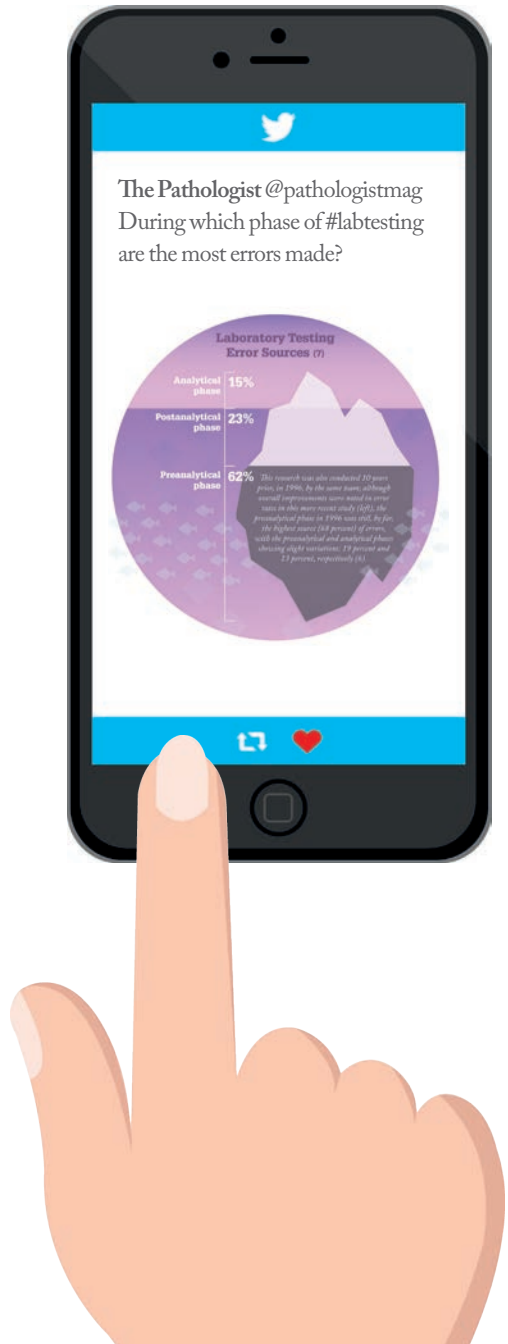


**Graph Lib** @graphlib
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9:15 PM - 8 Jun 2015

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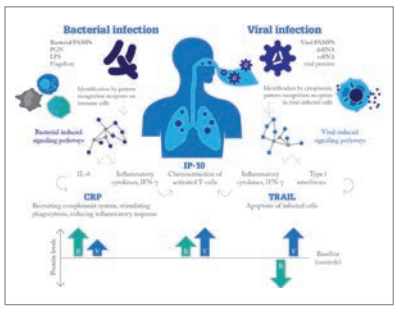


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Preanalytical accuracy in surgical pathology targeted by new recommendations @Pathologists *http://ow.ly/O0yxA*
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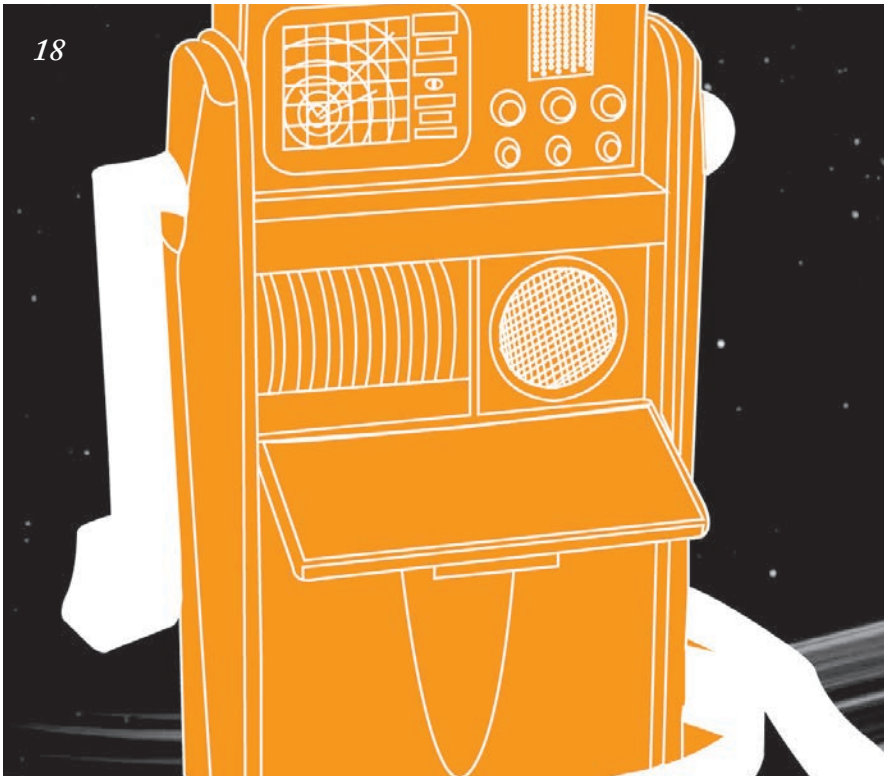


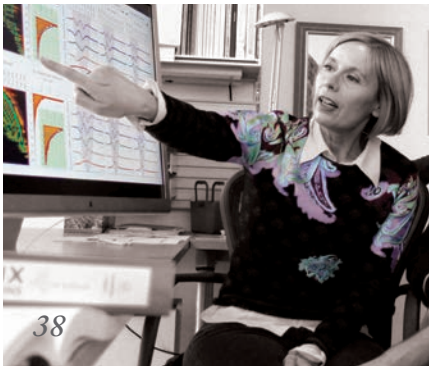





## On The Cover

*Conceptualized by Star Trek, the first-ever medical tricorder may no longer be the stuff of science fiction.*

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## In Practice



## NextGen



## Profession



## Sitting Down With



the Pathologist

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*Editor* - Fedra Pavlou
fedra.pavlou@texerepublishing.com

*Associate Editor* - Roisin McGuigan
roisin.mcguigan@texerepublishing.com

*Associate Editor* - Michael Schubert
michael.schubert@texerepublishing.com

*Senior Designer* - Marc Bird
marc.bird@texerepublishing.com

*Junior Designer* - Emily Strefford-Johnson
emily.johnson@texerepublishing.com

*Chief Executive Officer* - Andy Davies
andy.davies@texerepublishing.com

*Chief Operating Officer* - Tracey Peers
tracey.peers@texerepublishing.com

*Publisher* - Mark Goodrich
mark.goodrich@texerepublishing.com

*Audience Insight Manager* - Tracey Nicholls
tracey.nicholls@texerepublishing.com

*Traffic and Audience Associate* - Lindsey Vickers
lindsey.vickers@texerepublishing.com

*Traffic and Audience Associate* - Jody Fryett
jody.fryett@texerepublishing.com

*Digital Content Manager* - David Roberts
david.roberts@texerepublishing.com

*Mac Operator Web/Print* - Peter Bartley
peter.bartley@texerepublishing.com

*Tablet Producer* - Abygail Bradley
abygail.bradley@texerepublishing.com

*Apprentice, Social Media / Analytics* - Stephen Mayers
stephen.mayers@texerepublishing.com

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**General enquiries:**
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info@texerepublishing.com
+44 (0) 1565 752883
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# Autopsy on the Slab?

*Despite the intrinsic value of the ancient autopsy, it's already extinct in some hospitals. Can it be saved?*



Given my Greek heritage, I decided to trace the historic derivation of the word autopsy; it comes from the Greek words 'autos' (self) and 'opsis' (see). Though Rokitansky (1804–1878) is known as the father of the modern autopsy, crude versions of the practice date back to 3000 BC when people were quite skillfully performing human dissection (and mummification).

Fast forward five millennia or so, and the autopsy still holds a great deal of value. It remains the only definitive way to confirm cause of death and sometimes diagnose disease – and it provides an abundance of knowledge to trainee pathologists as well as a window into hereditary conditions for family members. Nevertheless, the rate of hospital autopsy is in a dire state of decline. Why? A well-cited catalyst is the fact that in 1971 the US Joint Commission on Accreditation of Healthcare (JCAHO) agreed to eliminate minimum autopsy requirements from the regulations for hospital accreditation (1, 2).

The continuous decline ever since has raised alarm bells within the pathology community: "For better or worse, the practice is on the verge of extinction," warned authors of a recent report from the UK (3), which found that autopsies were only performed in just over 0.5 percent of all UK hospital deaths. In fact, the procedure has been completely eradicated in nearly one in four UK National Healthcare Service trusts. The authors urge that immediate action be taken before autopsies completely disappear. In fairness, the impact of their absence is not yet fully known, but Europe doesn't appear keen to tempt fate. In March 2015, the European Critical Care Foundation announced its plan to raise the issue of autopsy decline with European institutions, and to work with partners and key stakeholders to "reverse this trend for the ultimate benefit of patients and healthcare systems." (4)

So, can the autopsy be saved from the slab before it's too late? Would a change of its macabre reputation among the public help? I guess we'll have to autos opsis. But it does bring to light the importance of raising the profile of pathology as a whole. Role models like RCPath's Suzy Lishman (@ilovepathology) are campaigning hard to educate the public on the value of pathology – and that's very welcome, but more voices are needed. If the public and politicians are unaware of the criticality of pathology in current patient care – and the future of personalized medicine – how can it receive the financial support it so desperately needs?

**Fedra Pavlou**
*Editor*


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2. *S. J. McPhee, "Maximizing the Benefits of Autopsy for Clinicians and Families: What Needs to be Done", Arch Pathol Lab Med, 120, 743–748 (1996).*
3. *A. Turnbull et al., "Hospital Autopsy: Endangered or Extinct?", J. Clin. Pathol., [epub ahead of print] (2015).*
4. *Human Tissue Authority, "European Critical Care Foundation," Accessed June 15, 2015. http://bit.ly/1G7d9c5.*

## Bert Gold

Bert ran a clinical molecular genetics laboratory at SmithKline Beecham Clinical Laboratories in California, USA, before joining the US National Institutes of Health National Cancer Institute in 2000. A nationally recognized authority in molecular diagnostic implementation, he is active in the Next Generation Sequencing and Circulating Tumor Cell Guideline committee of the Association for Molecular Pathology. A Fellow of the American College of Medical Genetics, he speaks nationally on the importance of genetics in medicine.

Read our interview with Bert regarding the importance of liquid biopsy in cancer diagnosis, and the barriers to its adoption, on page 12.

## Rasmus Bro

Working in chemometrics at the University of Copenhagen, Denmark, Rasmus uses complex measurement systems to analyze substances as diverse as blood samples and soil. His multidisciplinary work involves food and environmental analysis, pharmaceuticals, clinical chemistry, and more. Recognition for his research includes the 10th Herman Wold Gold Medal honoring "a person who has contributed significantly to the development and proliferation of chemometrics in research, development and production" as well as a prize from The Prince of Denmark's Foundation for "individuals who have increased the prestige of Denmark in research".

On page 10, Ramus describes a new blood test based on food science principles that could help to detect breast cancer earlier than ever.

## Dina Tiniakos

Dina is a clinical senior lecturer and honorary consultant histopathologist at the Institute of Cellular Medicine, Newcastle University, UK, and an associate professor of histology-embryology at the University of Athens, Greece. A member of the Council of the European Society of Pathology, she is also an invited member of two international groups specializing in hepatopathology – the International Liver Study Group "Gnomes" and the Laennec Liver Pathology Society. A passionate lover of art, she co-organizes "Art Paths" annual art exhibitions by pathologists.

We showcase some of Dina's own pathology artwork on page 49.

## Anthony Letai

An associate professor at the Dana-Farber Cancer Institute, Boston, USA, Anthony's laboratory invented a technique called "BH3 profiling" which can be used to identify the type of cancer cell block used to escape programmed cell death – and more recently, to predict patient response to conventional chemotherapy. "It was clear to me that despite a general impression that genetic testing can direct treatment with targeted agents, it does not do this effectively for most patients, and another strategy was needed."

Anthony discusses the development of Dynamic BH3 profiling on page 14.

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# Upfront

*Reporting on research, innovations, policies and personalities that are shaping pathology today.*

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## From Kitchen to Clinic

**A new blood test based on food science principles may hold the key to predicting breast cancer earlier than ever**

Breast cancer awareness is everywhere. And rightly so – it's the most common cancer in women around the world. Early detection is the key to successfully treating many cancers, and breast cancer is no exception to the rule; spotting a tumor before it has infiltrated or metastasized often results in less invasive treatment, fewer side effects, and better chances of eliminating the disease.

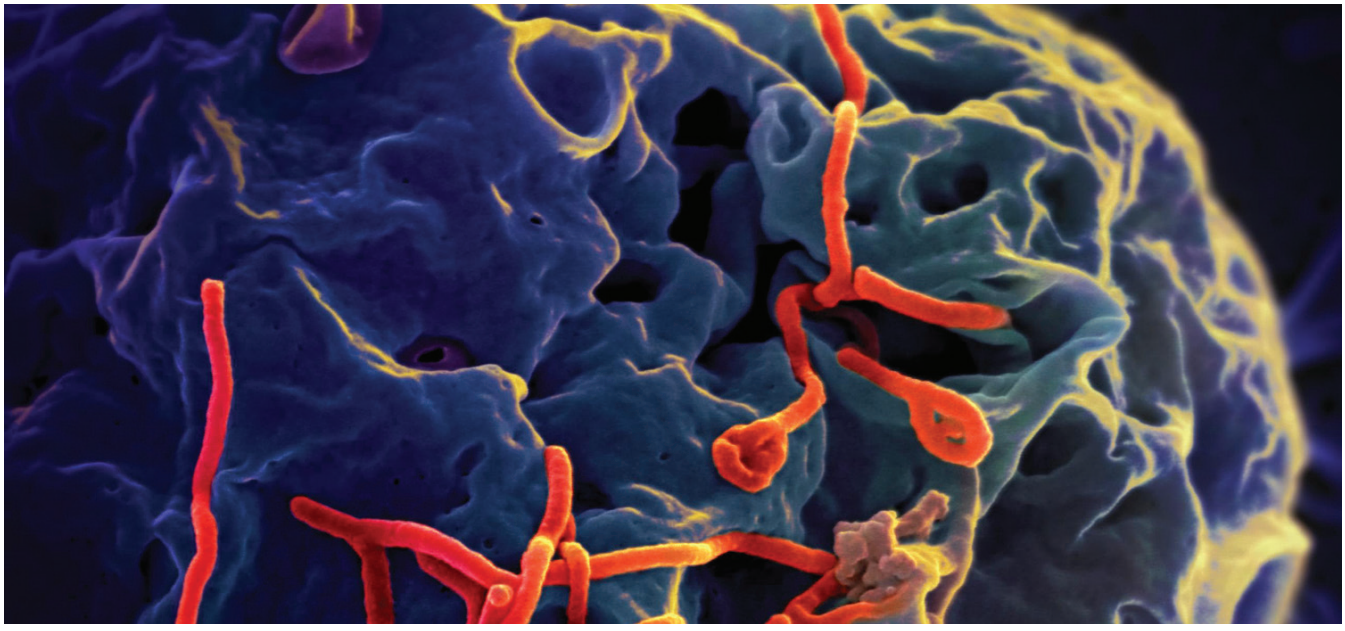
The current standard screen for breast cancer is the mammogram – but that method has its flaws. Many women are hesitant to book appointments because of time, trouble, cost, anxiety, or anticipation of a painful procedure. It's not only people's reluctance to be screened that reduces the effectiveness of mammography, though; scans can only show what is already present in the breast, and although factors like breast tissue density may suggest patients who require more careful follow-up, the predictive value of mammography is limited. That's the impediment Rasmus Bro, professor of chemometrics in the Department of Food Science at University of Copenhagen, decided to tackle with a new screening method that consists of a simple blood test (1). The big question: exactly how did a food scientist develop a test for breast cancer? The answer lies in the way industrial food researchers handle biological data – in a holistic and explorative way. They applied the same approach to blood sample analysis, looking at all of the metabolites in a sample rather than focusing on any one biomarker. "We can measure a blood sample of a healthy woman and tell if she will be diagnosed with breast cancer within two to five years," Bro says. "The accuracy is better than if you use mammography to test if the person has cancer." Bro and his colleagues are unsurprisingly pleased with the results of their first experiments. "We need to validate this much, much further," he acknowledges, "but it is a wonderful first result to have."

