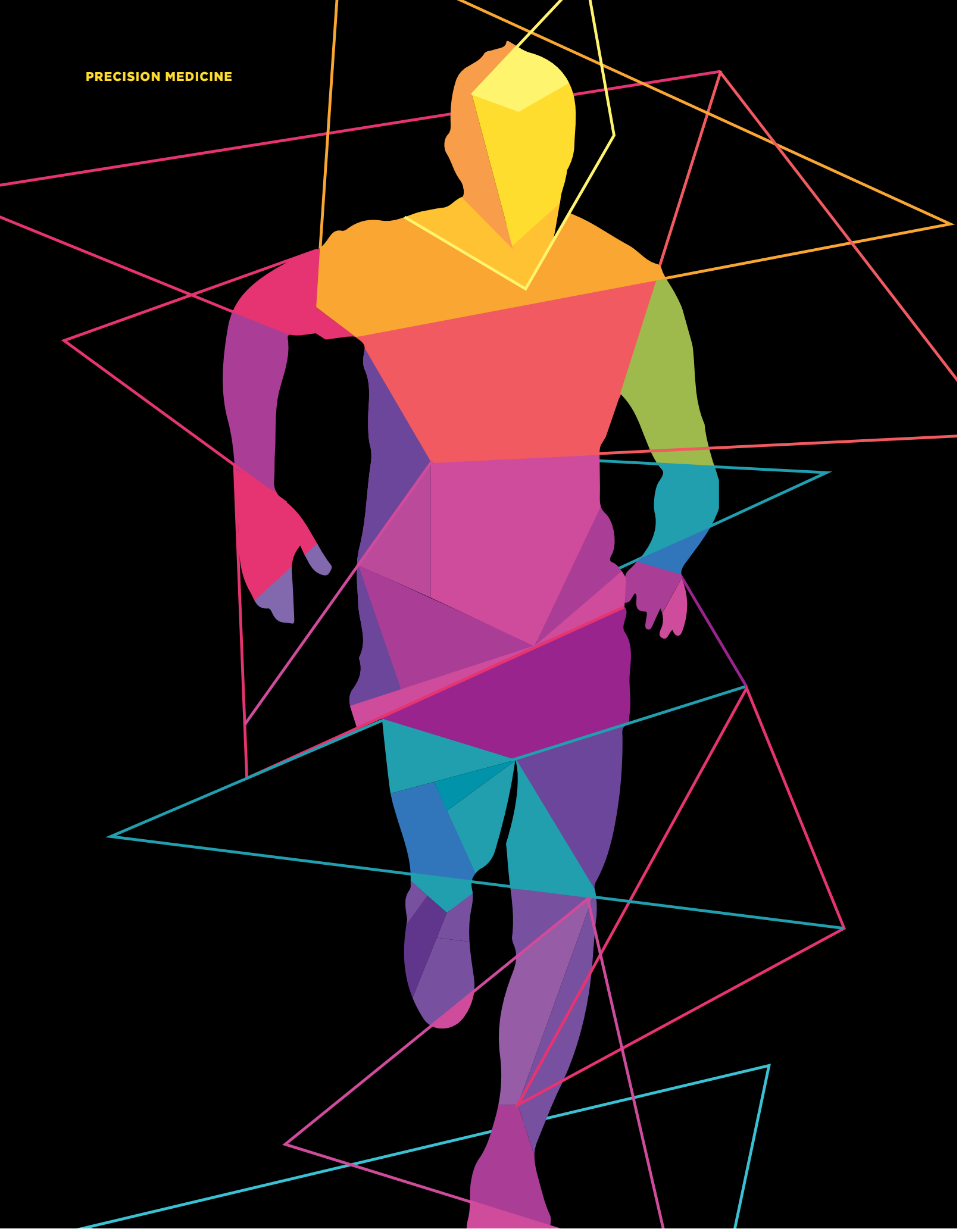

Precision Medicine

By Claudia S.Copeland, PhD

HARNESSING THE EXTRAORDINARY GROWTH IN MEDICAL DATA FOR PERSONALIZED DIAGNOSIS AND TREATMENT

If the prime mission of today's physician is medical decision-making, medical doctors are on the verge of a major upgrade in effectiveness. Advances in technology are bringing the worlds of bioinformatics, molecular biology, biochemistry, and medicine together to yield individual patient-based data as never seen before. From cancer recurrence risk to likely response to treatment, the era of using precise patient-based data to inform decision making is dawning. The potential of precision medicine extends well beyond genomics, however—future applications range from other "omics" data types, such as transcriptomics, proteomics, and metabolomics, to cutting-edge imaging technology. These advances can provide a wealth of information on individual patients and their illnesses. Together, they are laying the groundwork for a transformation in the dominant clinical paradigm: from general, illness-based medicine to patient-based, personalized medicine.

New Tools for Precision in Diagnosis and Treatment

To make effective clinical decisions, MDs can use laboratory tests, histories, and physical exams, but when it comes to difficult or unusual cases, finding the right diagnosis or treatment has traditionally been, in large part, a process of trial and error. A number of new tools are being developed to empower physicians to make more informed decisions up front, especially in the realm of complex, individual diseases like cancer. Some genomic assays are already mainstream, such as testing for BRCA genes. Several other approved genomic tests exist to classify different types of cancer based on tumor genetic profiles. Leading these are assays to distinguish different subtypes of breast cancer, such as estrogen receptor positive (the most common type of breast cancer, with a relatively good prognosis), progesterone receptor positive, HER2-positive, and triple negative. Of these, all but triple negative have specific treatments based on expressed genes. Even for subtypes that do not have individualized treatments, such as triple negative, knowledge of subtype is useful because it clearly establishes the importance of chemotherapy (in fact, some evidence suggests that chemotherapy is more effective in triple negative breast cancer than in hormone-receptor positive breast cancers) and other tailored treatment regimens, such as neoadjuvant therapy (chemotherapy before surgery).

