

Medical Solutions

Oncology Special Edition

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Routine

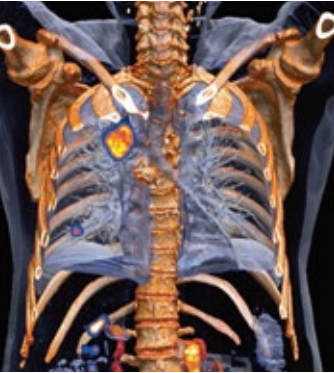
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Improving Cancer Care

Improving Cancer Care



Lung cancer remains the most frequent cancer worldwide. There were more than 1.8 million new cases (13% of total cancer incidence) and almost 1.6 million deaths (20% of total cancer mortality), as estimated in 2012.[6] Lung cancer is one of the most aggressive human cancers, with a 5-year overall survival of 10–15%.[7]

Cover image courtesy of University of Michigan, Ann Arbor, MI, USA

Oncology care is becoming increasingly relevant for healthcare organizations and professionals. Overall cancer rates are increasing due to rising life expectancy and growing populations. In 2030, more than 21 million men and women worldwide could develop cancer – 50% more than in 2012.[1] But not only the number of new diagnoses is steadily increasing, in the U.S. the number of people living five years after being diagnosed increased from 48.9 to 68.3% between 1975 and 2015.[2] In 2012, 32.6 million people were diagnosed with cancer worldwide.[3]

Because of the exponential growth in the number of patients and the related costs, it's key to identify advances tailored to improve care and patient outcomes. This special oncology issue of Medical Solutions aims to illustrate several of these approaches. The first section of the issue explores how liquid biopsies are starting to transform the clinical routine and how to utilize the rapidly growing genomic data. A deeper understanding of molecular heterogeneity and the evolution of tumors, in particular, has opened the door for personalized cancer care. The molecular dynamics of lung cancer, for example, can be tracked using genetic signatures in the blood.[4]

The second section focuses on new screening approaches. In certain cases, early detection

and early intervention can be the only way to avoid a manifest disease.[5] Breast cancer screening has become internationally established, despite many controversies, and is currently being further developed using methods such as tomosynthesis, whereas lung cancer screening using low-dose CT still has to pass long-term testing in the field.

The third section shows, among other things, the transformation of surgery using advanced image guidance and hybrid ORs and offers an outlook for future cancer care. Drug, interventional, and surgical treatment methods are constantly in flux. The care of cancer patients may become more and more individualized, but it will also become more interdisciplinary and increasingly less invasive.

Major opportunities and challenges await clinicians for improving outcomes in patients with looming or existing cancers. Healthcare organizations and researchers around the world will be challenged because the wide variety of different cancers, each one demanding novel solutions on prevention and early detection, as well as innovative treatment methods. The need for an interdisciplinary exchange of ideas worldwide regarding cancer diagnosis and treatment is already more important than ever.

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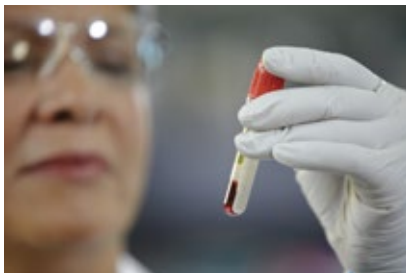
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Bringing Cancer Genome Diagnostics into Clinical Routine

How to quickly and reliably analyze the molecular tumor profile of individual patients.

Text: Martin Lindner

Growth in the field of cancer genomics has created a dramatic shift toward demand for personalized tumor diagnostics in routine settings. Today, patients are eligible to receive individualized therapy options tailored to fit their genetic tumor profile, based on a single blood withdrawal or tumor sample.

Precision medicine promises thorough, genome-based tumor evaluations which can then provide treatment options tailored to the patient's genetic profile.[1] The aim of this approach is to treat patients with targeted drugs known to have fewer side effects than conventional chemotherapy. The popularity of efficient and highly individualized therapy has, in turn, created an increasing demand for cancer genomics to be integrated into routine clinical settings.

Tackling Tumor-specific Mutations

Well-known examples include the use of specific antibodies to target breast cancer. In up to 20% of breast cancer patients, a faulty HER2 gene makes multiple copies of itself, thereby leading to an abundance of HER2 protein, which in turn results in aggressive cancer growth. Currently, breast cancer patients are routinely tested for their HER2 protein status to identify individuals who would benefit from therapies targeting the protein. A HER2-positive patient is then treated with an antibody to block the protein's activity. Statistics have shown that patients treated with HER2-targeted therapies had a five-year survival rate of over 85%.[2]

Targeted drugs have long been available for several tumor types.[3] For the most common type of lung cancer, non-small cell lung carcinoma, it is considered the diagnostic standard to screen for changes in EGFR and ALK genes. Mutations in both genes are known tumor drivers in lung cancer, with 10% to 35% of all patients harboring a mutation in the EGFR gene, and up to 5% of all patients having an altered version of the ALK gene.[4] Thus, the life expectancy of a patient with a proven alteration in either gene can be substantially prolonged using targeted agents.[5]

challenges. For example, clinically relevant genetic alterations can be detected even in small tumor samples using powerful high-throughput sequencing technologies, such as gene panels enriched for cancer-relevant genes. This process is called “hybrid capture-based next-generation sequencing.” The key is that this method can detect various genomic alterations – from simple point mutations to complex structural alterations, such as gene fusions or amplifications/deletions – using a single test and thus significantly reducing analysis and material costs.[8]

Diagnostic Challenges in Clinical Practice

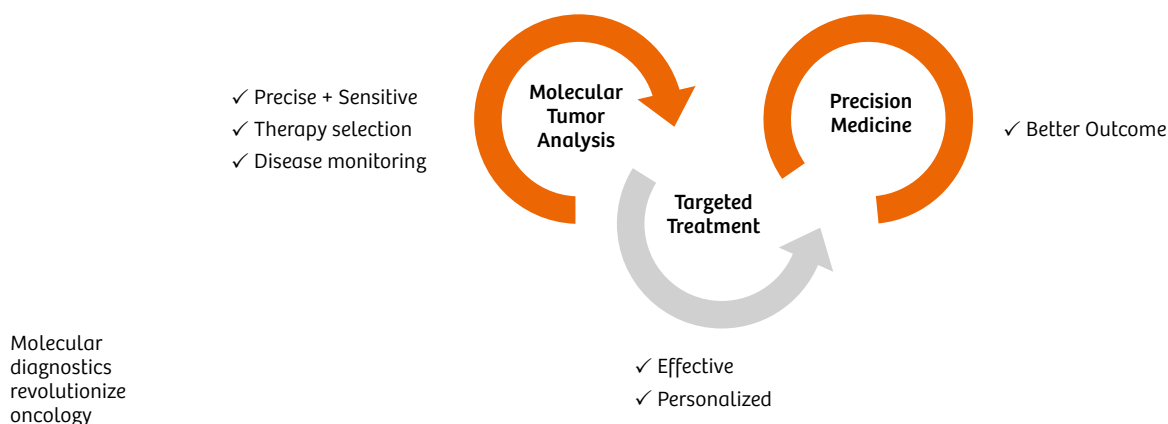
With advances in cancer research, the understanding of molecular cancer mechanisms will continue to grow rapidly in the future, thereby raising the question of how this knowledge can be incorporated into a clinical setting.[6]