Bro's motivation to study breast cancer testing stems from a long-standing desire to work toward clinical applications of his research. "Working in a food department and doing online measurements directly on white sugar, the back of a herring, or cheese, it was obvious to me how much information we usually find when we do chemical fingerprinting (measuring hundreds of chemicals without a strict predefined hypothesis). There is no difference between measuring a beef or a blood sample, so the temptation to try our methods in health-related issues was obvious."The next step is to validate their initial findings – but to do that, the project needs funding.

Meanwhile, Bro hopes to raise awareness of a different kind by showing others the power of combining multiple sets of information. "I hope that our results raise the awareness that it really pays to combine relevant information. We use 27 pieces of information including known risk factors such as hormone replacement treatment. None of them is able to reliably predict what will happen. It is only when we combine them that we can do that." *MS*

*Reference*

1. *R Bro, et al., "Forecasting individual breast cancer risk using plasma metabolomics and biocontours", Metabolomics (2015).*



# Viral Time Travel

## Checking past and present exposure to over 200 viruses in a single blood test

A drop of blood could soon tell you everything you need to know about a patient's infection history. Researchers from the Howard Hughes Medical Institute, MD, USA, have developed a method to identify current or past exposure to 206 known human viruses (more than 1,000 known strains), for roughly US$25 per sample.

Current viral blood tests are usually limited to testing for one virus at a time, but the test, known as VirScan, is able to check for exposure to multiple viruses at once. By synthesizing over 90,000 DNA fragments encoding segments of viral protein and introducing them to bacteriophage, then adding these to the blood sample to be tested, the team can analyze which viruses have previously been encountered by the immune system, either by exposure or vaccination.

The test has many potential applications, such as providing insight into virus-disease associations and connections between different populations and different diseases, and it could also shed light on why cancer immunotherapies work for some patients and not others. The technique could also be used to search for antibodies that attack the body's own tissue in autoimmune diseases associated with cancer.

"You can ask questions about all viruses rather than have to do things one at a time, so it allows you to discover connections between different populations or different diseases amongst groups of people. Now that we can look at all viruses, it's a complete game-changer," says lead author of the associated paper (1) Stephen Elledge.

After using VirScan on 569 people across four continents, including the US, Thailand and Peru, the researchers nearly doubled the number of previously established viral epitopes. They found an average of 10 viral species per person, but over 80 in two individuals – although due to the limitations of the technique, the authors speculate this could be an underestimation, as virus exposure in the distant past may not be detected. Processing 100 samples currently takes two to three days, but the authors hope this will improve as the test is developed further.

It's clear that virome-wide association studies, using techniques like VirScan, could have many epidemiological applications. Its creators further predict that the test could easily be adapted to test for other human pathogens, such as bacteria, fungi and protozoa, and they intend to further refine the test and increase its sensitivity after promising initial results. "In this paper alone we identified more antibody/peptide interactions to viral proteins than had been identified in the previous history of all viral exploration," says Elledge. *RM*

*Reference*

1. *GJ Xu, et al., "Viral immunology. Comprehensive serological profiling of human populations using a synthetic human virome", Science, 348, aaa0698 (2015). PMID: 26045439.*

# The (Immune–Brain) Missing Link

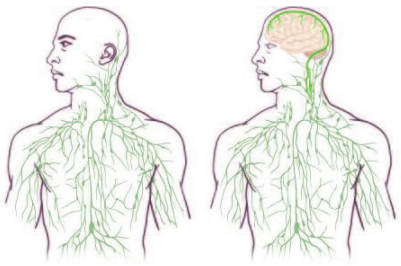
**Textbook-altering research has revealed lymphatic vessels that directly connect the brain and the immune system**

For decades, researchers have posited theories as to how the brain affects the immune system, ranging from afferent nerve pathways to neuropeptide receptors on lymphocytes. The one theory that has always been discounted is the presence of a direct lymphatic vessel connection between the brain and the immune system – and that's exactly what researchers at the University of Virginia School of Medicine (Charlottesville, VA, USA) have just discovered.

The lymphatic system has been extensively mapped using a variety of techniques, but these vessels, which line the dural sinuses, have never been detected before – possibly due to their unique location. Fortunately, postdoctoral fellow Antoine Louveau was trying to find out how T cells get into and out of the meninges, so he developed an immunohistochemistry technique that involves fixing whole-mount meninges while they are still attached to the skull cap, then dissecting and examining them (1). It was this technique that allowed the vessels to be spotted for the first time when Louveau's stains revealed a high concentration of immune cells near the dural sinuses. Noticing the vessel-like pattern of distribution, Louveau tested for the lymphatic endothelial cell marker Lyve-1, confirming the presence of two to three Lyve-1-expressing vessels that run parallel to the dural sinuses and are not part of the cardiovascular system. In a press release from the University of Virginia (2), principal investigator Jonathan Kipnis said, "I really did not believe there are structures in the body that we are not aware of. I thought the body was mapped." He believes that the lymphatic vessels are so close to a major blood vessel in the same area that they have previously been overlooked. Kevin Lee, chair of the Department of Neuroscience, added, "The first time these guys showed me the basic result, I just said one sentence: 'They'll have to change the textbooks.'"

The meningeal vessels are characteristic of initial lymphatics, which collect lymph from the interstitial fluid. But they also possess some unique features – the vessels are smaller and cover less total tissue area than most, starting from both eyes and traveling past the olfactory bulb to the sinuses. Injecting dye into the cerebrospinal fluid (CSF) showed that the meningeal lymphatic vessels are involved in CSF drainage from the ventricles; immunohistochemical staining revealed that they also provide passage for immune cells. Previous studies have shown that CSF elicits an immune response in cervical lymph nodes, a function whose proposed pathway runs via the nasal mucosa. Using dye to trace the passage of fluid from the ventricles to the deep cervical lymph nodes, Louveau and his colleagues suggested that lymphatic vessels in the meninges, rather than in the nasal mucosa, are the primary drainage route for CSF components.

But the real question is: what significance will this discovery have on the study and treatment of neurological diseases? Kipnis thinks the implications are far-reaching. "We will be able to better study neuro-immune communication in healthy and diseased brains," he says, highlighting the novel ability to conduct mechanistic studies on the brain's immune responses. He and his colleagues believe these vessels may be involved in neurological conditions from autism to multiple sclerosis – an example he gave was Alzheimer's disease, in which protein accumulation in the brain may be caused by inadequate meningeal lymphatic drainage. One thing is certain: any researcher who studies a neurological disease with immune system involvement should be very interested in this new discovery. *MS*



Maps of the lymphatic system: old (left) and updated to reflect UVA's discovery (right). Credit: University of Virginia Health System

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# A Liquid Revolution?

**A review of the clinical uses of liquid biopsy show it's poised to make a splash in pathology**

Liquid biopsy is now making its way into the clinic, but just how useful is it? In a bid to answer the question, the Association for Molecular Pathology decided to carry out its own literature review on the clinical utility of circulating tumor cells in cancer diagnosis (1). We spoke with first author Bert Gold, staff scientist at the National

Cancer Institute, MD, USA, about what they discovered…

### What prompted this review?

We realized the opportunity for further molecular characterization of cancers could be productive, both for the pathologist getting a better sense of what causes cancer, and for the treating clinician. The underlying aim is to try and treat all cancers in a more personalized way. The more we know about a tumor, the better we can choose the most appropriate therapy.

### What were your key findings?

Firstly, we discovered that FDA-approved liquid biopsy methods already existed for breast cancer at the time we began our review. While the review was still underway, tests appeared for prostate and colon cancer as well, which shows that this technology has already proven its use in some cancers.

Liquid biopsy is noninvasive compared with scanning and surgical biopsy. It allows clinicians to monitor patients. It also has the potential – much like what was discovered with viral burden in HIV cases – not only to give us information on prognosis, but to provide further insight into the workings of cancer, and how best to treat it.

However, we also found that in the US, third party payers are often unwilling to reimburse the use of liquid biopsy methods. It is often the case that innovative diagnostics are spurred on by third party payers' willingness to pay, but if no one pays, you can't do the test. This makes it much more difficult to figure out how to best utilize technologies – not everyone has the funds for large clinical studies.

### How will liquid biopsy impact diagnostics?

It could be revolutionary. Examining the genetic information from tumor DNA just by doing a liquid biopsy might teach us which drug to use. Our review didn't just look at the evidence for using tumor cells – exosomes and circulating tumor nucleic acids have promise, too. I think there are a variety of very positive outcomes that could be seen from the use of liquid biopsy in the coming years.

### Are further studies needed?

Absolutely! But we already know the technique works – liquid biopsy should already be regularly used in metastatic breast, colon and prostate cancer cases to help judge the relative severity of the disease, but that simply isn't happening in most cases. I believe this method would empower pathologists to look at the genetic information found in these cells, and this could trigger research to help us further understand this technology and its applications. Our goal needs to be to further evaluate liquid biopsies and their uses in particular cancers, with the aim of providing precision medicine.

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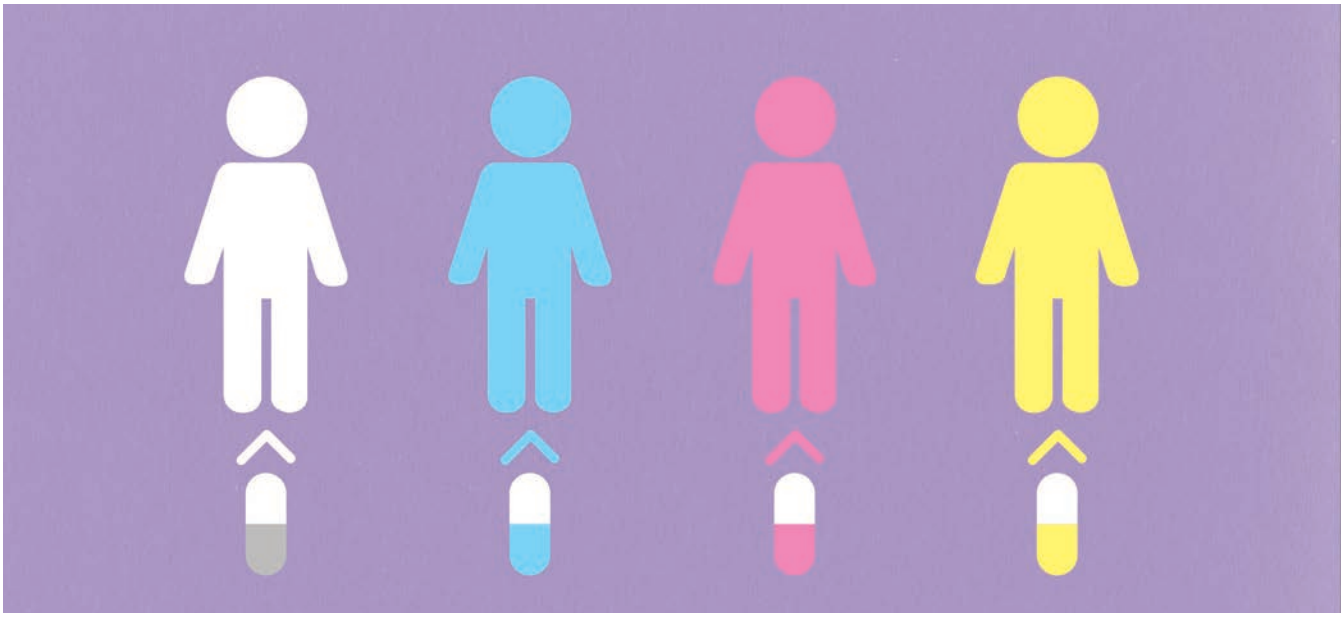

# (Not) All About That Base

**Genetic analysis isn't the only tool for delivering personalized treatment; a novel technique for matching tumors with appropriate therapies could prove a rapid and reliable alternative**

The origin of personalized medicine lies in the rapid advancement of genetic analysis in recent years. The cost of looking at a patient's DNA has dropped precipitously since the transition from Sanger-based to next-generation sequencing to the point where the US$1,000 genome is within our grasp (1). But with this blessing comes a curse – too often, people equate personalized medicine with sequencing, and therefore miss other opportunities for tailoring treatment to individual patients.

Anthony Letai and his research group at the Dana-Farber Cancer Institute (Boston, MA, USA) are taking a different approach. "As an oncologist and a researcher," Letai says, "it was clear to me that despite a general impression that genetic testing can direct treatment with targeted agents, it does not do this effectively for most patients, and another strategy was needed." So instead of using genetic analysis, Letai's team exposes actual tumor cells to a range of cancer drugs and measures their reactions to see whether or not each drug causes apoptotic signaling. "The key is that we make our measurement very early, so that long term *ex vivo* culture is not required. When we see significant death signaling, it turns out to be a good predictor that the drug will induce a response *in vivo*. It's a common sense approach that has been effectively exploited in the microbiology world for many decades in choosing antibiotics to treat bacterial infections." The technique, called Dynamic BH3 Profiling (DBP), takes less than a day to predict which agents are most likely to work against the tumor in question – providing answers within 16 hours in most cases (2).