Theoretically, tumor profiling based on gene expression could look at hundreds of genes in a tumor. While this level of precision would have been science fiction a few decades ago, it is currently in development and steadily marching forward towards approved clinical use. Already in wide use (and covered by most insurance and Medicare) is a gene expression assay known as the Oncotype Dx®To determine the chance of recurrence of breast cancer, the test analyzes the activity of 21 genes to yield a highly precise picture of the individual cancer the patient is suffering from, including the likelihood that the breast cancer will return and the likelihood of benefiting from chemotherapy at the early stage of the cancer. Based on the test results, the Oncotype DX assigns a Recurrence Score that reflects the likelihood of the cancer recurring. For example, for early stage invasive breast cancer, scores lower than 18 indicate a low risk of recurrence (suggesting that the benefit of chemotherapy is likely to be small and will not outweigh the risks of side effects); scores of 18-30 reflect an intermediate likelihood of recurrence (risk/benefit ratio unclear); and scores greater than 30 indicating a high risk of recurrence (benefits of chemotherapy likely outweigh

By The U.S. Food and Drug Administration (FDA_LaB_aTan Ta_2050) [Public domain], via Wikimedia Commons

risks of side effects). Another assay assesses the likelihood of benefiting from radiation therapy for ductal carcinoma in situ (DCIS), the most common type of non-invasive breast cancer.

As with all genomic tools, the results are an aid to diagnosis, along with other, more traditional factors such as tumor size and patient age. Other tailored genomic tests are also available, including the Breast Cancer Index test, used to predict the risk of node-negative, hormone-receptor-positive breast cancer coming back 5 to 10 years after diagnosis; the EndoPredict test, used to predict the risk of distant recurrence of early-stage, hormone-receptor-positive, HER2-negative breast cancer that is either node-negative or has up to three positive lymph nodes; the MammaPrint test, used to predict the risk of recurrence within 10 years after diagnosis of stage I or stage II breast cancer that is hormone-receptor-positive or hormone-receptor-negative; the Mammostrat test, used to predict the risk of recurrence of early-stage, hormone-receptor-positive breast cancer; and the Prosigna Breast Cancer Prognostic Gene Signature Assay (formerly called the PAM50 test), used in predicting the risk of recurrence for postmenopausal women within 10 years of diagnosis of early-stage, hormone-receptor positive cancer.