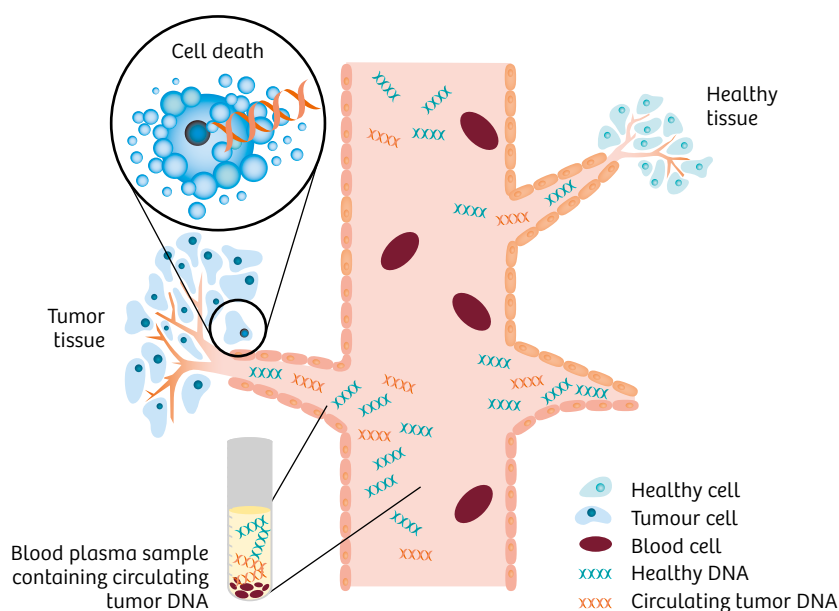
The present challenges being faced in routine testing centers require researchers to keep abreast of recent developments in order to thoroughly test patient samples. The need to perform multiple tests can lead to extended turnaround times, which in turn delay patient treatment. Furthermore, the limited availability of tissue samples poses a predicament for doctors, especially if several tests are needed for a comprehensive diagnosis.[7]

However, various technological developments in the past few years can help overcome these

Liquid Biopsies Support Therapeutic Decision-making

One of the most appealing prospects of the hybrid capture-based next-generation sequencing assay is that it can be performed not only on tumor tissue, but also using a blood sample, in what is known as a “liquid biopsy.” Tumors continuously release tumor cells and fragments of their DNA (circulating DNA) into the bloodstream. These are captured and sequenced to create a patient’s tumor molecular profile.[9] Liquid biopsies offer several advantages. Unlike tissue biopsies, blood sampling presents very little risk to patients and can easily be repeated when necessary. Additionally, liquid biopsies are a diagnostic alternative when the location of a tumor cannot be accurately determined or when a tissue biopsy cannot be performed.





Extraction and analysis of circulating tumor DNA from blood samples

Tumor as well as healthy cells release DNA into the blood whilst undergoing cell death. The circulating tumor DNA can be extracted from a blood sample for subsequent analysis. Using hybridcapture based next generation sequencing methods, all kinds of therapeutically relevant alterations – from simple point mutations to complex structural changes such as gene fusions – can be detected and quantified. The resulting molecular tumor profile provides information to control treatment efficacy and to observe emergence of possible resistance mechanisms.

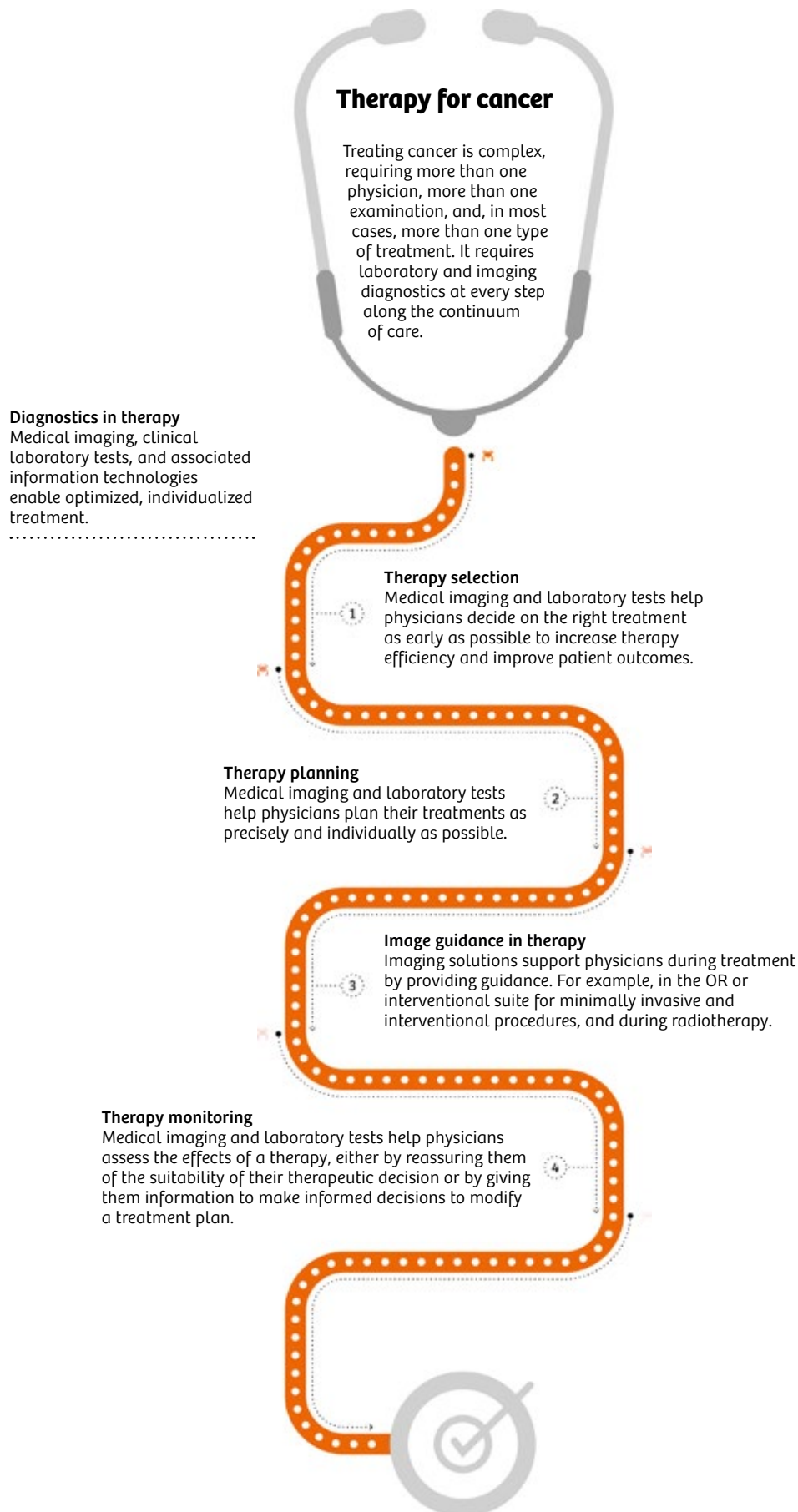
Reference: Graphic modified from Crowley et al, Nat Rev Clin Onc, 2013