Letai is optimistic that the new test could be clinically useful in the future, but only if they can overcome the perception that personalized medicine revolves around sequencing. "In our way of thinking," he says, "precision medicine is matching the right drugs to the right patient. Genetics is only one tool in doing that, and a tool that will not help direct many drugs in many tumors." The next step in bringing DBP to the clinic is prospective testing of the assay's predictive power – it's a long journey from these preliminary results to full approval, but it's one Letai hopes will be completed in the next few years. *MS*

*References*

1. *KA Wetterstrand, "DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP)" (2014). Available at: http://www.genome.gov/sequencingcosts. Accessed June 4, 2015.*
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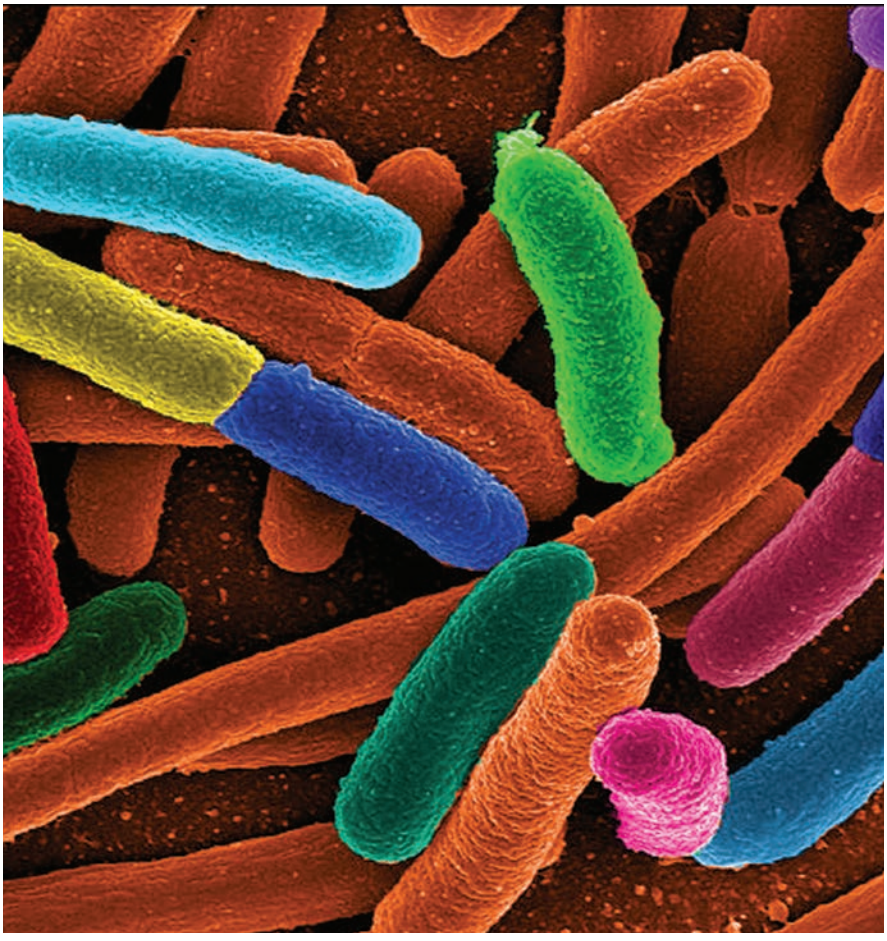
# "Friendly" Bacteria Help Diagnose Disease

## Two studies demonstrate how genetically engineered bacteria can be used to diagnose cancer and diabetes



Bacteria are an increasingly popular research focus for a range of disease states. But as well as causing diseases, bacteria could help to identify them – two studies published in Science Translational Medicine have demonstrated the diagnostic uses of genetically engineered bacteria in the detection of cancer and diabetes.

In one study, US researchers engineered *Escherichia coli* Nissle 1917, a strain often used in probiotic products, to produce the enzyme LacZ when in the presence of tumors. When the *E. coli* strain was fed to mice, it was shown that the bacteria were able to colonize tumors in the liver. Next, the mice were injected with LuGal, a conjugate of luciferin and galactose, which can be converted to luciferin by LacZ. Luciferin can then be detected in the urine using a simple assay; with as little as 1 microliter of urine, the test was able to detect the presence of the bioluminescent luciferin (1). Using this method, the team were able to detect metastatic tumors within 24 hours of introducing the bacterial strain to the mice.

Meanwhile at the University of Montpellier, France, bacteria were also put to work – this time, to detect elevated glucose levels in the urine, a key sign of diabetes. The team incorporated a genetic "switch" into *E. coli* which caused the bacteria to produce large amounts of fluorescent protein when exposed to high concentrations of glucose. Unlike the previous study, the bacteria were not introduced to the body, but instead simply added to human urine samples. The approach doesn't significantly improve on current glucose detection methods, but the developers are hopeful that as bacterial diagnostic methods improve, they will have a promising range of applications; engineered bacteria could potentially be developed to detect a range of clinically relevant biomarkers. "Our work is presently focused on the engineering of artificial genetic systems that can be modified on demand to detect different molecular disease markers," says first author of the associated paper (2), Alexis Courbet.

However, the use of bacteria as diagnostic tools still has challenges to overcome: the time to results is currently too long for urgent or emergency testing, and engineering bacteria that can respond to the right biomarkers is no simple task. The use of live, engineered bacteria in the lab could also raise safety issues. Certainly, any proposed methods will need further validation before seeing clinical use. *RM*

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# Scoping Out the African Eye Worm

## New mobile microscopy and software technology may replace slow and tedious manual examinations for Loa loa parasites

The African eye worm, *Loa loa*, is widely distributed across the rainforests of west and central Africa. Unfortunately, so are other parasites like the *Onchocerca volvulus* worm, which causes river blindness. And while the loiasis-causing worm is often asymptomatic or causes only mild irritation, many of the other parasites require treatment with drugs like ivermectin to prevent permanent or life-threatening symptoms.

But there is a serious problem: when *Loa loa* hosts take ivermectin, they can suffer severe adverse effects including encephalopathy, coma and even death (1) – but, until now, there has been no easy way to detect carriers of the parasite. The worms are tiny, and the traditional screening method involves manually counting the number of worms in a blood sample in order to determine if their density is great enough to prompt an adverse reaction to ivermectin treatment. It's a process so long and tedious that it would be impossible to implement on a large scale. One study determined that sites at the greatest risk of adverse events were those with 20 to 40 percent loiasis prevalence, which are not normally considered high-risk populations because of the small number of people estimated to have high *Loa loa* densities (2). It's clear that the relationship between worm densities and adverse risk isn't fully understood – so one group of scientists from the University of California, Berkeley (CA, USA) decided to eliminate the problem at its source with a rapid screening test to detect the *Loa loa* worm in blood.

A pilot test in Cameroon of CellScope Loa, a mobile phone-based video microscope, found that the device was as good as conventional blood smears in detecting levels of the *Loa loa* parasitic worm. (Credit: Tom Nutman, NIAID).

Researchers from Daniel Fletcher's bioengineering group used their own iPhone-based microscopy platform, CellScope, to view magnified blood samples on slides. In conjunction with the CellScope device, they wrote a software program that would detect *Loa loa* in the blood by analyzing wiggling motions, caused by the shifting of blood cells as worms move between them, during a five-second video. Dubbed CellScope Loa, the technology successfully estimated worm densities in 33 patients, providing similar results to those from the manual test – but with significant advantages. For one, the test can be completed in under two minutes; for another, the result can be tagged with a set of GPS coordinates as well, providing a detailed and accessible geographic record of *Loa loa* infections.

CellScope Loa could greatly improve life for millions of Africans seeking anti-parasite treatment – but only if Fletcher and his group can overcome one obstacle: scaling. At the moment, each device is assembled by hand in their laboratory, so before they can provide the number of devices needed for widespread Loa loa testing, they'll need to find an industry collaborator interested in taking on the challenge. *MS*

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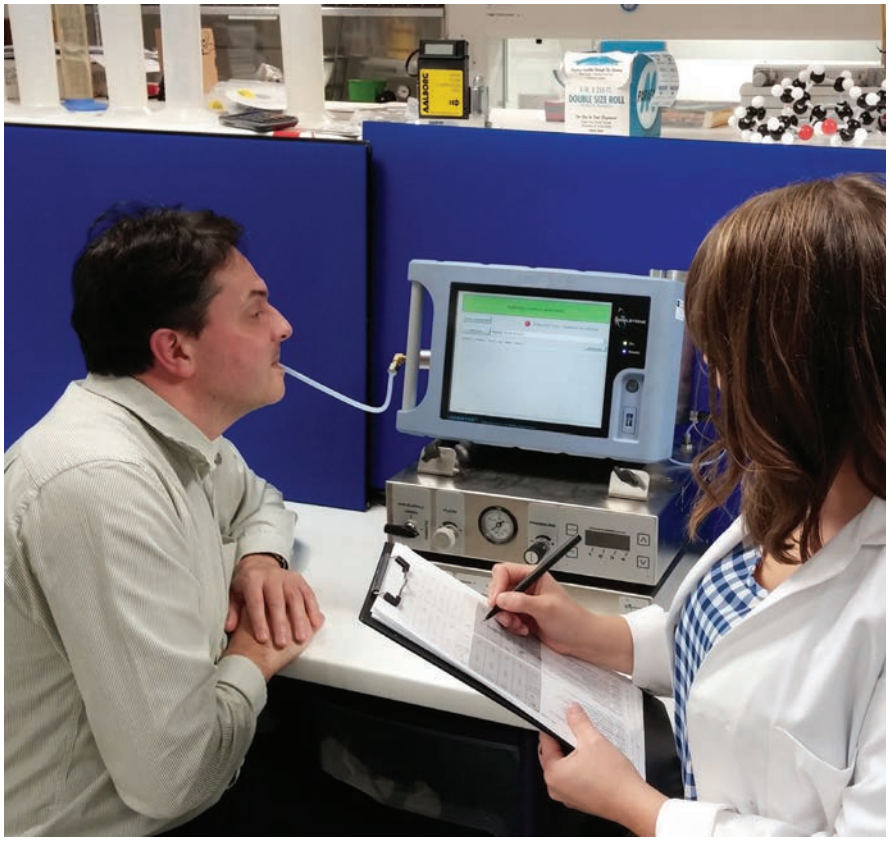

Credit: Danielle Toutoungi at Owlstone, Inc.

# High Hopes for Cancer Breathalyzer

**Microchip technology can detect very low quantities of lung cancer biomarkers in breath – and may offer a new noninvasive screening option**

Lung cancer is the leading cause of cancer death worldwide (1) – but a large part of the reason might be because so many patients go undiagnosed until they have advanced disease – survival is closely correlated with stage at diagnosis. Patients who present at stage I, for instance, have five-year survival rates of about 35 percent, while those presenting at stage IV rarely survive more than two years (2). It's clear that early diagnosis is key to improving lung cancer survival rates, but that's easier said than done. Unlike other common cancers, there's no easy screening tool for early-stage lung cancer. The best current option is low-dose computed tomography for high-risk individuals, but this can lead to overdiagnosis of abnormalities that don't require further investigation and also exposes patients to radiation.

Now there may be an alternative. Engineer Billy Boyle, cofounder and president of operations at Owlstone, Ltd. (Cambridge, UK), has developed a silicon microchip with a chemical sensor capable of detecting volatile organic compound (VOC) biomarkers in very low quantities. Using field asymmetric ion mobility spectrometry (FAIMS), the chip can rapidly monitor a wide range of chemicals below part-per-billion concentrations (3). It serves as the "brains" of a breathalyzer device that can identify lung cancer biomarkers with a simple breath test. The chip has already demonstrated an ability to accurately detect 12 biomarkers in breath specimens (4), and the Lung Cancer Indicator Detection (LuCID) project has now won a £1 million SBRI Healthcare award to take its technology to clinical trials. With that funding, Boyle plans to deliver a handheld breathalyzer device that can be used in the clinic

The FAIMS technology was originally intended for the detection of explosive devices in high-risk areas, but Boyle took things in a different direction after his wife's cancer diagnosis in 2012. In a press release from Owlstone, he said, "If you could change only one thing in the fight against cancer, it would be to detect the disease earlier where existing treatments are already proven to save lives. FAIMS technology has the potential to bring a quick and easy-to-use breath test to a GP's office. Our team will not rest until we help stop the daily devastation that cancer brings to patients and their families." *MS*

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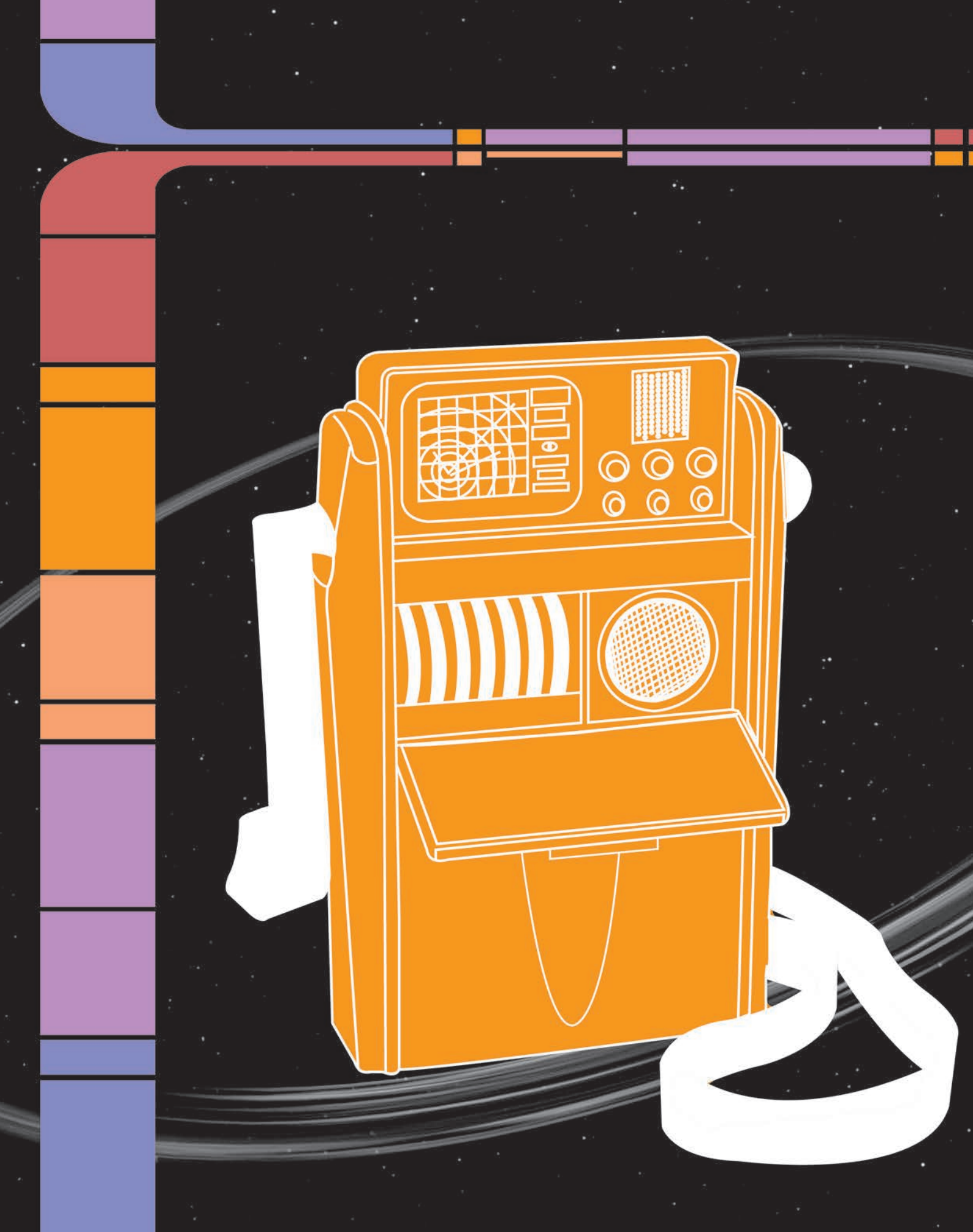


# Where No Healthcare Device Has Gone Before

As science fiction technology inches closer to reality, teams across the globe are competing to create the world's first medical tricorder

*By Michael Schubert, Fedra Pavlou, Roisin McGuigan*

"Computer – activate emergency medical hologram!" How many medical professionals, whether working in a lab or on a ward, wish they could tap into futuristic technology when workloads become unmanageable? Sadly, holographic doctors are still out of reach – but other medical devices from the world of science fiction are coming ever closer to reality.