In addition to breast cancer, molecular testing is now a routine part of patient care for lung cancers, colorectal cancers, melanomas, leukemias, and others. In fact, Oncotype Dx tests similar to the ones for breast cancer have also been developed for two other cancer types: colon cancer and prostate cancer. The Oncotype DX® Colon Cancer Assay analyzes the expression of 12 genes in a sample of colon tumor tissue to quantify recurrence risk. The Oncotype DX Prostate Cancer Test measures the amount of RNA expressed by 17 genes predictive of risk and probable treatment response. Such a test may be especially helpful for this type of cancer, since aggressive treatment can lead to sexual, bowel, and bladder side effects that are highly distressing for patients. An assay that can identify men who can safely forgo aggressive treatment in favor of a program of active surveillance and monitoring over time can radically improve the quality of life for these patients.

The CDC lists over 90 genomic tests

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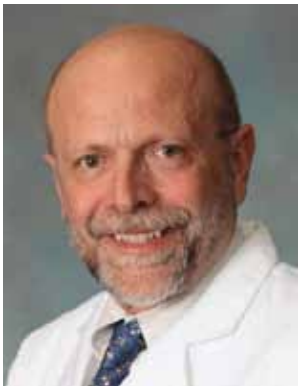
THE GENOMIC ACCESS PROGRAM

In order to assist with verifying insurance coverage and obtaining reimbursement, Genomic Health, the makers of the Oncotype Dx assay, offer a program called the Genomic Access Program. If you do not have or cannot secure insurance coverage, the Genomic Access Program may be able to help. Various forms of financial assistance and payment plans are available for people facing financial hardships or those who are uninsured or underinsured. The Oncotype DX test costs about $4,000. For insurance- and payment-related questions, call 1-866-ONCOTYPE (1-866-662-6897).

Dr. Miele believes that "a critical element in the use of precision medicine is clear clinical guidance for health care providers, patients and patient families."



Dr. Lucio Miele

with Tier 2 approval (FDA label mentions biomarkers; Medicare/Medicaid coverage with evidence development; clinical practice guidelines and systematic review either support use of the test or do not discourage use of the test). These include prognostic, preventative, or diagnostic tests for several diseases, including prostate cancer, non-small cell lung cancer, acute myeloid leukemia, colorectal cancer, single gene disorders, and rare familial diseases. There are also Tier 2 pharmacogenomic tests, to predict drug response for a wide array of conditions, from arthritis and bronchitis to insomnia and depression.

Dr. Lucio Miele, head of the LSU School of Medicine Department of Genetics, described some of the genomic techniques currently being used at LSU: "We use primarily exome panels and gene expression tests. Exome panels are used in several settings (congenital disorders subject to "diagnostic odysseys", neurology, and oncology). Gene expression tests are routinely used in the management of breast cancer and are being expanded to other indications. Specifically in oncology, we are currently enrolling patients in the MATCH clinical trial, a large NCI-funded study which assigns patients to one of 24 different treatment arms depending on the results of a genomic panel. Additionally, we will soon offer pharmacogenomics testing, to determine how the genetic makeup of specific patients affects the way their bodies handle different medications."

Small Companies: The Vanguard of Clinical Genomics

New tests are being developed every day, and many are moving towards approval. Meanwhile, though, several small companies are moving forward with genetic tests that have not yet gone through the clinical approval process, with results given to the physician in the form of a "research report" rather than a "clinical report". It is made clear to both the patient and the physician that this is NOT a clinical lab report, but the physician can use the information as supplementary data; it is up to the physician to evaluate what can or cannot be concluded from the data. Dr. Ayyamperumal Jeyaprakash is Chief Research Officer of NCF Diagnostics and DNA Technologies in Gainesville, Florida, a company that has designed several proprietary gene tests to detect mutations linked to heritable diseases. Dr. Jeyaprakash, who uses next generation sequencing (NGS, the powerful sequencing technique that is enabling affordable whole-genome sequencing) for screening crop plants for plant pathogens, explains that NGS testing for human diseases is still in the research stage. Some companies are doing it, but since it is considered research data, insurance companies will not pay for it. Instead, the current focus in human disease is on more specific tests.