Liquid biopsies are not expected to replace established tissue analyses and imaging methods in the future. However, the method is a promising addition, especially for monitoring progress and the effectiveness of a therapy. It is, therefore, now possible to use circulating tumor DNA to verify treatment success[10] and detect resistance to drugs in the blood at an early stage.[11] A recent case report shows how

valuable this is for the therapeutic decision-making process. A liquid biopsy from a lung cancer patient revealed that the tumor had become resistant to a previously effective cancer drug, but would respond to a newer drug in the same drug class. Switching therapies quickly shrank the tumor and significantly improved the patient's condition.[12] ●

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Drugs and Diagnostics Make Good Companions for Patient Outcomes

Doctors increasingly pair therapies with customized tests that enable proper patient selection or predict a patient's response

Text: Catherine Shaffer

Traditionally, diagnosis and treatment of disease have been separate procedures, with the choice of treatment being the therapy that has provided the best benefit for the most people. Increased understanding of tumor biology as well as advances in molecular diagnostics and imaging, however, have made it possible to personalize therapy, giving doctors powerful tools to choose the best therapy for an individual patient from a range of options. Increasingly, drug therapies are being paired with customized diagnostic tests known as

companion diagnostics. These tests enable proper selection of patients for a specific drug therapy and thereby help to improve the overall therapeutic efficiency.

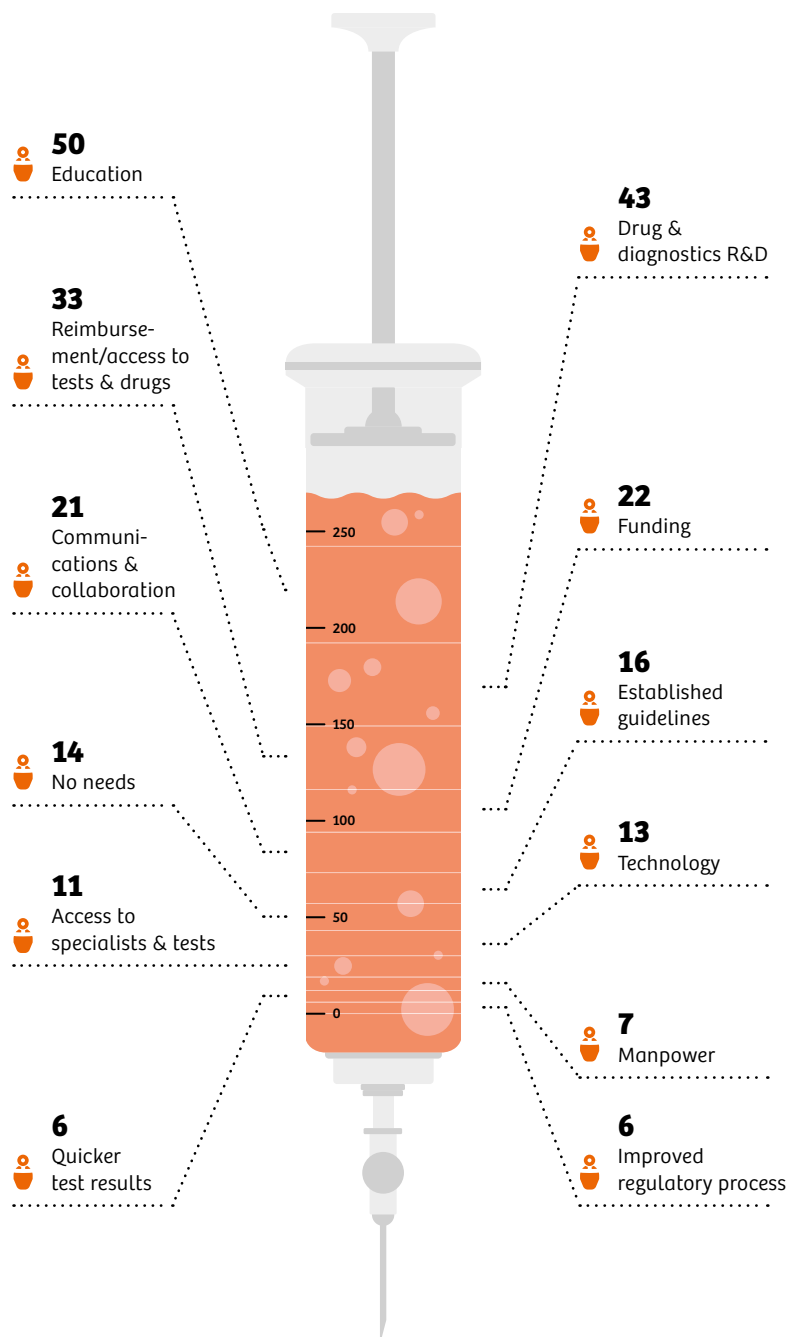
For example, there are about 20 such tests approved in the U.S., with many more in development.[1] The tests are typically based on genetic markers, but some are also based on proteins or medical imaging. Most of the progress has been in the area of cancer, where matching the right drug and the right patient can be crucial.

Genetic Markers for Cancer Treatment

The HER2 gene, for example, is a model companion diagnostic marker. The gene contributes to the growth of aggressive breast cancer when it is expressed at abnormally high levels in the body. Testing of the corresponding HER2 protein status has become part of the standard battery of diagnostic procedures for breast cancer, because there are now several

Personalized medicine

To better understand what health-care professionals (HCPs) perceive to be the biggest challenges and opportunities associated with “personalized medicine,” Novartis Oncology conducted a study of 276 HCPs in seven countries. In answering the question “What is needed to achieve full implementation of personalized medicine and to ultimately enhance a patient management and care?” the following areas were identified (number of mentions – each respondent may have mentioned more than one area):



drugs that specifically target HER2-positive tumors. Indeed, the concept has been revolutionary for the clinical management of the disease. While in the past, being positive for HER2 worsened a patient's prognosis, because of the aggressive overgrowth caused by the HER2 gene, personalized therapy using HER2 as a companion diagnostic marker has now brought survival rates in line with patients who do not overexpress that gene. One recent study shows an almost 90% overall five-year survival rate for early-stage breast cancer patients positive for HER2.[2]

There are now companion diagnostic tests available for personalized treatment of other tumors like ovarian cancer, non-small cell lung carcinoma, and colorectal cancer.

New Tech for New Tests

Newer technologies in drug development open up new possibilities for companion diagnostics. For example, antibody-drug conjugates (which combine an antibody with a standard drug) target specific surface antigens on various tumors. Of course, it would be necessary to know if these antigens are at all present on the cancer cells before starting the therapy. One approach is through analyzing circulating tumor cells in the blood with novel automated laboratory platforms, which have shown promise as a mode of detection of such antigen-positive cancers in recent investigations.[3]

Imaging technologies like positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can also be used to create a companion diagnostic test. Imaging can provide a whole-body view on the entire tumor load and is a noninvasive alternative to tests based on tissue or fluid samples. In addition, imaging tests can often provide faster results than those based on nucleic acids or proteins.