You may be aware of the Ansari XPRIZE for suborbital flight, the highly publicized "space race" that provided a US$10 million prize purse to the first team to design and build a reusable, functioning manned spacecraft. Fewer people know that the XPRIZE story didn't end when SpaceShipOne took to the stars – instead, XPRIZE competitions continue to set lofty goals for new technologies, with a mission to spur "radical breakthroughs for the benefit of humanity." These competitions differ significantly from other prizes in that, while most are retrospective, XPRIZEs provide the goal and let participants from all disciplines compete to see who can reach it first.

In expanding the scope of competition, one of the current prizes up for grabs is the Qualcomm Tricorder XPRIZE. The goal? To develop a consumer-friendly, noninvasive healthcare device that can diagnose a wide variety of medical conditions and record a range of metrics for general health. The goal is to create innovative technologies for precision diagnostics, so that users can reliably monitor their own or others' health regardless of time, place or the availability of traditional medical and laboratory equipment. In other words, bringing healthcare to the disadvantaged, the remote, the busy and anyone else who needs it.

The concept of a tricorder comes from the world of Star Trek, where it's a device used to scan anything and everything – including, in the case of doctors, their patients. On television, the tricorder not only provides its user with a vast array of information about the patient, but even offers instant diagnostic capabilities. The XPRIZE asks: why should such a useful tool be limited to fiction? Why not make it a reality?

That's the goal for all eight of the teams currently participating as finalists in the competition. Their task is to create the first affordable, portable, wireless, consumer-friendly medical diagnostic device that can be used by physicians and patients alike. The tricorder must be able to assess at least 16 distinct conditions, monitor at least five vital signs, demonstrate safety and user-friendliness, and send data to the cloud, where it can be stored and accessed by the patient or doctor. The three-and-a-half-year competition is approaching its final months, so each of the teams already has a prototype device; their next step is to test it on a consumer group, evaluating both the health and user experience aspects. The solution that performs best will take home the grand prize – but regardless of which team attains the Qualcomm Tricorder XPRIZE, the real winners will be patients and healthcare providers around the world.

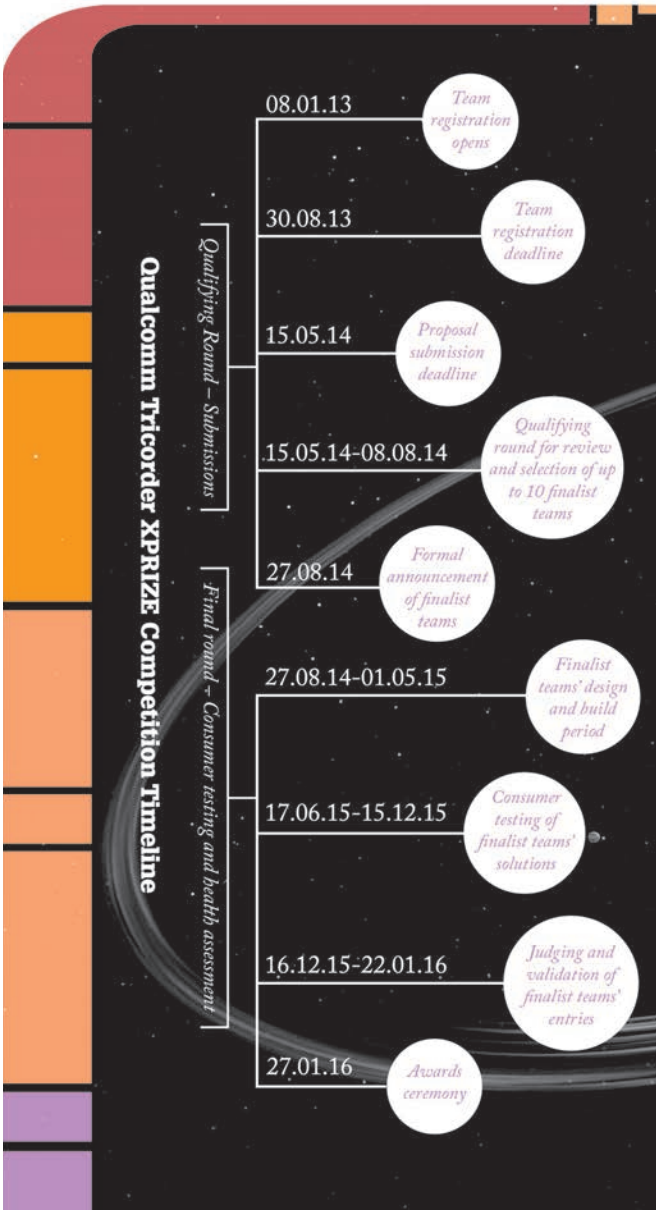
*We spoke with Grant Campany, Senior Director, Qualcomm Tricorder XPRIZE*

**The Pathologist: What drove your decision to actually launch an XPRIZE competition in the diagnostics arena?**

**Grant Campany:** When you consider the "big picture", you can segment the globe into two segments – the developing world, and the developed world. The developing world has a population of millions who have no access to healthcare; not only are there resource constraints in terms of equipment, but there's a shortage of medical professionals as well. Africa is a good example – the continent has 25 percent of the world's population, but only one percent of the world's doctors. Countries like China and India are similar in having hundreds of millions of people without the ability to access medical care. It's a huge problem, but it's also a tremendous opportunity.

Then you look at the developed world – and even within the United States, there's increasing pressure on both the government and private insurers to keep healthcare costs low. A key cost driver in America is that many people just don't have access to tools and providers that might give them early diagnoses of serious or chronic illnesses, thereby preventing long-term decline. It's especially true of vulnerable populations like the elderly or those with low incomes, who may be reluctant to go to the doctor simply because of the logistics involved – not just in paying for the visit, but in obtaining transportation, finding the time, arranging assistance or childcare if it's needed, and all sorts of other complicating factors. So you can imagine that there's plenty of opportunity, even in the developed world, to look at how we bring healthcare to consumers. If we can prevent the need to actually get into a car, drive or take public transport, and then wait as much as a few hours before the doctor can see you, we'd be improving access for a lot of people.

Now imagine that you have a tool that enables doctors to extend their reach into their patients' homes and allows them to monitor patients – even high-risk ones – remotely through the Internet. The aim of the Qualcomm Tricorder XPRIZE is to motivate teams from around the world to develop the kinds of tools that will allow doctors, regardless of location, to have access to their patients – which makes life much more convenient for both parties and increases productivity using resources we already have, like cloud computing. The rules of the competition include developing tricorders with the ability to transmit data directly to the cloud, because we don't just want innovative technology – we want to set the stage for eventual commercial use. By putting both the clinical and the IT infrastructure in place, we can use the XPRIZE competition as a learning experience before scaling up to bring tricorder technology to the world.




**TP: Are you worried that such a technology-driven device might be somewhat restrictive in the developing world?**

**GC:** As technology advances, the cost of the sensors and technologies needed for a tricorder continually decreases. For instance, as recently as five years ago, it would have been difficult to make such a sensitive device portable at all, let alone affordable. So when we consider the tools we'll need to provide tricorder services in the future, I think it's going to be

an opportunity to invest early in providing that infrastructure. Lots of companies are currently creating wireless healthcare for the home, so I think we'll see tremendous progress in the next five to 10 years.

Cellular service already exists even in many of the poorest and most remote areas of the world – so we know that many people, regardless of where they live, have mobile phones and are able to transmit data to the cloud. For the initial stages, we plan to purchase tablets with data connections to serve as the media bridge between the tricorders and the cloud. It essentially mimics what's likely to happen in the real world. If you're using a tricorder in a clinic where patients come for diagnosis, all you really need is a phone to transmit the data – and that transmission might go to a local hospital where staff are remotely monitoring patient readouts on a digital dashboard. That way, they can keep abreast of patients who can't make it to the hospital, and also get an idea of the general health of the population. It's true that a lot of infrastructure will be needed in order for governments and insurance providers to manage larger patient populations, but I think that infrastructure is already on the verge of being created.

**TP: What kind of work are you doing with governments and national agencies to bring about improvements to their infrastructures?**

**GC:** We're all familiar with the process of regulatory review for medical devices before they can go to market – especially when we're talking about diagnostic tools. About two years ago, we formed a relationship with the United States Food and Drug Administration (FDA), who created a first-of-its-kind helpdesk for us so that our teams could have direct access to knowledgeable volunteers to ask questions. That not only opens the door to the FDA, but allows everyone involved to start building relationships with key people in the review process – which is important because we want them to get to know the creators of new technologies, but also to understand what those technologies are and how they're going to be used. The idea is that if the FDA understands what we're doing, it'll be easier to identify potential barriers and provide guidance, so that the tricorders can make it through the review process and reach the market – and maybe that will even help to simplify the process in other countries.

**TP: Is the primary goal for teams to obtain funds to further develop and market their product?**

**GC:** We've discovered that the prize purse usually isn't the main incentive for teams to compete. We offer a worldwide stage upon on which teams can be recognized for their achievements, which gives them immediate visibility and allows them to build their brand – a benefit that's almost priceless. The XPRIZE also creates a lot of awareness about what they're doing, not just with industry experts, but with the general public. We want to help people around the world also understand what's being done and how new technologies can improve their quality of life. I think winning the XPRIZE is almost like the Olympics; we even have three prize purses – first, second and third. The grand prize is US$7,000,000, then the runner up is $2,000,000 and the third place is $1,000,000. All three of our winners will be recognized for their performance.

I think competitions like the XPRIZE are a great way of driving innovation, because we're able to encourage ideas that we know are going to be dramatic breakthroughs. We try to simultaneously push the technological envelope and close an economic gap – because typically these are the kinds of innovations that aren't getting financed. Without an XPRIZE, these ideas would have nowhere to turn for funding. So we're creating incentives for people to focus on developing technology that wouldn't exist any other way.

**TP: What do you expect will be the outcome of the Qualcomm Tricorder XPRIZE competition?**

**GC:** I'm expecting to see several things. One is that I think we'll learn how people behave with these types of devices. In June, the teams are delivering 30 working prototypes to the University of California, San Diego Medical Center's Clinical and Translational Research Institute. We're recruiting up to 300 participants from the hospital who have one of the 15 conditions for which we're going to be testing to volunteer as consumer testers; we'll be giving each of them a device, which will show us how they use the tricorders at home.

We don't just want technologies that work, we want technologies that people are going to embrace – in fact 45 percent of each team's score depends on the user experience. We'll be conducting surveys following every consumer testing session, so we'll have specific information on their experiences with the device. That will be invaluable to the teams as they think about the tweaks and refinements they need to make so that their devices are as user-friendly as possible.

I also think it's very important for the general public to understand the amount of effort that goes into the development of these technologies. It's all about improving the health of patients worldwide – and what's often missed in competitions are the real human stories behind the teams. The people who are competing for this XPRIZE are very passionate. People have real, personal reasons for participating. Some team members are emergency room doctors; some have lost loved ones; they all want to stop people from getting sick and dying.

# Team DMI


For Eugene Chan, the leader of team DMI, the journey toward rapid, portable point-of-care diagnostics began even before the announcement of the Qualcomm Tricorder XPRIZE. Chan was inspired during his days as an internal medicine specialist at Brigham and Women's Hospital, when he realized that he was seeing patients without having access to the laboratory information he needed. "I wished I had the capability to simply whip something out of my pocket and diagnose the patient on the spot," he says. And now, with their rHEALTH X1 tricorder prototype, DMI is hoping to do just that.

The team's main goal is to give patients the power traditionally held by their healthcare providers. They want consumers to be able to access better diagnostic information, and they want to see that information at patients' fingertips – in some cases, literally. To diagnose a patient's condition, the rHEALTH X1 takes a drop of blood and applies it to nano-scale test strips that can determine the contents of the sample. The device is fitted with internal lasers that read the nano-strips, allowing the associated software to determine exactly what's in that drop of blood and return one of hundreds of possible diagnoses from a single test.

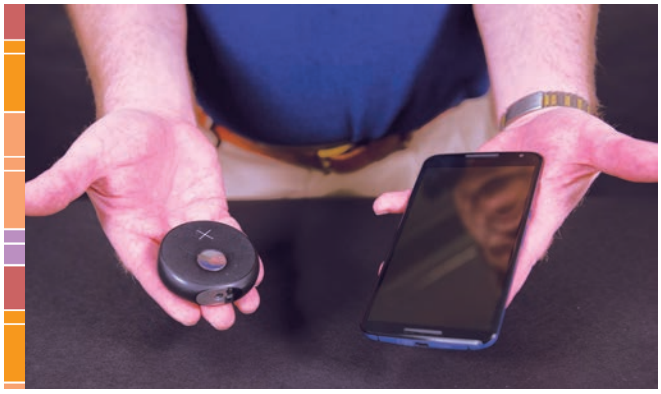
So far, the tricorder has been tested in over 22 different categories, including not just vital signs, but hematology, bowel markers, blood chemistry, and even small molecules – all of which have been tested both internally and externally, including validation against FDA gold standards. It's that level of detail that Chan thinks has put his team in the running for the ultimate prize. "Our team is fantastic in terms of being able to put technologies together," he says, "but at the core of our technology is a vision for the future. All of the current technologies for point-of-care diagnosis are focused on performing one test and yielding one result, so we turned that on its head and focused on providing as many tests as we possibly can from a single drop of blood."

For DMI, the advice provided by the FDA has been invaluable. They've provided the team with insight into multifunctional devices. "The paradigm for getting blood tests approved is one at a time," Chan explains, "and if you want to get all the tests approved on a timely basis it would require a much more expedited stream. So the advice from the FDA in that respect has been fantastic." And the FDA aren't the only people in DMI's corner – the team has funding from NASA, the National Institutes of Health, and the Gates Foundation. "Our organization tends to innovate a lot and create really exceptional technologies, and the rHEALTH X1 falls squarely in that pocket," says Chan. "I think we're very fortunate to have the support we do." One of the reasons the team has managed to garner backing from so many funding groups is that the tricorder isn't their first attempt at high-level diagnostic innovation. DMI was the winner of the Nokia Sensing XCHALLENGE with their rHEALTH sensor technology, which not only took the grand prize, but was also awarded a trip to zero gravity with NASA. "You have to anticipate everything that's going to happen even before you step on the airplane," Chan says. "So how do you do that without ever being in that situation? It's things like this that I'm most proud of – seeing how we can be thrown into unexpected issues and react to it fantastically well." The XCHALLENGE trophy is now in the lobby of DMI's headquarters where its presence fosters the enthusiasm and motivation the team will need to succeed in yet another competition.

*"It's things like this that I'm most proud of – seeing how we can be thrown into unexpected issues and react to it fantastically well."*

"I think, in our case, the technology stands in a class of its own. This competition has been great, and I feel like we've taken what's technically feasible and then pushed it even further. And that's really what the XPRIZE is about – not repackaging existing products, but pushing the boundaries of what's possible from a personal and a technological standpoint."

# Team SCANADU/Intelesens



In his 32 years at Ulster University, Jim McLaughlin has done his time in the healthcare sensor industry. Among his many spinout companies is one called Intelesens, which develops intelligent systems to monitor patients' vital signs. "I suppose the dream we always had was to take that wearable vital sign system and add other systems to it," says McLaughlin, who imagines a device capable of measuring everything from blood pressure to spirometry. But that isn't his only source of inspiration – he's also drawing on the computing power of a standard mobile phone, especially with regard to low-energy Bluetooth communication between devices. "We knew the technology was right," he says, "so we were just looking for an application."