Getting approval for a clinical test is a highly standardized process that is quite different from that of developing a scientific technique, Dr. Jeyaprakash explains. "I will describe a test that I designed. First, the lab needs to be approved by the Board. They come and check that you have got all the equipment and facilities. Then the lab workers need to get licensed to handle DNA. Without a molecular biology license you cannot work in the clinical lab. A PCR, Real-Time PCR, and Sanger Sequencing assay was designed to detect one mutation in the prothrombin gene (G21210A). If a G [has been mutated] to A in this gene, the patient is identified as positive for venous thrombosis or heart disease. The NIH has spent a lot of money and found out that this mutation is very important in humans. They do not even look at other mutations in this gene. My real-time PCR test is then tried on 20-40 patients. The same patients are also tested by another well-known DNA test like PCR-RFLP. If the tests are 100% matching, then I receive 6 blind samples from the Medical Board every 6 months. My real-time PCR test should pass every 6 months and score 100%. After this, I am allowed to sell the test. Patients can send samples only through the doctor. I do the testing, generate a 'Clinical Report' and pass it on to the doctor. He can now treat the patient using this information. I now have Heart Disease Gene tests and Drug Sensitivity Gene tests."

DNA is not the only biological sequence data with clinical potential. Beyond genomics lies the analytical potential of transcriptomics (RNA sequence analysis), proteomics (amino acid sequence analysis), metabolomics (analysis of small-molecule metabolites), and other "omics" analyses. New Orleans-based Pine Biotech is developing a platform to provide a user-friendly interface for non-bioinformatician biologists and clinicians to harness the power of multi-omics analysis. "Collectively, we have been investing time and money into understanding the molecular machinery inside every cell," states CEO Elia Brodsky,

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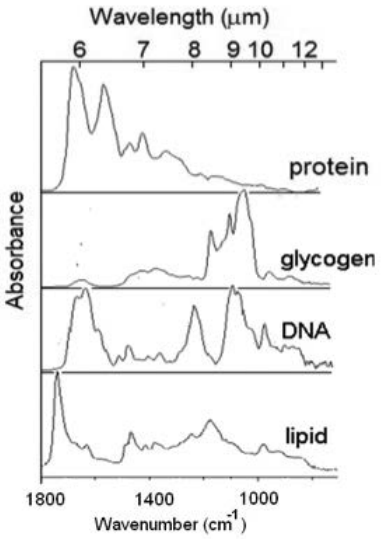
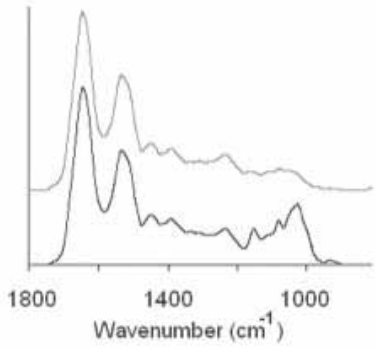
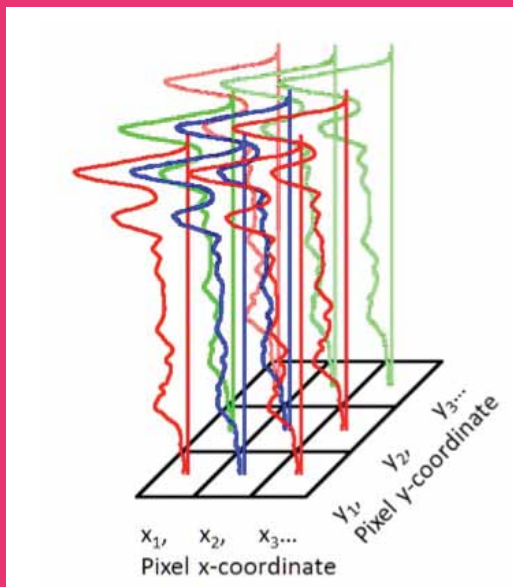