Molecular Imaging on the Rise

One technology, which is in clinical trials in Europe and the United States, aims at imaging the cellular receptor for folic acid with a SPECT scanner and a specific radioimaging probe.[4] Cancer cells need folic acid to rapidly grow and thus often overexpress the receptor. When such folate-receptor positive malignancies are detected through molecular imaging, patients could possibly be treated more successfully with a corresponding receptor-targeted drug.

Diagnostics and therapeutics merge even more when drug candidates are modified through the addition of a fluorescence-imaging marker for optical imaging. The fluorescent drug “lights up” like a neon sign when it encounters a cancer cell. For example, this approach has been tested for lymphoma cells in laboratory studies with mice. In the future, it might allow doctors to see the drug fighting cancer in real time and assess a response in an individual patient. ●

Catherine Shaffer

is a science writer specializing in biotechnology and pharmaceuticals. A former lab scientist with a master's degree in biochemistry, she has covered advances in drug technology for over 15 years. Catherine is based in Ann Arbor, Michigan, USA.

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Professor Peter Fasching
from Erlangen University
Hospital

Big Data in Cancer Care

Peter Fasching, MD, a gynecologist at Erlangen University Hospital in Germany, works closely with international teams to research the role that genomes play in breast cancer. Read about the challenge of transferring this knowledge to clinical practice, and the potential of smart data for personalized medicine.

Professor Fasching, does data make us healthy?

Fasching: Not yet, but we are on the threshold of being able to use the enormous volumes of data collected in research and clinical practice to truly make people better.

You mean, for example, using a patient's genomic data.

Fasching: Yes. We have known the human genetic code – with its three billion DNA building blocks – since the year 2000, and we have learned much more about it since then,

such as how genes are regulated and translated into proteins. So how can we now use all this data to benefit individual patients? As a comparison, a basic Microsoft Excel spreadsheet can currently contain around 16,000 columns. Even if we only wanted information on one million DNA components at our fingertips when treating a patient, it would still exceed our powers of imagination.

What is your solution?

Fasching: It will be important to identify patterns and regularities in the data with, for example, machine learning (i.e. with adaptive computer programs), and to then apply them to individual cases. That's something that we, as physicians, need to learn – and it is already changing research.

You research the role that the genome plays in breast cancer. What are your findings?

Fasching: Here at Erlangen University Hospital, we have a database with information on around 12,000 patients who have participated in our Bavarian Breast Cancer Case-Control Study. For all of these women, we have pseudonymized data about the genome and about some of the

practically the entire genetic blueprint for less obvious genetic risks. The key to progress will be to correlate this completely new dimension of knowledge with what we already know about cancer.

What might this mean specifically?

Fasching: The first use for these genome-wide analyses is to determine the prognosis of the illness. We already use gene expression tests to identify breast cancer patients who, thanks to their favorable genomic activity profile, have a lower risk of relapse and therefore do not need to undergo chemotherapy after surgery. Naturally, this information is extremely important to individual patients.

Do doctors need a molecular-biological profile for each patient in order to provide this kind of personalized medicine?

Fasching: It is undoubtedly technically possible to create individual genomic profiles today. On the one hand, it's a question of cost. Genome analysis requires a great deal of time and effort. We also have to establish how we want

“We can now scan practically the entire genetic blueprint for less obvious genetic risks.”

protein patterns in the tumor cells. We are not unique in this; similar breast cancer databases exist in many countries. In fact, many of today's research questions can only be answered through international cooperation. One recent collaboration, which involved over 200,000 patients and also included our data, showed that variants in more than 70 genes influence the risk of breast cancer. While we have long known about the serious effects of a few specific breast cancer genes (the most well-known ones being BRCA1 and BRCA2), we can now scan

Genome analysis
requires a great deal
of time and effort.
.....





The hospital works closely with international research teams.



Intelligent IT platforms are needed to sort huge volumes of data.

to manage the new data in the future – for example, where the data will be stored, who can access it, and how patients and their families will deal with all this new information. But there is another issue: it is simply an enormous challenge to interpret genome-wide analyses so that they can actually be used in clinical decision-making – i.e. to translate smart data into specific medical care. There is a gap between the knowledge that variations in over 70 areas of the genome influence the risk of breast cancer, and the question of what the doctor should do when it comes to the individual patient. We want to close this gap because we believe that the data can indeed help to personalize patient care. Using the data is the only way to better meet the needs of our patients.

You are collaborating with several other research institutes on a project about clinical data intelligence. It is by no means solely about genomic data.

Fasching: That's correct – for example, we also want to link imaging data with genetic analyses or the patient's history. To do that, we need intelligent IT platforms.

A type of clinical supercomputer?

Fasching: First we have to develop software solutions for sorting the increasing volumes of clinical data so that we can understand the data better and see how they are connected. In the future, we might have computerized decision-support systems that could, for example, flag up genetic risk constellations or patterns in imaging data that might be relevant to a breast cancer patient's prognosis, and then generate treatment suggestions for doctors. New, integrated diagnostic devices are also conceivable.

What do you envisage exactly?

Fasching: An idea that we are currently investigating is improved mammography screening. Mammograms often do not produce reliable assessments in women with dense breast tissue, and an additional ultrasound can be useful. Our vision is to equip a combined mammography and ultrasound device with software that not only increases the informative value of the mammogram, but also integrates data about a patient's individual cancer risk. This enhanced screening would then be offered to high-risk patients, and we could provide personalized screenings. This is a simple example of how sensible data integration can drive the future of cancer medicine. ●

Pros, Cons, and Future of Breast Cancer Screening

Text: Martin Lindner

Despite considerable controversy around the world, mammography has become the standard for the systematic early detection of breast cancer. New imaging technologies and the trend toward personalized medicine are ushering in a new era of screening.

The Rise of Mass Screening Programs

Breast cancer screening is currently a global standard of preventive medicine.[1] Debates on the pros and cons have been raging since it was introduced in the early 1970s – and are far from over. Parallel to Western industrialized nations, interest in screening is also becoming increasingly common in countries such as China, Saudi Arabia, and Brazil. At the same time, new imaging technologies and the trend toward personalized care and treatment are gaining ground internationally. What does the future hold for breast cancer screening?

Screening mammograms have been a long-standing practice in North America, Europe, Australia, and Japan. “The strategy provides many important advantages,” confirms mammography screening expert Sylvia Heywang-Köbrunner, who recently contributed to the current position on the subject adopted by the International Agency for Research on Cancer (IARC).[2] According to Heywang-Köbrunner, there is strong evidence that a significant number of breast cancer deaths can be prevented through regular mammogram screenings and more timely treatment.



Milestones of a Medical Paradigm

“Breast cancer screenings can be compared to other prevention efforts, such as those for high blood pressure or diabetes,” comments radiologist Ingvar Andersson from Lund University in Malmö, Sweden.[3] One of the field’s pioneers, Andersson has been researching different screening exams since the 1970s and is currently working for the diagnostic company Unilabs, which is responsible for the screening program in southern Sweden. Andersson recalls that, in addition to the development

of specialized X-ray devices and sensitive screen-film combinations in the 1960s and 1970s, the roots of this medical paradigm also lie in the Health Insurance Plan Study in New York. The longterm study, which began in 1963, showed the efficacy of mass screenings for breast cancer over an observation period of many years.[4]

Further randomized trials in Sweden and elsewhere confirmed the effect, and technology also improved, particularly with the introduction of digital mammography in early 2000. Today, more than two dozen countries around the world have breast cancer screening



"In the future, the screening will be more personalized than it is now."