That application was the medical tricorder, a device with personal as well as practical significance for McLaughlin. "My father died in a hospital when he was 65, and for three or four days he didn't get any proper analysis done. I always look back on that and think that, if there had been rapid diagnostics, his life could have been saved. When I went into research, that thought drove me the whole way through – the concept that we could have rapid point-of-care diagnostics, rapid diagnostics from the home to the hospital." The technology hits close to home going forward, too. "My mum is currently ill with atrial fibrillation, so I would see the benefits in caring for her. And as the elderly sector of our community grows, there's definitely a time coming when hospitals will not be able to cope. So we'll need improved early warning and monitoring systems to get patients out of hospitals faster, or stop them being hospitalized in the first place." So it's with the goal of saving lives and empowering patients that McLaughlin and his team took on the challenge of creating a multifunctional medical diagnostic device.

The heart of the tricorder that SCANADU/Intelesens has developed for the Qualcomm XPRIZE Competition is its mobile phone software. The app asks questions about a user's symptoms, then references them against statistics based on age, gender and other characteristics to narrow down the possibilities. Then the investigative process begins – touching the device to your head measures temperature, heart rate, blood pressure, and SpO2; placing a patch on your body takes an electrocardiogram and a respiration rate; peripherals can examine other health aspects such as spirometry; and finally, a palm-sized reader that was developed by the Ulster University can run a variety of blood and urine tests for problems ranging from diabetes to pneumonia. The tricorder can even recommend next steps once it reaches a diagnosis.

The merging of the two teams has been a boon in many ways – whereas Intelesens funded and created many of the peripherals and technical aspects, SCANADU provided the noninvasive measuring device, the user interface, and much of the app development and design. Both groups have brought not only unique skills, but also unique connections and perspectives to the table – while SCANADU has younger members with energy and enthusiasm, Intelesens brings in the experience and guidance of people who have spent their lives in industry. But there is a downside; combining an American team with one from Northern Ireland results in a lot of long-distance collaboration… and a workday that lasts from six in the morning until well after midnight. With challenges like those to overcome, it's clear that both teams are dedicated to making their tricorder a reality, no matter what it takes.

It's not just the end product that might benefit patients, though. McLaughlin thinks that one of the reasons his team's device has made it into the final eight is because of the individual technologies they're developing. "From SCANADU, there's some nice noninvasive blood pressure technology," he says, "and from Intelesens, we're seeing some mature wearable technology." By this point in the project, every participant has learned a lot, and has also had the opportunity to teach. Biochemists have learned coding; engineers have learned medicine; and, McLaughlin feels, all of this holds promise for the future. "I think we're about to see a whole generation of powerful apps for everyday life – be it in healthcare or other uses. So some of the platforms we're developing now will be very suitable for that."

With recent advances in portable technology, McLaughlin sees his team's vision coming ever closer to reality. Between phones developed for wearable devices, low-energy Bluetooth for instant connections, and increasingly user-friendly apps, he feels it's just a matter of time before a wide swathe of traditional systems can be replaced by electronic versions. Though there are still snags to be worked out – data security, for instance, or simply the challenge of convincing people to give up their old methods – team SCANADU/Intelesens is confident that the world is waiting for their tricorder.

## Team Aezon


Team Aezon was founded when its leader, Tatiana Rypinski, noticed that technology's healthcare potential wasn't being fully explored. "Today we use technology to check the news, the weather, our emails, Facebook, our texts and our tweets. Yet with this wealth of information-gathering ability, we don't check our bodies." Resources are stretched thin for medical providers around the globe – so if clinic and hospital systems are overloaded, it's time for patients to start taking charge of their own health. That's why Rypinski decided to use the Qualcomm Tricorder XPRIZE competition to extend healthcare's reach. "I was excited to have the opportunity to work on an intricate and futuristic project with the potential to have a great impact on the delivery and accessibility of healthcare," she says, highlighting her team's desire to make good health something everyone can have – even if they can't easily get to a doctor.

One thing that sets Aezon apart from the other XPRIZE contenders is that the team's members are all full-time students. Rypinski, whose background is in robotics and prosthetic design, is in the biomedical engineering program at Johns Hopkins University. Her teammates come from a variety of academic programs at Johns Hopkins, which enables each aspect of the tricorder project to have its own specialized sub-team consisting of students with relevant skill sets. But the groups don't stay separate – once a week, all of the sub-teams come together for "integration meetings" that allow them to pick one another's brains for troubleshooting. "The multidisciplinary team is a huge advantage," Rypinski explains, "because someone with a different skill set or academic background often sees an innovative way to solve another sub-team's problem."

Aezon's blessing is also its curse, though; as university students they have limited time and financial resources to bring great ideas to life. Though they're partnered with several companies experienced in delivering mobile biomedical solutions, in the end, it's up to team Aezon to balance the financial and time pressures of full-time education and participation in such a high-profile competition. Even with this unique added challenge, Rypinski and her colleagues remain optimistic. "It can be an advantage," she says, "because our constraints force us to operate strategically and creatively." Between the team's experience in bioengineering and its members' can-do attitude, developing a tricorder may only be the start of their career in healthcare innovation.

## Team CLOUD DX


Cloud DX is an advanced group of programmers, software architects, biomedical engineers and entrepreneurs from Canada with an eye for creating a unique wearable device. Their tricorder, the Vitaliti, is part lifestyle monitor and part medical tool – all users have access to data like their heart and respiration rates, core body temperature, posture index, sleep cycles, and even fitness information like the number of steps taken and calories burned in a given time period. The necklace and cuff also record four channels of data including a pulse wave (sphygmogram), two-lead electrocardiogram, pulse oxygen and temperature; from there, proprietary cloud-based algorithms take over to calculate physiological parameters – blood pressure, pulse rate, arrhythmia detection and characterization, cardiac decoupling, blood oxygen saturation, and augmentation index. The results are available instantly on any phone or tablet running the associated app, but can also be stored and retrieved in the cloud so that users can do even more with the data. That's not all, though – Cloud DX

has also partnered with LRE Medical GmbH (Oceanside, CA, USA) and Cortex Design Inc. (Toronto, ON, Canada) to develop a portable desktop in vitro diagnostic platform that can run advanced assays on samples of patients' blood, urine or saliva. The diagnostic tool that ultimately made it to the XPRIZE finals includes the team's FDA-cleared Pulsewave health monitoring technology, specialized Cloud Diagnostics software architecture, Vitaliti portable chromatography, and a proprietary user interface.

*"The benefits of this digital revolution will truly give the consumer a role in their own healthcare."*

Team leader Sonny Kohli is no stranger to lofty goals – not only is he currently a practicing physician at Oakville Trafalgar Memorial Hospital and an assistant clinical professor of medicine at McMaster University, he's also a former astronaut candidate with the Canadian Space Agency (CSA). To make his bid for the stars, Kohli studied at the International Space University (ISU), trained as a flight surgeon with the Canadian Forces, and earned a CSA scholarship to NASA's Johnson Space Center and Wyle Laboratories. While at ISU, he helped to deploy the Image Reversal in Space experiment on the International Space Station, examining how the brain perceives two- and three-dimensional images in zero gravity.

The rest of Cloud DX is as impressive as its leader. As part of Biosign Technologies Inc. (Mississauga, ON, Canada), they achieved FDA clearance for their most recent product after only 97 days, significantly shorter than the average 137-day approval time. Because Cloud DX is already an experienced medical device manufacturer, the team is optimistic about their entry into the competition – and Kohli has a few words of wisdom to share about the competition itself. "The Qualcomm Tricorder XPRIZE will ignite a wave of innovation around the concept of remote diagnostics," he says, "but the technology developed also needs to be accepted by physicians. The winning team will have to demonstrate that the data they generate can be trusted – then the benefits of this digital revolution will truly give the consumer a role in their own healthcare."

## Team Dynamical Biomarkers Group

One team from Taiwan, Dynamical Biomarkers Group (DBG), comes at the tricorder contest from a unique perspective. "In Taiwan," the team's statement says, "universal healthcare is available to all, so we deeply understand the urgency in controlling the cost and wise use of medical resources." When medical care is free in such a densely populated area as Taiwan, the demand on those resources is not only high, but growing – so the members of team DBG have taken it upon themselves to alleviate the pressure.

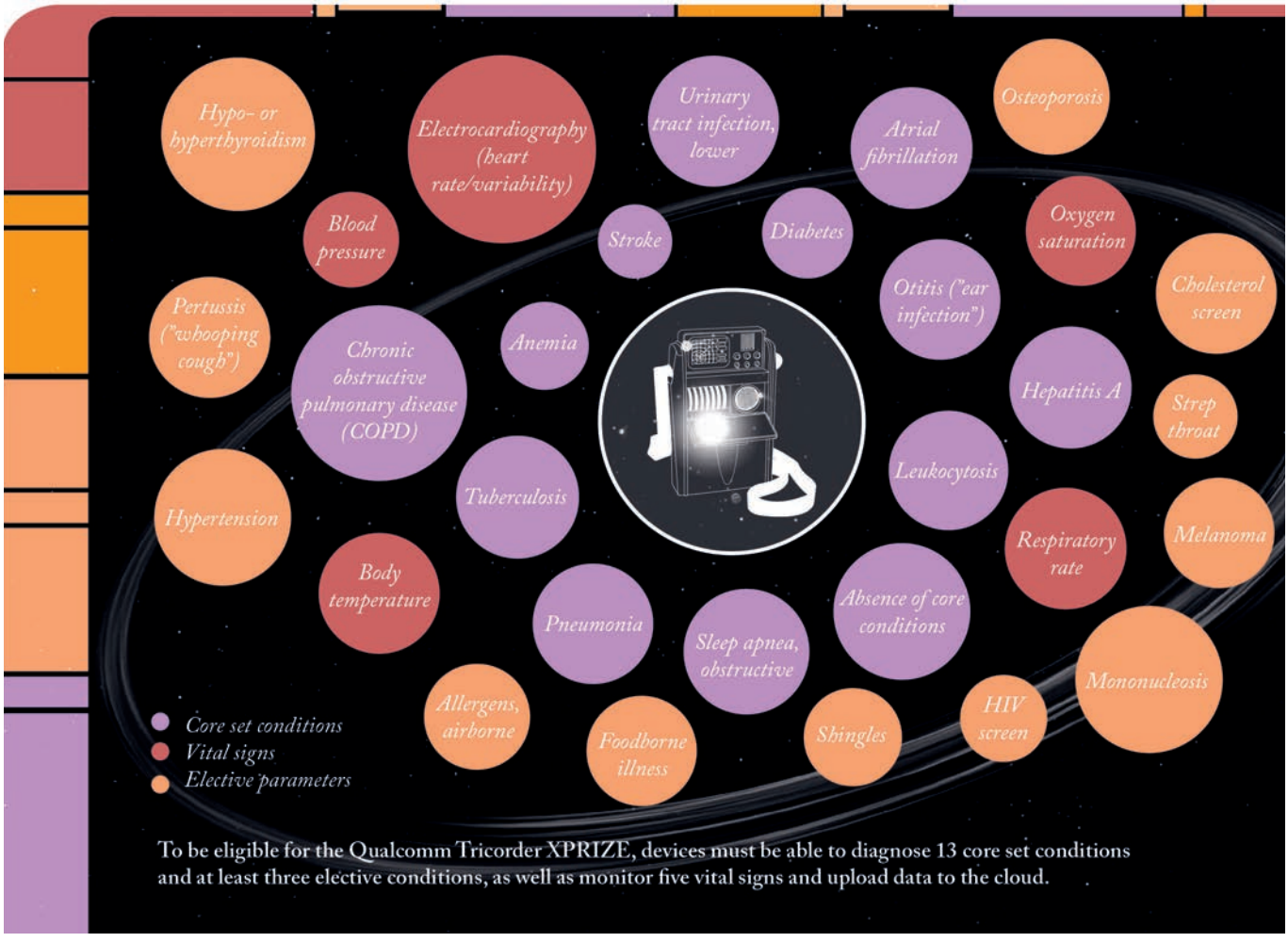
Unlike many of their competitors, DBG is not a commercial team; rather, it's an outgrowth of the Center for Dynamical Biomarkers and Translational Medicine at Taiwan's National Central University, it does receive sponsorship from HTC Corporation (New Taipei City). The group includes clinicians, engineers and researchers from many different disciplines – medicine, computer science, physics and mathematics. "To address the challenge of ever-increasing cost and limited accessibility of healthcare, we have to think outside the box," they say. "Disruptive technology is one of the components that is crucial for any solution. It is inspiring to see XPRIZE, one of the world's most innovative organizations, willing to take up the enormous task of providing a platform to test these disruptive technologies."

Chung-Kang Peng, the team's leader, is K.-T. Li Chair Professor and the dean of National Central University's College of Health Sciences and Technology. Spanning the globe with his team, Peng is also co-director of the Rey Institute for Nonlinear Dynamics in Medicine at the Beth Israel Deaconess Medical Center, Harvard Medical School. His colleagues come from universities around Taiwan and

the United States, as well as from the studio engineering team at HTC. The team is noteworthy not just for its members' academic qualifications, but also because it's the only East Asian team participating in the competition.

To develop their tricorder, the team has divided into five groups – vitals, blood, breath, image and urine. Each group has incorporated technologies for signal analysis, image processing, biomarker detection, microfluidic engineering and biochip fabrication into their Smart subsystems: the Vital-Sense-Patch, Blood Sense, Exhaler, Scope and Urine Sense modules. Each one focuses on the interface between human and machine to allow consumers simple and intuitive use of the modules, which connect wirelessly to a smartphone app that carries out analysis and generates a disease diagnosis. Though much of DBG's technology is yet to be revealed, the group certainly has the credentials and motivation it needs to create an accessible healthcare solution.

*"When medical care is free in such a densely populated area as Taiwan, the demand on those resources is not only high, but growing."*




To be eligible for the Qualcomm Tricorder XPRIZE, devices must be able to diagnose 13 core set conditions and at least three elective conditions, as well as monitor five vital signs and upload data to the cloud.

## Team Danvantri

Danvantri is the name of the Hindu god of medicine and physician to the gods. He's also known as the deity who promoted Ayurveda, or "life knowledge," to the people of India – and team Danvantri is doing its best to live up to the name. Their goal is to give everyone on the planet access to their own and their family's vital health data, so that no one has to depend on a doctor unless medical treatment is truly necessary.

The team's offering for the Qualcomm Tricorder XPRIZE is a device called B.O.L.T., which features a base unit that connects to any mobile device as well as a set of accessories including a cuff for blood pressure measurements, an infrared thermometer for temperature, and a pulse oximeter for blood oxygen levels. Though this aspect of the device is currently awaiting clinical trials, Danvantri isn't resting on its laurels – the team is still working hard to integrate electrocardiography, spirometry, blood chemistry and glucose analysis. In keeping with their goal of bringing healthcare to the masses, B.O.L.T. has a simple-to-use interface featuring a "happiness meter" that interprets the wearer's vital statistics into a dial that ranges from "needs attention" to "all is well," with corresponding colors – so even users with no medical experience can understand their overall health and know when to take action. "Along with XPRIZE," says the team's leader, Sridharan Mani, "we hope to create a platform for everyone to stay healthy and fit independent of visits to clinics." B.O.L.T. isn't just for the home, though. Its small size allows it to be carried anywhere, and its wide variety of monitoring and diagnostic options make it a useful tool for clinicians and paramedics in rural areas

*"We hope to create a platform for everyone to stay healthy and fit independent of visits to clinics."*

where medical equipment may not be affordable or portable enough. The device also offers trend monitoring and graphical reporting based on mobile and cloud platforms, allowing users to get a health snapshot at any point, or to track the change in their general health status over time.