LEFT Infrared absorption spectra of typical constituents of cells and tissue.
ABOVE Examples of two pixel spectra of liver tissue. The top represents a spectrum of diseased liver, whereas the bottom spectrum is from normal liver tissue. The two spectra differ mostly in the glycogen content.



"Researchers now know that the complex network of relationships between genetic code, proteins and intra-cellular communication holds the key to solving some of the most pressing challenges in healthcare - from cancer to chronic diseases, to infectious diseases. This data can be captured on an individual level and analyzed for previously undetectable irregularities." His vision is to "enable researchers and clinicians to extract real insight from omics data; we hope that new and more effective approaches to diagnostics and therapeutics will be developed. Eventually, the efficiency of early detection and new targeted therapeutics will translate into longer, healthier lives for patients, with fewer side effects and cheaper treatments or even completely new ways to manage disease."

The view from LSU dovetails with Pine's mission of providing user friendly tools and support for omics analyses. Emphasizing the role of guidance and accessibility in the adoption of precision medicine tools, Dr. Miele believes that "a critical element in the use of precision medicine is clear clinical guidance for health care providers, patients and patient families. The role of certified genetics counselors in this process is critical. Provider education is equally important. LSUHSC will organize CME events focused on precision medicine, beginning in the spring of 2017. Precision medicine is the way of the future, and we need to keep accumulating data to refine our predictive algorithms and clinical guidance. Additionally, the incorporation of genomic/multi-omic data into electronic health records in ways that are easily accessible for analysis (as opposed to reports in PDF format) is a fundamental need for clinical use of genomics. The data science aspect is the most crucial one, and requires close interactions between clinicians, geneticists, bioinformaticians and biostatisticians."

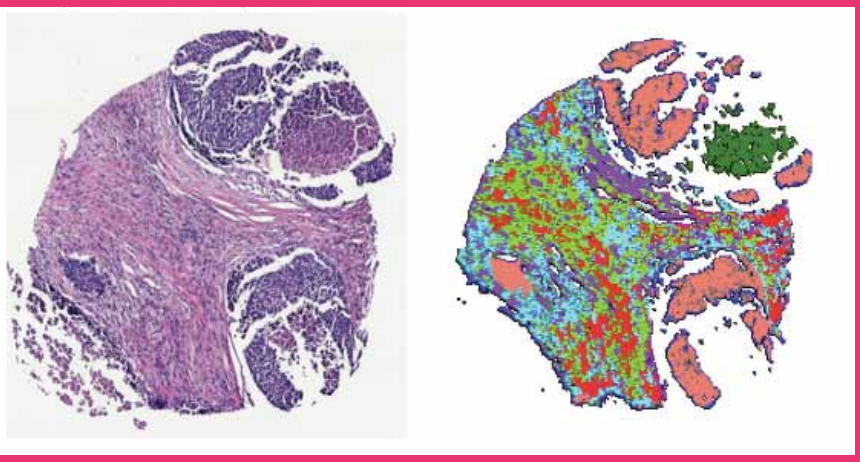
Visualizing Tissue Biochemistry

Sequence data are not the only type of patient information used in precision medicine. One particularly innovative approach to diagnosis is being developed by Cireca Theranostics, LLC. Cireca combines biochemistry, infrared spectroscopy, and imaging technology with powerful software to develop images from histological slides–images of things the human eye can't see. Chemists have long used light shone on or through a sample to determine characteristics of chemicals. By looking at specific wavelengths of light absorbed or reflected by a sample, functional groups and other characteristics of the chemical can be determined. For example, proteins will have a different infrared spectroscopy "signature" from those of lipids, fats, and carbohydrates. At Cireca, they work with this basic principle to determine key biochemical characteristics of tissue samples; most notably, characteristics associated with cancer tissue. Key to the technique, known as infrared spectral histopathology, is the fact that cancer tissue differs from normal tissue on a biochemical level, and these differences can be visualized using spectroscopy-based imagery. Using this technique has an additional advantage: none of the sample needs to be destroyed to run the test; light is simply shone through the histopathology slides, leaving the samples unaltered and available for any other analysis.