Ingvar Andersson
Lund University, Malmö, Sweden

programs. "Knowledge about breast cancer and the possibilities of screening are also much more firmly anchored in the minds of women," adds Andersson. According to the latest IARC scientific paper, the risk of dying from breast cancer has dropped by more than 20% in areas where women have access to screening mammograms, and by as much as 40% among women who actually participate and undergo screening mammograms regularly.

The Problems of a Mass Screening Program

Nevertheless, the controversy about breast cancer screenings is by no means resolved. Some critics consider the benefits of comprehensive routine mammography outside clinical studies to be debatable.[5] Others argue that the original large preventive effect of the screening has decreased in the last few decades. Because many breast cancer tumors can be treated more effectively today, very early diagnosis is no longer as important as it used to be.[6]

Even proponents of population-wide screening programs admit that the approach presents specific problems. For example, most women who take advantage of screenings do not develop breast cancer, but some may find themselves confronted with an inconclusive or suspicious finding in the initial screening mammogram – leading to a so-called recall.

Recalls and Overdiagnoses

Heywang-Köbrunner says it is estimated that on average one in five women who regularly participate in an organized mammography program for 20 years receives one recall during these 20 years. Most initial suspicions can be dispelled by a harmless additional test, such as another mammogram or an ultrasound examination. However, the uncertainty associated with these so-called false positive diagnoses can cause women a great deal of anxiety while they wait. "The psychological effects should not be ignored," states Andersson.

"However, the most significant problem is overdiagnosis," he adds. By this, he means tumors that would never be noticed without screening but once detected will typically result in surgery and radiation. Reasons why they would not have been detected include very slow tumor growth or early death from another cause. Estimates for the total number of overdiagnoses are difficult to determine and depend heavily on the defined period of observation. What is clear, though, is that for all women whose lives were saved by a screening, there were others who had to undergo treatment that in retrospect may have been unnecessary.

Trends and New Technologies

These difficulties can be partly remedied by new strategic approaches. "In the future, the screening will be more personalized than it is now," predicts Andersson. He explains that the individual cancer risk is likely to be evaluated more precisely based on genetic analyses or biomarkers. This could then influence the type and intensity of the screening and help avoid unnecessary treatment. Imaging technologies

are also changing. Heywang-Köbrunner explains that breast tomosynthesis is an important innovation. The ability to view the breast in slices rather than as a single projection helps tumors to be detected more often and earlier, and to be more clearly defined.

“A combination of tomosynthesis and ultrasound in one and the same device would also be beneficial,” says Andersson. Such customized hardware could be very advantageous for efficient screening in women with dense breast tissue, for example. Andersson also suggests another idea: Software for routine use in computer-assisted tumor detection. “One important barrier to mammography screening is a lack of competent radiologists prepared to read a large number of normal mammograms daily,” he says. “A computer-assisted detection (CAD) system that could rule out breast cancer with a high degree of accuracy and thus relieve radiologists from reading a significant proportion of screening mammograms would be highly desirable.” ●

Martin Lindner

is an award-winning science writer based in Berlin, Germany. He went into journalism after studying medicine and earning a PhD in the history of medicine. His articles have appeared in many major German and Swiss newspapers and magazines.



“The strategy of screening mammograms provides many important advantages.”

Sylvia Heywang-Köbrunner
contributed to the IARC position
on breast screening.

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Tomosynthesis is the Better Mammography Method

Text: Martin Lindner

Despite considerable controversy around the world, mammography has become the standard for the systematic early detection of breast cancer. New imaging technologies like tomosynthesis could usher in a new era of screening and help to develop a strategy for screening that is as rational and efficient as possible.

The latest interim results of a large cohort study in Malmö, Sweden, suggest that breast tomosynthesis, a relatively new imaging process for the 3D depiction of the breast, could replace conventional 2D mammography in the future and thereby change the practice of breast cancer screening internationally.[1] “Tomosynthesis is the better mammography method,” explains radiologist and senior author of the study Sophia Zackrisson of

Lund University. “The method offers significant advantages, particularly for screening.”

Two-view digital mammography is currently the world’s gold standard for breast cancer screening. However, it is also known that this X-ray technique does not detect all breast tumors; in fact, up to one-third of all cancers may remain undetected, especially in women with very dense breast tissue.[2] One reason for this is that overlapping breast tissue can cover tumors and thus prevent them from being seen on the 2D mammogram. With tomosynthesis, however, the X-ray tube moves in an arc over the breast, taking low-dose images across a range of angles. This imaging data is used to calculate onemillimeter-thin layers of the entire breast tissue. The layers are then displayed as a stack that the radiologist can scan through, rather like a flip book.

Kristina Lång, MD, PhD,
Lund University, Malmö, Sweden
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Not a Mix of Technologies, but a Rational Strategy

Studies done in the past few years have shown that more tumors are discovered when tomosynthesis is used in addition to mammography.[3] However, the Malmö study has taken a different approach. “We did not want to simply add different technologies, but rather develop a strategy for screening that is as rational and efficient as possible,” states Zackrisson. The clinical trial, which began in 2010 in Malmö, was therefore designed from the very beginning to examine whether tomosynthesis is superior to mammography as a stand-alone procedure in the screening and could replace it as the standard method.

According to the preliminary results, this appears to be the case. An interim analysis of 7,500 of the planned 15,000 study participants shows that one-view tomosynthesis detects up to 43% more cancers than two-view mammography, and also reduces radiation exposure. Furthermore, the force needed to compress the breast could also be significantly reduced.

“For many women, breast compression during the mammogram is very painful,” says Zackrisson’s colleague, Kristina Lång. It is therefore possible that tomosynthesis screening would also increase participation.

Outstanding Issues Should be Resolved in the Future

It remains to be seen whether the new method actually detects particularly aggressive cancers better. Another possible scenario is that the additional tumors detected are actually changes posing little risk, and that tomosynthesis could occasionally lead to over-diagnosis. One aspect that plays a role is that the time needed to assess tomosynthesis is higher due to the large number of slices displayed for each breast. In addition, the preliminary results show that more women needed to be called back for additional diagnostic testing to clarify the results. However, this recall rate increased in proportion with the cancer detection rate, which is consistent for

Sophia Zackrisson, MD, PhD,
is one of the principal investigators.



the screening programs where the recall rate with 2D was already very low.

“We also observed that the recall rate, as well as the time needed to read the images, decreased with the doctor’s increased experience,” reports Lång. “There is apparently a significant learning curve here.” The definitive assessment of the procedure will be made in the years ahead, after the study has ended. The Malmö researchers also want to present a detailed analysis of the cost efficiency of the new methods.

“Tomosynthesis is the better mammography method.”

Sophia Zackrisson,
Lund University, Sweden

An International Comparison of Screening Programs

In addition to enhancing screening methods, it is also very important to provide access to screening programs worldwide. According to a 2012 survey by the International Cancer Screening Network, more than two dozen countries worldwide have organized breast cancer screening programs.[4] After the first pilot projects in 1977 in Japan, the approach spread to North America, Europe, and Australia in the 1980s and 1990s, and more recently to countries such as China, Singapore, Saudi Arabia, and some parts of Brazil.[5] A global comparison shows differences as well as similarities between countries.