Danvantri team members have collectively logged over 200,000 man-hours working in embedded systems and IT – experience that serves them well in their attempts to develop a cost-effective device for preventative healthcare. "We want to make healthcare affordable and we want to make life easier for everyone," says the team's mission statement – and with the B.O.L.T. device already available for purchase in India, they're well on their way.

## Team Final Frontier Medical Devices

Final Frontier Medical Devices was formed specifically for the Qualcomm Tricorder XPRIZE by Basil Harris, an experienced emergency department physician with a doctorate in engineering. Harris' years in emergency medicine convinced him that the American healthcare system "is on an unsustainable course, rife with disjointed, uncoordinated care, added costs from unnecessary or duplicative medical testing, and little opportunity for patients to be meaningfully engaged in their own health." Harsh words, but ones that have had a motivating effect. Harris decided to fill the gap.

To do that, he and his teammates, all members of Basil Leaf Technologies (Paoli, PA, USA), are developing a portable device called DxtER (pronounced "Dexter") to relieve pressure on the healthcare system. "Once you strip away the action part of an ED – the trauma, hemorrhaging, and cardiac arrests," Basil Leaf Tech's website reads, "you are left with the other 90 percent of patients who may not have an 'emergency' or be in imminent danger, but are looking for a

timely diagnosis and a course of action. A surprising number of people today have nowhere else to get this help." DxtER is based on the same diagnostic processes used in clinical medicine, and is capable of identifying numerous medical conditions. The algorithms it uses were written with Harris' emergency department experience in mind, refined based on actual patient charts, and then verified in a matched case-control study that evaluated DxtER's ability to independently diagnose 16 different conditions. The next step? A prospective, multi-round, pilot clinical diagnostic trial in the emergency room itself.

*"Once you strip away the action part of an ED – the trauma, hemorrhaging, and cardiac arrests, you are left with the other 90 percent of patients who may not have an 'emergency' or be in imminent danger, but are looking for a timely diagnosis and a course of action."*

DxtER's creators include not only physicians, but also engineers, designers, health policy experts, and mobile technology and sensor professionals. The members of team Final Frontier believe that their tricorder will revolutionize the way healthcare is delivered – freeing up emergency departments for patients with truly critical needs and giving individual users the ability to take appropriate action on their own health. "Our company is at the forefront of a new era of consumer medical technology," says Harris. "An entirely new market is emerging that engages consumers and puts them in the driver's seat. Our device is smart and simple, giving people the help and answers they need when they need them the most."

## Team SCANurse

The seed of team SCANurse germinated when leader Anil Vaidya heard the announcement of the Qualcomm Tricorder XPRIZE. The details immediately resonated with Vaidya, a healthcare industry worker who says he's always wondered why these kinds of devices aren't already on the market. "From my point of view," he explains, "the health industry is split between biologists and people who are more of the engineering type. And there certainly seems to be a difference in our thought processes." Vaidya decided that it might possible to develop engineering solutions to make certain types of diagnoses – and the desire to satisfy that unmet need inspired him to become an XPRIZE participant.

Team SCANurse itself consists mainly of people Vaidya would categorize as "engineering types." With his biomedical background, he often finds himself speaking both languages – providing biological or chemical information to his technically minded colleagues. But translating the other way, from engineering back to biomedical science, is more difficult; Vaidya says, "Working with biologists and chemists who said it couldn't be done a certain way has always been frustrating." As a result, he's chosen to fill the limited slots available on his team with professionals in engineering, software and design. The core of the group is in London, where the actual tricorder build occurs – but because many of the team's experts live elsewhere, they spend a lot of time on the phone. The distance doesn't bother Vaidya though. "We're a very small team," he says, "so when we get funding, we use it to get the best people on board."

SCANurse's device was first conceived of when it occurred to Vaidya that many disease states can actually be diagnosed through a standard procedure – one he refers to

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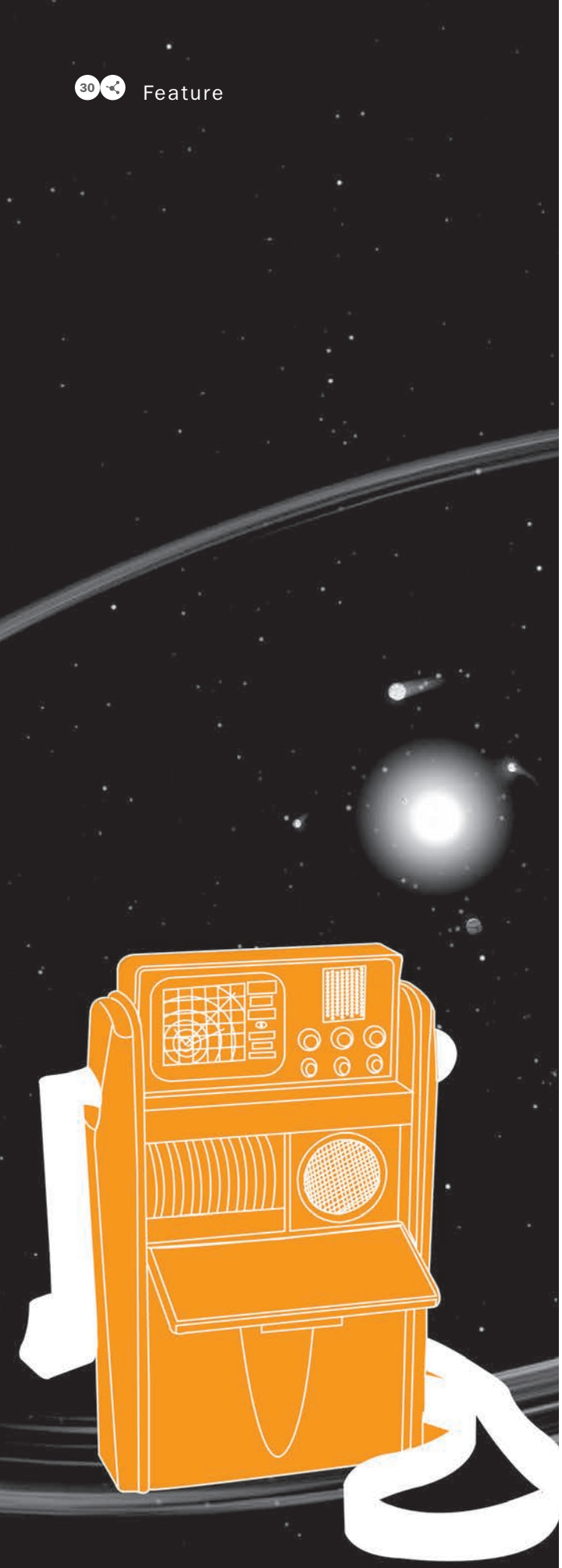

> *"The health industry is split between biologists and people who are more of the engineering type. And there certainly seems to be a difference in our thought processes."*

as a "pure engineering" solution. Though unable to share proprietary details, he explains, "We're using traditional types of technologies in optics, movement recognition and even sound. We're just using them in more novel ways." The key to their device is that it isn't an attempt to create a new gold standard for diagnostics – unlike many teams, SCANurse isn't looking at blood sampling for biomarkers because he feels that it's not very consumer-friendly. As a home service, they've decided that the tricorder should look at less invasive signals to indicate the likelihood that the user has a given medical condition. They're also pushing for good user interface design, using small field trials with device prototypes, so that they can incorporate the needs of their patient populations. In the end, SCANurse would like to create a tricorder that is not only painless, but also simple to operate.

That's the reason Vaidya thinks SCANurse was selected for the final stage of the competition – and the thing he hopes will set his team apart in the race to the top. "I think we just came up with a more novel solution," he says. "I like to think that because we're looking at it from both the design and the engineering way of doing things, that it gave us a bit of a boost. There are some amazing teams in the running for this, so I hope that what we've got places us in a slightly different league." But even if the XPRIZE results don't put SCANurse on top, their goals go beyond the competition; Vaidya hopes to find investors with the vision to see where the team's product is going. Ultimately, the team wants to see people taking control of their own health – and the tricorder can help them do that by changing the landscape of diagnostics.

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# The CAD Challenge

**Diagnosing coronary artery disease is not easy with current tools – especially in women – but a new blood test may be safer, easier and more reliable.**

*By Michael Schubert*

The concept that diseases can present differently in men and women is fast gaining traction, among doctors and in the general public. There are numerous articles and infographics circulating around the Internet that illustrate, for example, the difference between heart attack symptoms experienced by men and by women. But recently, a panel of experts from a wide variety of specialties – cardiology, medical technology, personalized medicine, women's health, patient advocacy, health economics and even payers – convened at the Heart House (Washington, DC, USA) to discuss a less publicized topic: the diagnosis of coronary artery disease (CAD) in women (1).

CAD and related disorders are the leading cause of morbidity and mortality in both sexes, but because women's symptoms are so variable and so different, diagnosis of such disorders in female patients is a real challenge. The expert panel determined that physicians have difficulty with diagnosis because women present with atypical symptoms and a lower probability of disease, have fatty tissue in the breast area that can lead to false positives in cardiac imaging, and women are more likely to present with difficult-to-identify microvascular CAD. The challenges to spotting CAD have historically meant that doctors rely on a progressive testing pathway that begins with noninvasive imaging for women deemed to be at low risk of disease, with more intensive examinations, such as invasive coronary angiography (ICA), in those at higher risk. But this ends in a testing catch-22: because of the diagnostic uncertainty of imaging procedures, women with a low likelihood of disease are being tested too much, exposing them to risks and complications – while those with a higher likelihood who get false negatives from imaging tests may never receive the more extensive examinations that would accurately indicate the presence of disease.

Much like the problem itself, the potential solution is multi-faceted; clinicians need improved understanding of sex-specific differences in the pathophysiology of CAD, whereas patients need to be aware of the differences between men's and women's symptoms. Health care providers – from doctors to payers – should be educated about the risks and benefits of imaging tests, and the when it might be necessary to perform additional tests. They should also be aware of new advances in CAD testing, and in particular new forms of genomic testing that can overcome the challenges of current methods. The expert panel also proposed that doctors incorporate a new age, sex and gene expression score (ASGES) assay into their evaluations of patients with potential obstructive CAD.

## Symptom conundrum

Although females constitute about half of the world's population, many more women than men die of heart disease each year – a trend that, at least in the United States, has been the case for the past 30 years (2). Although the risk of death from heart disease is greater than that of breast cancer for women at all ages, their risk of CAD becomes even greater as they undergo menopause, a factor that only increases concern for the nearly 650 million women in the world over 55 (3). Unfortunately, the gold standard of diagnostic testing – the progression from exercise electrocardiography and myocardial perfusion imaging to diagnostic catheterization – often results in false negative results or in unnecessary invasive procedures and the risks associated with them. It's clear that better testing methods are needed to exclude patients at low risk of cardiac disease from invasive tests, saving time and money and ensuring that the true root causes of their symptoms are investigated as soon as possible.

One reason women are so often overlooked is that the atypical symptoms of CAD are more subtle. For instance, many patients at risk of heart disease are taught to be aware of pain or pressure in the chest, neck, shoulder, arm, back or jaw. They're warned that they might experience a pounding or arrhythmic heartbeat, abdominal pain, nausea, dizziness and cold or clammy skin. But women's symptoms tend to be more difficult to recognize; while they might feel an unusual sensation or mild discomfort, it's typically not even accompanied by chest pain at all. Women

## *At a Glance*

- *Coronary artery disease (CAD) is more often overlooked in women than in men, due to differences in symptoms and disease characteristics*
- *Current imaging and catheterization tools can lead to overtesting in women at low risk and undertesting in women at higher risk for CAD*
- *Researchers have developed an algorithm that examines patients' age, sex and the expression of multiple CAD-associated genes*
- *The algorithm, called ASGES, has been clinically validated in multiple trials and appears to be more sensitive than the current testing gold standard*

with angina frequently report weakness, shortness of breath, fatigue, nausea or indigestion – but without chest pain, many don't realize that their symptoms are indicative of a cardiovascular issue. To add to the confusion, men experience a linear relationship between age and CAD prevalence, but in women, the onset of the disease is delayed until perimenopause, then accelerates to a similar rate as is seen in men. Even the biology of the disease is different – men more often present with atherosclerotic plaque, whereas women are more likely to have smaller arteries and fewer lesions, leading to frequent false positives in most common diagnostic tests for CAD.

## Solved with a blood test?

Knowing that the current CAD testing methods are all either risky or only moderately effective, a group of scientists from across the United States developed a minimally invasive blood test to reliably assess a patient's likelihood of obstructive CAD. The study involved two cohorts of case and control pairs matched for age and sex; the first cohort was taken from the Duke University CATHGEN registry, a retrospective blood repository, and the second from the PREDICT (Personalized Risk Evaluation and Diagnosis in the Coronary Tree) study of patients referred for coronary angiography. After the researchers applied microarray analysis to select genes for further investigation (based on a combination of statistical significance, biological relevance, and prior association with CAD), they performed RT-PCR on the 113 chosen genes and used them to develop an algorithm for CAD assessment. The final algorithm focuses on age, sex and the expression of 23 genes, 20 of which were determined to be CAD-associated and three of which serve as normalization genes (4).

Not only does the ASGES algorithm allow the reliable determination of obstructive CAD risk based only on a patient's age, sex, and a single whole blood draw, but it even highlights sex-specific differences in CAD-associated gene expression. Most of the genes involved in the test correlate with either the lymphocyte or the neutrophil fraction; those in the neutrophil fraction display strong expression differences – 95 percent of neutrophil genes were upregulated in men, whereas in women, 98 percent were downregulated. Findings like this reinforce gender-based differences in CAD pathophysiology and fit well with previous research, including the fact that increased granulocyte counts correlate with higher CAD risk in men, but not in women (5,6). The algorithm was validated in two large-scale studies, PREDICT and COMPASS (Coronary Obstruction Detection by Molecular Personalized Gene Expression) (7,8). In both, ASGES was an independent predictor of obstructive CAD in both males and females, with a higher sensitivity (89 percent) and negative predictive value (96 percent) than myocardial perfusion imaging for the detection of CAD. Now, over 1,000 patients have been examined using the algorithm, and the differences in referral rates for downstream testing have been significant, especially in women – not only are fewer patients sent for additional testing, thus lowering costs and reducing the risk of complications, but the rate of major cardiovascular events during follow-up is lower as well.

Diagnostics should provide doctors with reliable results that inform their clinical decisions and improve outcomes, ideally with minimal risk to the patient. But neither imaging nor catheterization meets those needs: in the case of CAD the former is too inconclusive, the latter too invasive, especially when applied to patients who are unlikely to have the disease. The requirement for a low-risk, high-return test is clear – and ASGES ticks many boxes. This is good news for anyone being evaluated for CAD, but nowhere are the benefits so clear as for women, who may finally have a test that meets their unique needs.

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# Big Data, Hidden Knowledge

**Novel mathematical tools show promise in predicting ovarian cancer patient survival and sensitivity to platinum-based chemotherapy.**

*By Fedra Pavlou*

Ovarian cancer is an unusually harsh form of cancer. Almost 80 percent of the patients diagnosed – about 50,000 annually in the US and Europe alone – are in advanced tumor stages at diagnosis, and most are expected to die within five years. The statistics already look gloomy, and they are compounded by the frightening fact that about 25 percent of primary ovarian cancer tumors are resistant to platinum-based chemotherapy, the first-line treatment for over 30 years now. And no pathology laboratory diagnostic exists that distinguishes between resistant and sensitive tumors before treatment. Not only has treatment remained largely unchanged for three decades, but so too has the diagnosis and prognosis of ovarian cancer. Until now, the best indicator for how a woman will fare and how her cancer should be treated, has been the tumor's stage at diagnosis.