Bioinformatic analysis of the spectroscopy data is essential to the technique, explain Cireca scientists Max Diem and Aysegul Ergin. Infrared spectral imaging is carried out on 5 mm-thick tissue sections measuring from a few mm2 to cm2 in area. The slide image is then divided into pixels

LEFT For spectral imaging, 100,000 to millions of infrared spectra are collected from pixels ca. 5 µm on the edge of the tissue sample. The pixel size is about the size of the nucleus of a cell. These spectra constitute a "hyperspectral datacube" shown at left. Here, each pixel spectrum is defined by the x and y coordinate of the pixel from which the spectrum was collected. The protein and glycogen peaks in this datacube are clearly detectable.

RIGHT Infrared spectral imaging allows the rich infrared spectral signatures of biological compounds to be exploited. Here, a section of tissue was stained using the classical H&E stain, and imaged using a standard microscope (left). The right image represents the infrared-based pseudocolor (SHP) image from the same tissue, obtained using the Cireca methodology. The structures detectable by a pathologist in the left image correspond very closely to the features in the right image.



Dr. Ayyamperumal Jeyaprakash

Dr. Aysegul Ergin

of about 5 mm square, which represent a cube with all edges 5 mm in length. Within each of these pixels, between 100,000 and several million infrared spectra are collected. Collectively, these spectra constitute a "hyperspectral datacube". Powerful computational technology then assembles this massive amount of imaging data and either uses it for machine learning analysis or transforms it into a color representation, called a "pseudo-color image", with all similar spectra assigned the same color. Looking at such an image side-by-side with a normal H&E stained histopathology image, they clearly represent the same sample, with the H&E image showing the morphology of the tissue and the Cireca image visualizing the biochemical nature of the tissue. Essentially, this allows a pathologist to look at the cells in a tissue sample "inside and out", with a level of precision far surpassing anything possible with a conventional image.

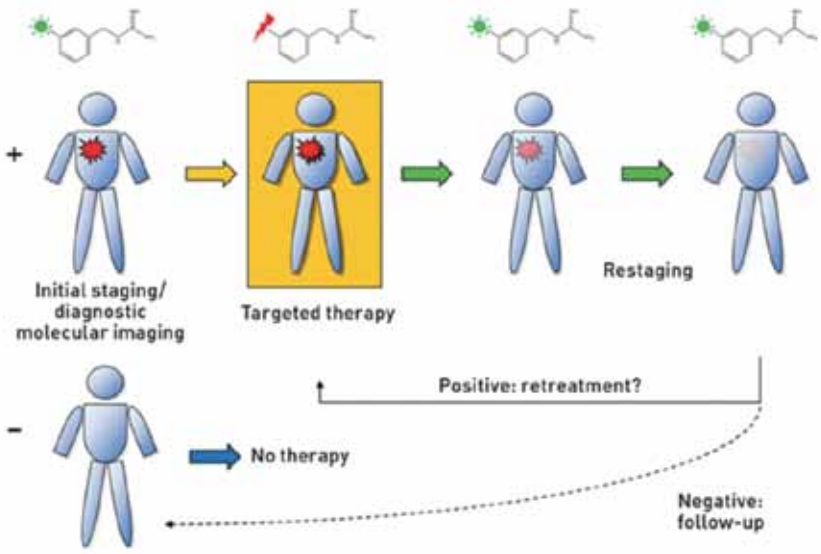
Cireca's goal is to enable pathologists and oncologists to gain a highly precise picture of a biopsy sample. "Patients want to know exactly what type of cancer they have, they need to know this," Stan Remiszewski, Vice President of Research & Development at Cireca, explains. "Oncologists want to prescribe therapies with precision and target tumors with the most effective therapy, but they first must know as much as possible about the cancer cells and tumors they are facing. It's essential to know more than we do today to improve the chances for every patient having this terrible disease." The data Cireca provides, he continues, could be particularly useful for both early detection of cancer and late-disease precision treatment planning. "We bring new information in the form of a biochemical signature of the tumor cells and microenvironment, working with very small samples that are otherwise not useable with conventional methods for diagnosis. We think this will add precision where its needed: early in the disease cycle, and when it's so advanced that surgery isn't possible and the remaining hope is well-targeted therapy [based on] as much information as possible."