For example, women in the Scandinavian countries, the United Kingdom, and Germany receive a personal invitation for screening at predetermined intervals. In other countries, by contrast, participants are recruited through media campaigns or referred by their doctor. Screening programs are only available in certain regions of China, Saudi Arabia, Spain, and Switzerland.

Opportunistic Screening

One special case is “opportunistic screening,” in which women undergo the exam at their request or as part of routine medical care. Opportunistic screening plays an important role in the United States, for example. In Latin

America, where there are national screening recommendations but no organized mammography programs, most screenings are performed at the patient’s request, and often by a private-sector doctor.[6] The main problems with opportunistic screenings are that the necessary intense training for staff, and the quality assurance of imaging, image interpretation, and further work-up are not generally guaranteed to the same level as for organized screening programs. On average, this leads to higher risks of side effects and higher costs, without proof of a comparable effect.

Mammography is the standard screening technology around the world. It is sometimes supplemented by the doctor palpating the breast or examining it with ultrasound. Special centers, general medical facilities, and sometimes mobile screening units perform the examinations, primarily at two-year intervals. Many organized programs concentrate on patients between the ages of 50 and 70, but women are routinely screened starting at the age of 40 and after the age of 70 in Sweden, Australia, South Korea, Japan, and the United States. Participation rates also vary considerably: they stand at almost 20% in Japan and Saudi Arabia, at around 50% in Canada and Switzerland, and at over 80% in the Netherlands and Finland.

Mammography is the standard screening technology around the world



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The Growing World Market for Screenings

Breast cancer is the most common cancer in women worldwide, and the number of women affected continues to increase.[7] There is thus a large need for early detection options. While breast cancer occurs extremely frequently in industrialized countries with Western lifestyles, the largest increase in disease rates is expected in less developed countries.[8] By 2018, the total number of women worldwide who qualify for breast cancer screening could reach around 250 million.[9]

A driving force behind this development is the aging of the world population. It is well known that the probability of developing breast cancer increases with age. Also, a rising standard of living with greater educational opportunities for women results in later births and shorter lactation periods. This leads indirectly to a higher risk of breast cancer due to changing hormonal influences. China is therefore one of the largest markets for breast cancer screenings, along with the United States, Brazil, Japan, and Germany. China has experienced a rapid increase in disease rates since the early 1990s. Various regional screening programs have been developed in China since then. However, experts

do not anticipate nationwide mammography screenings based on Western-style models in the near future. In fact, it is possible that ultrasound screening will play a role, as the procedure offers advantages for Asian women, who tend to have denser breast tissue and small breasts, and often develop cancer at an earlier age.[10]

While screening services are frequently offered by the private healthcare sector in emerging and developing countries like India, public screening programs are barely affordable in these countries.[11] Cultural barriers can also stand in the way of breast examinations for early detection.[12]

On the other hand, in industrialized countries with organized screening programs, the services are paid for through taxes or by health insurance companies (sometimes with a co-payment from the patient) at predetermined rates. The total cost of the German mammography screening program, which screens around half of the women who are entitled to use the program, amounts to approximately US\$200 million to US\$250 million per year. That equates to about €70 or €80 per screening mammogram, including double reading, centralized quality assurance, and subsequent assessment examinations.[13] ●

Martin Lindner is an award-winning science writer based in Berlin, Germany. He went into journalism after studying medicine and earning a PhD in the history of medicine. His articles have appeared in many major German and Swiss newspapers and magazines.

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Non-invasive Detection of Prostate Cancer

Text: Sandro Benini | Photos: Marcelo Kahn

Medical Solutions features the story of Jorge Fernández de la Torre who uses magnetic resonance imaging in the detection of prostate cancer. The fact that his facility can also offer the exam without using an invasive endorectal coil has increased patient acceptance.

Hospital San José in Monterrey, Mexico, is part of Tec de Monterrey, one of the country's most prestigious universities. It is a general hospital with 200 beds, but it is widely known for its work in diagnosing and treating prostate cancer. The insidious thing about this disease – which is the most frequent form of cancer in men – is the fact that it often remains undetected for a long time.





Hospital San José
in Monterrey, Mexico
.....



Avoiding Unpleasant Diagnostic Methods

A major reason is that many patients find the diagnostic methods unpleasant or even humiliating, as the hospital's chief radiologist Dr. Jorge Fernández de la Torre, MD, explains.

"The shame experienced with a rectal examination of the prostate is particularly high in the Mexican and Latin American cultures," he says. This holds true for a simple digital prostate exam as well as for more advanced diagnostic procedures like magnetic resonance imaging (MRI) with the aid of a rectal probe.

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Introduction of a New Approach

MRI has grown to become a mainstay in the diagnosis and management of prostate cancer.[1] Until recently, however, the examination usually involved a special probe (an MRI coil) inserted into the rectum in order to acquire the images. This is exactly where a new approach, as implemented by Fernández de la Torre, MD, in his hospital in Monterrey, comes into play. Instead of using the endorectal MRI coil, he applies only a standard surface coil, placed on the pelvis like a collar. This is possible thanks to the high element density of Siemens Tim® technology, which provides excellent signal-to-noise ratio (SNR).



Dr. Jorge Fernández de la Torre, MD,
chief radiologist at
Hospital San José
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Increased Patient Acceptance

Using only external body coils offers more comfort to the patient and physicians all over the world have shown that the reliability appears to be comparable to the invasive approach.[2] According to de la Torre, the introduction of this approach in Mexico showed corresponding results.

Motivated by Personal Experience

The radiologist's motivation in seeking innovative diagnostic possibilities is based on very personal experience: "My mother died of cancer shortly after I started college. Watching her suffer really stirred up my emotions. I would like to save other people from a fate like hers," the doctor says.

Hope of Establishing a New Standard Method

Thanks to state-of-the-art equipment, such as the MRI system, a PET/CT scanner, and a SPECT scanner, Hospital San José has an integrative approach to diagnosing and treating all kinds of cancers – a unique approach in northern Mexico. A tour through the radiology department and the patient rooms shows that the hospital is modern, clean, and bright. Fernández de la Torre, MD, now hopes to make the non-invasive prostate MRI examination standard in the early detection of prostate cancer, eventually leading to a lower mortality rate. This would certainly be the type of the medical success he dreamed when he was a college student. ●

Sandro Benini
was born in Zurich, Switzerland in 1967. He has a Master's degree in German and Italian Literature and Linguistics from the Universities of Zurich and Bologna, Italy. After working for several Swiss magazines and newspapers, he has been a Latin American correspondent for the Swiss daily newspaper Tages-Anzeiger for seven years.



A modern, clean, and bright atmosphere adds to patient comfort in the scanner room.
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How High-Flying Is Low Dose CT?

Text: Kathleen Raven

When the National Lung Screening Trial (NLST) launched in the U.S. in 2002, neither American nor European medical organizations endorsed specific lung cancer screening guidelines. Furthermore, the existing strategies missed crucial lung cancer diagnoses because the disease can be asymptomatic until the advanced stages.