*"Treatment remained largely unchanged for three decades, but so too has the diagnosis..."*

Orly Alter and her students at the University of Utah's Genomic Signal Processing Lab have been working on possible solutions to the problem of tumor assessment, by developing mathematical tools for interpreting interrelated datasets. They hope that their tools will improve understanding of cancer at the molecular level, and be the basis of personalized prognostic and diagnostic laboratory tests. One of their first disease targets: ovarian cancer.

"Our algorithms extend a mathematical technique called the singular value decomposition or SVD. The SVD helps us understand data arranged in two-dimensional tables, known as matrices, by breaking the data down into individual components. In physics, for example, the SVD describes the activity of a prism, which splits white light into its component colors," explains Alter, who has a PhD in applied physics. "So it seems natural to

## *At a Glance*

- *Most ovarian cancer cases are diagnosed in advanced stages, and no diagnostic exists that distinguishes tumors that are resistant to traditional chemotherapy from those that aren't*
- *A team based at the University of Utah have developed a mathematical tool that analyzes DNA profiles from the Cancer Genome Atlas to discover patterns of DNA anomalies*
- *Using this approach, they have been able to predict a woman's outcome significantly better than can be done with the tumor's stage; it is also the first known indicator of how well a woman will respond to platinum therapy*
- *These DNA patterns could be the basis of a personalized prognostic and diagnostic laboratory test. The researchers continue to assess the patterns in ovarian cancer and plan to expand their mathematical modeling to other tumor types*

me that generalizations of the SVD can separate the multidimensional data that arise in medicine into mathematical patterns that have biological meaning."

The team decided to try their most recent algorithm on ovarian cancer data, after they had successfully tested a previous algorithm on glioblastoma (GBM) data (1). Why ovarian cancer? "To be honest, simply because it was the next disease after GBM in the Cancer Genome Atlas [or TCGA, a US national database containing data from thousands of cancer patients]. It was only after we started our work in this area that we really appreciated why this type of ovarian cancer, ovarian serous cystadenocarcinoma, is one of the initial diseases to be studied by TCGA," Alter says.

## The value of patterns

Alter and her team develop algorithms to uncover patterns in datasets arranged in multidimensional tables, known as tensors (Figure 1). Rather than simplifying big data (a common approach), they have actually made use of the complex structure of the data to tease out the patterns within. So, for example, by modeling DNA profiles of tumor and normal cells from the same set of patients, they were able to separate the patterns of DNA anomalies – which occur only in tumor genomes – from those that occur in the genomes of normal cells in the body, and from variations caused by experimental inconsistencies.

According to Alter, their mathematical tools uncovered patterns of DNA anomalies that predict a woman's outcome significantly better than tumor stage (Figure 2) (2). "These patterns are the first known indicator of how well a patient will respond to platinum therapy," she says. "We found, for example, that among patients that were diagnosed at late stages, the DNA patterns distinguished about 60 percent short-term survivors, with a median survival time of three years, from about 10 percent long-term survivors, with a median survival time almost twice as long. Among patients treated with platinum-based chemotherapy drugs, the DNA patterns distinguished those with platinum-resistant tumors (about 55 percent), with a median survival time of three years, from those with platinum-sensitive tumors (about 15 percent), with a median survival time of more than seven years. We then computationally

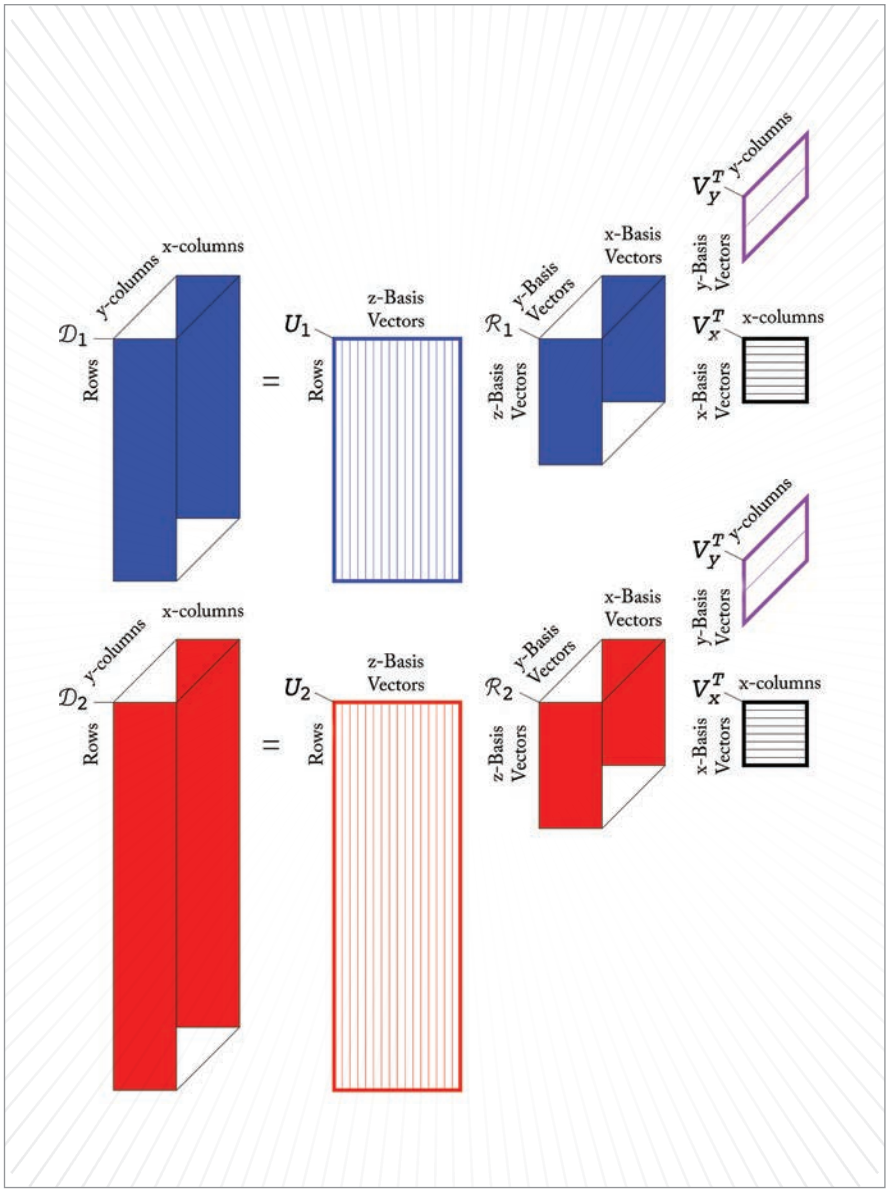


Figure 1. The tensor generalized SVD. Alter and her team develop algorithms to uncover patterns in datasets arranged in multidimensional tables, known as tensors. Rather than simplifying the big data, as is commonly done, the algorithms make use of the complexity of the data in order to tease out the patterns within them. Credit: Theodore E. Schomay and Orly Alter, University of Utah.

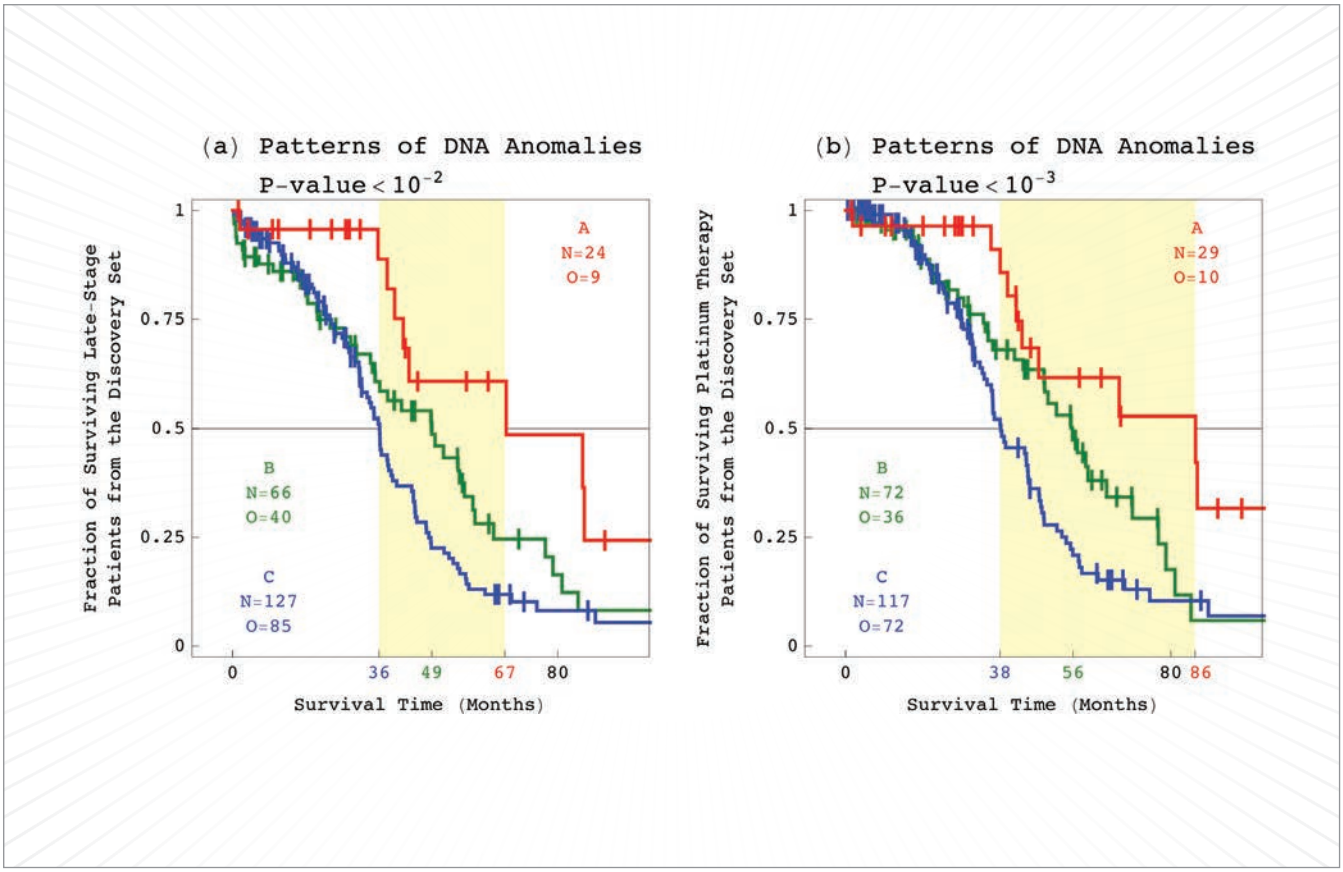


Figure 2. A personalized prognostic and diagnostic laboratory test for ovarian cancer would predict both the patient's survival and the tumor's sensitivity to platinum-based chemotherapy; doctors could tailor treatment accordingly. *Credit: Katherine A. Aiello and Orly Alter, University of Utah.*

validated the results by using data from independent sets of patients.

"Because these patterns link a tumor's genome with a patient's phenotype, they offer insights into the cancer's formation and growth. For example, one of the patterns points to a combination of genetic changes, the cellular function of which is similar to one that was shown by Robert Weinberg's lab at MIT to convert human normal cells to tumor cells" (3,4).

## What this means for patients

How does this translate into benefit for the patient? "Based on our results so far, we believe that our DNA patterns could be the basis of a personalized prognostic and diagnostic laboratory test, pending experimental revalidation in the clinic," Alter says. "This test would predict both the patient's survival and the tumor's sensitivity to platinum-based chemotherapy. Doctors could then tailor treatment accordingly."

The hope is that, for those with a poor prognosis, doctors can focus on taking measures to improve quality of life. For those with platinum-resistant tumors, doctors can suggest other appropriate, approved therapies. "Because no diagnostic currently exists that distinguishes between resistant and sensitive tumors before the treatment," says Alter, "these drugs can only be administered after the platinum-based treatment fails. A pathology laboratory test based upon the DNA patterns we uncovered would, therefore, eliminate a lot of unnecessary suffering and expense."

How would this work in practice? Alter explains, "The test would analyze DNA, which can be robustly measured from formalin-fixed paraffin-embedded [or FFPE] samples. We believe this is more reliable than pathology laboratory tests that depend on measuring such easily degradable biomarkers as RNA. The test can also be used with all existing, off-the-shelf platforms for measuring DNA profiles, such as DNA microarrays and next-generation sequencing."

*"This test would predict both the patient's survival and the tumor's sensitivity to platinum-based chemotherapy."*

The specific genes found to be perturbed could be the basis for drug therapies. Alter explains, "For example, some of the genes that we assessed during our research – the p21-encoding *CDKN1A* and the p38-encoding *MAPK14* on 6p, and *RAD51AP1* on 12p – are already known to interact with existing drugs, but were not recognized previously as targets for therapy in ovarian cancer. Pending clinical trials, these existing drugs may be found to benefit some of the patients."

## Next steps?

What direction will this research move in next? "First, we are working to translate our basic science to the clinic. To this end, we are setting up collaborations with medical doctors and pathologists to experimentally revalidate the patterns," says Alter.

"Second, we are working to develop prognostic and diagnostic tests for other cancers. Ultimately we plan to cover most cancers studied by TCGA and similar consortia, such as the International Cancer Genome Consortium. There are currently data available for at least 14 additional cancers at TCGA. In developing these tests, we plan to make use of data from the X chromosome," she adds.

The US National Human Genome Research Institute noted that fewer than 1 percent of genomic associations with a disease map to the X chromosome (5). This is because the X chromosome is regularly excluded from most genomic data analyses, such as the 2011 TCGA report on ovarian cancer. The normal female genome includes two copies of the X chromosome, whereas the male genome includes just one. Excluding the X chromosome removes the normal variation between the female and male patients from the data, but may also remove variations that are due to the differences among the tumors, which may be linked to variations among the disease outcomes.

"Our algorithms not only find patterns of DNA variation, but also tell us which patterns are exclusive to the tumors, and which are common to the normal and tumor genomes," explains Alter. "This means that we can separate the normal variation in the number of copies of the X chromosome, which is common to the normal and tumor genomes, from the tumor-exclusive patterns, which do not occur in the normal cells, while still including the X chromosome in the analyses. When the X chromosome is associated with a disease, our mathematical tools would be able to identify this association as a tumor-exclusive pattern that maps to the X chromosome. For example, analyzing the ovarian cancer data, one of the patterns of DNA anomalies we uncovered maps to the X chromosome, which is perhaps not surprising for this gynecological cancer, but would be missed by X chromosome-excluding analyses of the same data.

"Third, we are developing additional algorithms that extend the SVD to more than two datasets arranged in tensors. These algorithms will enable the comparison of more than just two cell types. For example, we could use these algorithms to model data from recurrent tumor cells together with data from primary tumor and normal cells. These models will identify not just what patterns are exclusive to the tumor cells, but also what patterns are similar and dissimilar between the primary and recurrent tumor cells," she says.