Visualizing Drugs in the Human Body

In another perspective on "inside-out" imaging, Vyripharm Biopharmaceuticals of Houston is focused on personalized medicine via real-time visualization of drug metabolism. Vyripharm is developing drugs with

Dr. Elias Jackson

chemical markers that allow them to be visualized as they move through the body, using standard clinical imaging methods such as PET, CT, or MRI. Using this technology, doctors can make precise, personalized decisions about optimal dose and which drug will work best in that particular patient, President of Research and Development Elias Jackson explains. To visualize the action of a drug–uptake, metabolism, etc.–in the patient, Vyripharm uses "a chelator-based technology that allows us to add a metal to the drug that will allow for an imaging of the drug in the actual patient's body." So, in a hypothetical clinical use, "in the beginning, the patient will come in and the physician will do the imaging with the medication, to calculate the correct dosage with the patient--see how much is being taken up by the body. Based on that, the physician will determine how much to put the patient on. Depending on the patient, the doctor may monitor him or her, giving the drug with the imaging agent [as treatment]. The patient would come in at the end of each week and we'll take an image, or they could just come in at lunch and take an image. If everything's great, they can just move forward with the medication." If not, though, the doctor has gained power in a few major ways: first, he or she can see what is happening with the drug and decide on the next drug to try based on individual patient characteristics; for example, the drug may not localize well to the target organ in this patient. Second, it saves the time involved in a watch-and-wait process of trying a drug, seeing if it works, and if not, trying a different drug, etc. While payers are interested in this because saving time and testing means saving money, the value goes well beyond simple efficiency–time wasted can mean progression of a disease and unnecessary patient suffering.



Perhaps most importantly, though, this imaging technology enables precision dosing, and that can save lives. "Individuals respond differently to different drugs," emphasizes Dr. Jackson, "there are a lot of deaths and serious adverse effects surrounding the misdosing of drugs. It's terrible that physicians have to deal with that since their goal is to help patients." Getting the dose right can save lives before a drug even gets to the doctor's office. Precise dosing in clinical trials could allow effective, life-saving drugs to be approved that would not have been approved otherwise. "There are drugs that have had potential, but there was no way to determine the correct dose. Many drugs haven't made it to the market because of adverse effects; they couldn't get the right dose." While many important traditional drugs, such as morphine, have narrow therapeutic index ranges, a new drug with a low therapeutic index will most probably not be approved, no matter how effective it may be. "A dose of 10 mg may be good for some people, but fatal for others. It may be effective, but that therapeutic window might be so narrow that 5 people in the trial die. Now [using drug imaging technology] we can avoid those fatalities."

Dr. Jackson can't emphasize the importance of precision dosing enough. He pauses after telling of volunteers who suffered severe neurological injury (one of them died) in a clinical trial in France. The dose in the hospitalized volunteers was 40X the clinical dose, and this high dose overwhelmed the elimination mechanisms in their bodies. Had dosing been done with more precision, accumulation would have been detected early, the volunteers would have been taken off the drug, and the drug might be available today, albeit with an overdose warning. "If our technology had been used, the correct doses for those drugs would have been used, saving those patients. It's basically a game-changer." ■