Study Shows Reduction in Mortality

Lung cancer is typically diagnosed in the advanced stages, when surgical cure is not an option. The NLST set out to investigate whether lung cancer screening with low-dose computed tomography (LDCT) could tackle the problem. This study of more than 53,000 men and women with a history of heavy smoking showed that annual LDCT screening is an irreplaceable component in fighting lung cancer. Participants screened with LDCT had a 20% lower risk of dying from lung cancer than patients in a control group that was given standard chest X-rays. This reduction in mortality is likely due to earlier tumor detection and treatment.

Notably, the death rate from other causes was also lower in the LDCT arm. "The important message here is that CT screening itself did not promote early morbidity or mortality. Participants were not exposed to downstream complications they could have died from," says Denise Aberle, MD, Professor of Radiology at UCLA Medical Center in Los Angeles, and one of the principal investigators on the NLST. David Naidich, MD, Professor of Radiology at New York University School of Medicine, who served on the oversight committee of the study, agrees that the trial eliminated concerns that the risks of annual LDCT scans might outweigh the benefits. With modern CT scanners, the radiation exposure involved would be small, he says.

Stage Shift

Indeed, the NLST team achieved a rare feat in the field of screening studies. "We identified more early-stage lung cancers in the LDCT arm, but found fewer late-stage cancers, which means we saw a true stage shift," Aberle says. A common concern with cancer screening is that it may result in false-positive findings or lead-time bias, only detecting the disease earlier without altering its course. As the NLST mortality results show, however, this is obviously not the case.

The results are all the more important given that lung cancer is the leading cause of cancer-related deaths worldwide, and that better management of the disease is urgently required. In the U.S., "mortality from lung cancer far exceeds mortality from breast, prostate, and colon cancer combined," Naidich notes. The breakthrough study also caught the attention of the U.S. Clinical Research Forum, which awarded Aberle a clinical research award in 2014.

"We identified more earlystage lung cancers in the LDCT arm, but found fewer late-stage cancers, which means we saw a true stage shift."

Denise Aberle, MD,
Professor of Radiology
at UCLA Medical Center





“Mortality from lung cancer far exceeds mortality from breast, prostate, and colon cancer combined”

David Naidich, MD,
served on the oversight
committee of the study

Translating Research into Routine Care

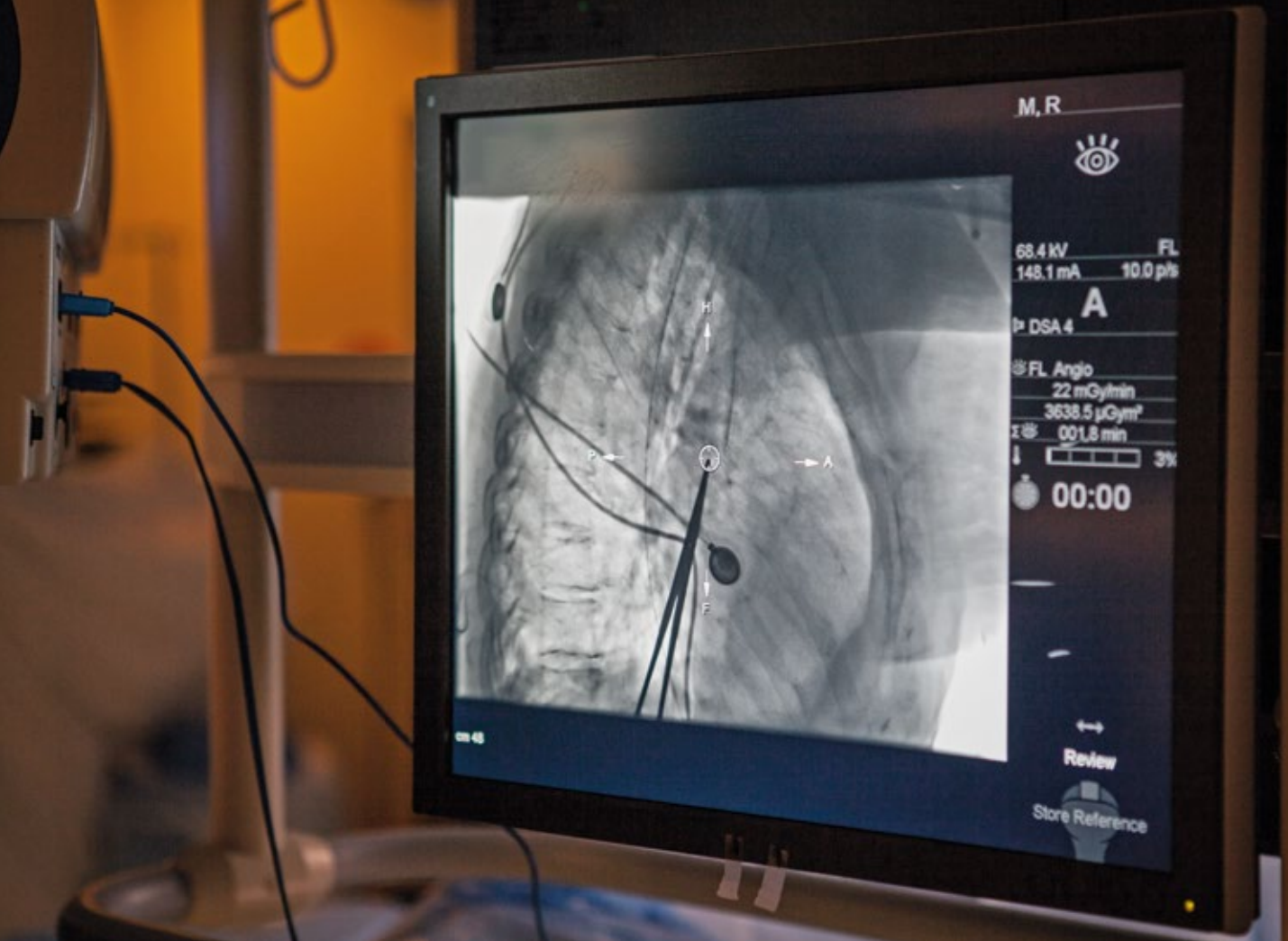
Meanwhile, the U.S. Preventive Services Task Force (USPSTF), which issues the country's screening guidelines, has recommended that people who fall within the NLST patient population and who are aged between 55 and 80 should receive annual lung cancer screenings.[1] The procedure is now covered by the country's private and government insurers for older people with a long history of heavy smoking.[2] This could have an important impact on healthcare delivery and the use of CT screening in the U.S. Given the USPSTF recommendations and reimbursement coverage, this could result in up to 8 million additional LDCT screens each year.[3]

The NLST results also caught the interest of medical organizations in Europe, Aberle and Naidich say. Aberle explains that a lung cancer screening trial called NELSON, which is taking place in the Netherlands and Belgium, will combine its results with the Danish Lung Cancer Screening Trial (DLCST) to include about 22,000 patients total. In China, where lung cancer has been increasing rapidly in the past few decades, at least one LDCT cancer screening trial of 3,000 participants is underway in Shanghai.[4] Other countries can benefit by running their own trials in order to find the best approach to lung cancer screening, Aberle says.