Alter has high hopes for these mathematical tools: "It may very well be that the data needed to better treat cancer are already published. The ovarian cancer data, for example, were published back in 2011. The bottleneck to discovery is in the analysis of the data, and we hope to have found a way to overcome the bottleneck and provide the means for improved prognostics, diagnostics and disease management."

*Orly Alter is associate professor of bioengineering, adjunct associate professor of human genetics, and faculty member of the Scientific Computing and Imaging Institute, University of Utah, US.*

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# Color Power for Cancer Management

**A new staining method could offer a noninvasive alternative to cystoscopy when monitoring bladder cancer.**

*By Yael Glickman*

With over 400,000 cases diagnosed annually, urinary bladder cancer is the most common malignancy of the urinary system. At any one time, there are 2.7 million people with a history of bladder cancer worldwide (1) – and with an up to 80 percent risk of recurrence, these people require lifelong surveillance, making bladder cancer one of the most expensive malignancies to manage (2).

As with most cancers, early detection is the key to improving outcomes – the five year survival rate decreases dramatically by over 95 percent for flat tumors, to five percent for distant ones (3). Today, cystoscopy remains the standard for diagnosis and monitoring, despite its invasiveness and high cost; patients with a history of bladder cancer undergo up to 14 cystoscopy exams in the five years following diagnosis. It therefore, goes without saying that there is a real demand for a noninvasive method, but current alternatives are less than ideal.

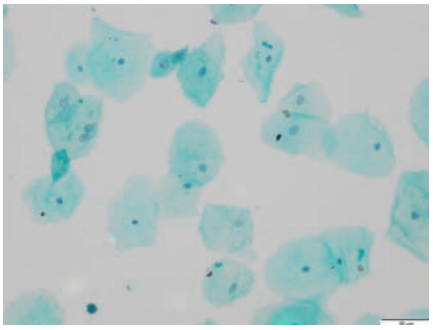
We have recently developed an approach which we believe enhances current noninvasive methods including urine cytology– that could greatly increase test sensitivity and offer a noninvasive alternative.

## Urine cytology, 70 years on

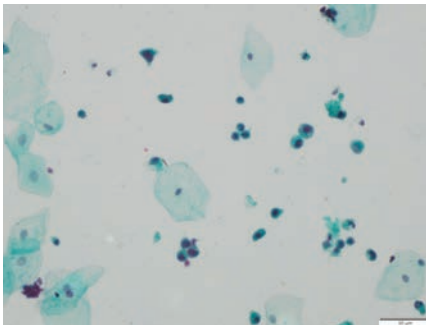
Currently, urine cytology is the established noninvasive method for detecting and monitoring bladder cancer. Following a report by Lambl et al. in 1856 describing the first use of exfoliative cytology for detection of cancer cells in urine, Papanicolaou and Marshall officially introduced urine cytology in the mid nineteen-forties. Since this landmark development, great advances in the preparation of urine specimens have been made, addressing the challenges caused by the small number of urothelial cells in the urine. Sedimentation flasks were rapidly replaced by centrifuges; cyto-centrifuges were later introduced, so too was the membrane-filter method, and more recently, liquid-based technology.

Many studies have reported the high specificity of urine cytology, and its significant clinical value when diagnosing high grade tumors. But the detection of low grade tumors remains an issue – the subtle morphological differences between reactive cell changes and low grade papillary carcinoma, among other factors, makes sensitivity a problem, and urine cytology has limited uses in patient management. This has led to the development of additional methods, including protein-based urinary markers, cytokeratin markers, and fluorescence in situ hybridization (FISH). However, none of these approaches have yet been widely integrated into routine patient management because of high cost, low accuracy, and/or high complexity. As

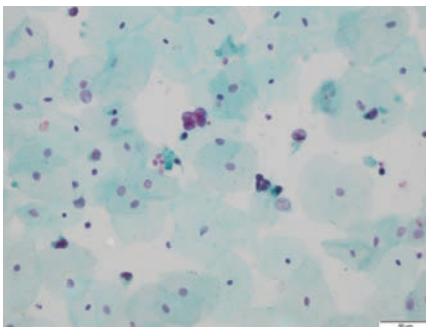
Figure 1. Different staining results found in non-cancerous and cancerous urothelial cells.



Urine, negative. 40x
Normal urothelial cells featuring green nuclei.



Urine, low grade. 40x
Low grade urothelial carcinoma cells with purple nuclei and high nucleus/cytoplasm ratio.



Urine, high grade. 40x
High grade urothelial carcinoma cells with purple nuclei and for which cytoplasm may not be observed.

### *At a Glance*

- *Current detection methods for bladder cancer are either invasive, or lack sensitivity for low-grade tumors*
- *New biomarkers have been identified but these can be expensive, or require complex testing techniques*
- *I describe a new staining approach that could complement urine cytology by highlighting cancerous cells while preserving cell morphology*
- *Noninvasive diagnosis and management could make screening feasible, particularly when combined with digital pathology methods*

well as the implications for existing patients, this means that bladder cancer screening, which could be beneficial for high-risk populations, is not currently possible, due to the lack of accurate and cost-effective biomarkers. So despite major developments, Papanicolaou's staining procedure is still the most common technique for the microscopic examination of exfoliated tumor cells obtained from urine or bladder washes.

## Sophisticated staining

I believe that the new staining platform developed by our team, in the form of a histochemical assay, could address the drawbacks of current methods.

How does it work? Using a proprietary plant extract and three generic dyes, the CellDetect stain colors the nuclei of neoplastic cells reddish-purple, while normal cells are counter-stained with green (Figure 1). The most likely theory is that this difference in color is caused by the change in energy metabolism found in cancer cells, which leads to a rise in cellular pH and a fall in extracellular pH. By also preserving the important morphological characteristics of cells, this technique can improve diagnostic performance and allow results to be obtained faster.

So far, this method has been validated for both cervical and bladder cancer diagnosis (4–6). Proof-of-concept has also been established for prostate and lung cancers, and circulating tumor cells. Using standard processes routinely used in pathology labs, the staining platform is applicable to both cyto-centrifugation

*"As well as improving manual detection of early stage tumors, it is hoped that the staining platform could also have applications in digital pathology."*

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and liquid-based technologies.

Tests of the staining method yielded promising results – an open-label study assessing the use of the stain found it showed superior sensitivity across all tumor grades when compared with standard urine cytology (4). A blinded, multicenter trial involving over 200 patients with a history of bladder cancer showed 84.7 percent sensitivity for early stage tumors: double the sensitivity of conventional staining (7). I believe this is because the method can further pinpoint suspicious cells, even at an early stage, and this can help cytopathologists to focus their morphological examination on these highlighted cells. As well as improving manual detection of early stage tumors, it is hoped that the staining platform could also have applications in digital pathology.

*"The method can further pinpoint suspicious cells, even at an early stage"*

## Enhancing digital screening

Digital pathology is driven by a need for improved workflow efficiency and reduced costs, and it is now used for gaining second opinions, training, archiving and sharing (8). Recent advances in the implementation of Whole Slide Imaging (WSI), combined with the development of increasingly sophisticated analytical tools, have paved the way for automated quantitative scoring of immunohistochemistry slides – for example, a recent US survey of 174 pathologists and labs using digital pathology found that HER2 scoring was the first use of digitalization, ahead of education and consultation (9). I think this use of automated image-analysis for the quantification of breast cancer biomarkers clearly demonstrates the eagerness of the pathology community to embrace new tools to assist clinical diagnosis.

In the field of cytopathology, automated tools have also seen success, particularly for cervical cancer screening. Two main approaches are currently used: the "primary screening system", which triages negative slides and identifies those that do not require further review; and the "interactive screening system", which pre-selects suspicious fields of view for review by the cytotechnologist. The analytical tools used in both systems, which mainly rely on morphologic changes associated with malignancy, could benefit from additional features that enhance diagnostic power.

The development of robust and accurate algorithms combining color and morphology may also motivate the implementation of further screening platforms. National screening programs already exist for breast, cervical and bowel cancers, and more recently, lung cancer in the US. Since prevention is recognized by the World Health Organization as the most cost-effective long-term strategy for the control of cancer, the development of reliable automated tools may support the creation of more screening programs in the future.

Although the staining method described here could potentially have a role in future screening programs, perhaps its most immediate advantage is its potential to improve manual analysis of urothelial cells. It's clear that more is needed to improve the diagnosis of bladder cancer, and I believe a reliable, noninvasive method for detecting cancerous cells has the potential to become an important component of bladder cancer diagnosis and management.

*After studying and training at the Weizmann Institute, Israel, and Tufts University, MA, USA, Yael embarked on a career in the field of medical devices, with a focus on the development of innovative technologies for cancer diagnosis. Recognizing the key role of pathology in cancer diagnosis and management, Yael recently joined the team at Micromedic Technologies, and is involved in the development of a cytopathology staining platform for early cancer detection.*

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"Sidi Abdelmoumen Saint's mausoleum near the city of Casablanca"
Description: Watercolor painting
Artist: Mariam Amrani, Rabat, Morocco

"CYCLADIC"
Description: Collage of digital histological and still images, printed on canvas and stretched on a wooden panel
Artist: Anna Batistatou, Ioannina, Greece

# The Beauty of Pathology

## Awaken the artist in you

Pathology and art – two disciplines which, to the lay person, may not seem to have much in common, but have an intrinsic link. Every day pathologists look at shapes and colors on slides. Aside from the very crucial diagnosis that this analysis delivers, it can also bring the artist out in a person, triggering a comparison of what they see through the microscope with a completely unrelated image or encouraging the picking up of a paintbrush. And it's happening all around the world; pathologists are enjoying sharing their artistic observations and stunning images. Just look at the #PathArt hashtag on Twitter and prepare to be amazed.

In recognition of the artistic splendor of pathology, the European Society of Pathology (ESP) has been running art exhibitions since 2013 to tempt the inner artist out of pathologists. The next exhibition, organized by Sanja Milenkovic, Anna Batistatou and Dina Tiniakos, known as Art Paths, is due to take place at the 27th European Congress of Pathology in Serbia (September 5–9, 2015, Belgrade). And the society wants you to get involved. If you fancy yourself a budding artist or photographer, here's your opportunity to show off that talent.

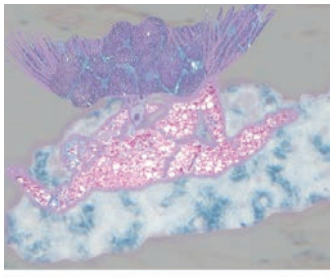
For entry submissions to be considered for the exhibition entitled "The soul of laboratory life", they must fall into one of two categories:

- Dynamic expression – exclusive photos that show every day, interesting, funny, unusual scenes of laboratory life, or facial expressions of people from the lab.
- Artistic expression – photos of creative works including oil, acrylic, pastel, watercolor, mixed media, collage, pencil drawings, computer-generated images, and other media in which we can see realistic or imaginary laboratory life.

Here we present a small collection of past exhibit entries.

*Interested? Go to www.esp-congress.org/virtual-exhibition to find out more. Good luck!*

"Poppy cells"
Description: Collage of digital images, printed on canvas and stretched on a wooden panel
Artist: Anna Batistatou, Ioannina, Greece



"Tityus-Esthetic Microscopic Transition EMT"
Description: Diptych including Michelangelo Buonarroti's "Tityus", artistic composition of histologic images of liver tissue, and watercolor
Artists: Dina Tiniakos, Newcastle upon Tyne, UK/Athens, Greece, and Maria Tiniakos, Athens, Greece

"House in Ioannina"
Description: Acrylics on collage of digital images, printed on canvas and stretched on a wooden panel
Artist: Anna Batistatou, Ioannina, Greece

# Partner Power

**Sitting Down With…**
**Mamar Gelaye,** Chief Executive Officer, Omnyx, LLC Pittsburgh, Pennsylvania, USA

What motivates you?

Because I grew up in academia, I think the intersection between it and clinical practice is an area where so much work needs to be done; we have more research and knowledge than we have efficacy and outcome.

For the pathology world, there is a tremendous shortage of new capacity and educational resources. The next generation of pathologists not only need to be adept in anatomical pathology but they need to be knowledgeable in molecular biology and genomics too. That's where new technology comes in; it's the platform of the future and that's what we as an industry are driving.

Can you explain the Omnyx ethos?

By design, we're an extremely entrepreneurial organization that's committed to transforming the industry. Our mission as a company is far more than developing digital pathology technology, it's about transposing knowledge into valuable clinical use.

Omnyx was formed through a joint venture between GE Healthcare and UPMC (University of Pittsburgh Medical Center). GE Healthcare, of course, has a tremendous lineage in invention. And we're fortunate to have UPMC – an impressive institution with vast pathology resources and a commitment to transform healthcare at its core. They're inventors. It's really inspiring to work with clinicians who not only do great patient care, but also want to spend time with software engineers inventing platforms. I consider it to be an honor to work with them.

Omnyx is the offspring of these two very formidable institutes and we're helping pathology transform. How? By focusing on three core factors: software (which must be a knowledge-driven platform that supports pathologists and strengthens their confidence in a diagnosis); scanning (technology that allows for rendering the same, if not better, standard of image that is used when looking through a microscope); change management (helping the human side of change so that pathologists believe the new capabilities are better than traditional methods and they help influence the choice of treatment options).

How do you deliver on your mission?

We do what we do as a company because patients deserve higher quality and predictability in healthcare. Partnership is integral to us and we're really excited about the work we're doing with our partners to take on this challenge. A good example is our collaboration with David Snead and Ian Cree at Coventry Warwickshire NHS Trust in the UK. The trust has created a Center of Excellence for digital pathology. It's a huge commitment on the part of the Trust, and it's driven by the desire to increase efficiency and quality across the UK National Health Service (NHS). I think we have a shared vision to establish research and care protocols that will support the transition from how pathology is practiced today to how it's utilized in the future.

More recently we've partnered with Clarient, part of the Life Science division at GE Healthcare. Clarient is one of the largest reference labs in the US and will soon use Omnyx digital technology to transform their pathology practice. This represents a multi-year alliance; we will work closely to invent, create and really bring to bear the kinds of software and inventions that will make a difference for clinicians.

We also work with institutions throughout the US, the UK, the Middle East and elsewhere. And I think that's one of the reasons our solutions are really compelling, because they're not singularly designed or influenced. That's one of the benefits of being a very small company owned by two larger companies – we can take more risk. And in fact it's incumbent on us to do those things that are really going to accelerate the industry.

So you don't consider Omnyx to be a traditional vendor?

No. We consider ourselves a partner. We like to collaborate with thought leaders and institutions that have the same vision we do. I think there's a tremendous amount of data, but not often insight. The ability to aggregate data is needed, but the ability to present insight to a clinician at the point of decision-making is crucial. This is what our technologies are working towards.

I think the challenges are pretty big with this, globally. As a pathologist's educational needs continue to grow, so too will the importance of networking and sharing expertise and knowledge. When you network practices together then it can create a harmonized ecosystem of skills that can support improved patient outcomes. Technology helps facilitates this.

What is your biggest challenge?

Our platform needs to demonstrate real value; its solutions need to be suitable for multiple business models in healthcare and that's a real opportunity for us. I seldom meet leaders of healthcare institutions that don't feel a sense of responsibility to make things better for the patient. But I think the gap between idea and execution of idea is the biggest challenge in healthcare.

We're a company that's not only visionary, we're also very active in piloting our ideas, working with customers, doing a proof-of-concept and seeing value. And then going from one small success to an even larger one. I think the hardest part is making that change happen and making it last – but when we put the patient's health first, I think collectively as an industry we can make an impact.

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