Challenges in LDCT Screening

However, important issues remain unresolved. As the authors of the NLST report point out, many of the centers involved in the trial are recognized for their expertise in cancer diagnosis and treatment, leaving open the question as to whether community facilities would perform equally well. Likewise, the European Society of Radiology and the European Respiratory Society have issued a white paper recommending the use of LDCT screening only at certified multidisciplinary centers that can ensure standardized operating procedures and offer long-term clinical follow-up that includes smoking cessation programs.[5] In 2014, a group of Swiss experts cautioned that, before implementing large-scale LDCT screening in clinical routine, the population to be screened and the possible psychological consequences of taking part in such programs as well as guidelines on a workup of indeterminate screening results would have to be clearly defined.[6] A recent cost-effectiveness study stated that, within the U.S. health system, each quality-adjusted life year gained through LDCT screening could carry additional costs (compared to no screening) of US\$81,000. However, estimates vary widely.[7]

Another major issue is how to convince high-risk patients, particularly those from underprivileged communities, to seek lung



The National Lung Screening Trial – Key Facts

The National Lung Screening Trial (NLST) was launched in 2002. It randomly assigned around 53,000 current or former heavy smokers to receive either low-dose computed tomography or chest X-rays for three annual screens. Eligible male and female participants in the study were aged between 55 and 74 years and had a history of at least 30 pack-years (i.e. 30 years of smoking one pack per day), and, if former smokers, had quit within the past 15 years. Patients were enrolled at 33 medical centers across the U.S. All of the multi-detector CT scanners deployed were at least four-slice systems.

Screening exams were labeled as “positive” if a lung nodule 4 mm in diameter or larger was observed on CT scans, or if a “suspicious” nodule or mass was detected on radiographs. The rate of adherence to screening was over 90%, though with a portion of lung cancer cases diagnosed only in the post-screening phase. About 6 years after the first enrollment, patients in the LDCT group showed 20% lower mortality from lung cancer compared with the radiography arm (likely due to earlier treatment) and a 6.7% relative decrease in death from other causes.[8]

cancer screening. These populations suffer disproportionately from lung cancer because they often present with very advanced disease. Aberle suggests that university medical centers could do a better job of community engagement by providing resources and local training to the community healthcare workers who serve these populations. It is unreasonable to expect that such high-risk patients will leave their communities to travel to major academic centers for screening and care. Models for community engagement and outreach, where healthcare is incorporated into the community, must be implemented.



Other smoking-related diseases are detectable with lung screening.

What Happens Next

At the same time, it seems likely that people beyond the parameters of the original NLST study population could also benefit from well-planned lung cancer screening programs. “A lot of people get lung cancer who do not satisfy the NLST eligibility criteria,” states Aberle. She points out that the NLST criteria apply to less than 30% of people who are diagnosed with lung cancer in the U.S. One approach to expanding screening eligibility, she says, could be to build risk prediction models that take into account patients’ exposure to known respiratory carcinogens, air pollution, underlying lung disease, and family history of lung cancer.

Lung cancer screening in connection with other forms of screening and counseling is very attractive. LDCT works for lung cancer screening because it can detect even very small nodules within the aerated lung. Furthermore, other smoking-related diseases are detectable with lung screening.

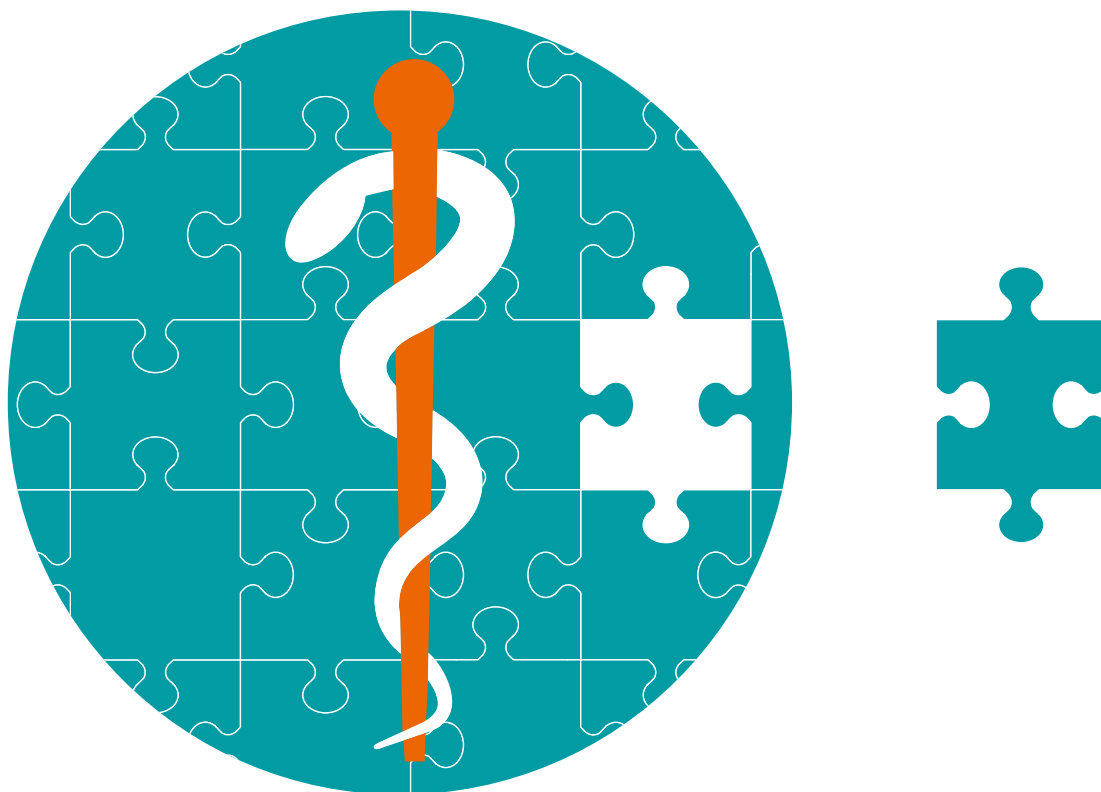
Coronary artery calcium assessment has been shown to provide a personalized estimation of the risk of heart attack or death from coronary artery disease. Due to the high contrast between calcium and soft tissues, coronary artery calcium can be evaluated on lung screening to improve risk prediction for cardiovascular events.

Similarly, emphysema is a smoking-related condition that is readily identified on LDCT screening and independently contributes to the risk of lung cancer in individual patients. Finally, the incorporation of smoking cessation counseling and medications into the screening process will significantly reduce tobacco-related diseases. The NLST results should be viewed as just the beginning of our understanding of screening and preventive services for tobacco-related diseases. ●

Kathleen Raven has covered lung cancer clinical trials for Bio-pharm Insight, consumer health for Reuters Health, and biomedical news for Nature Medicine. She is a freelance writer based in New Haven, Connecticut, USA.

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Towards Future's Therapies

Text: Martin Lindner

Genomic data, versatile imaging systems, and hybrid operating rooms are all setting the foundation for a new kind of medical care. In the future, treatment could be more customized, interdisciplinary, and less invasive than ever before – while at the same time offering more flexible forms of healthcare.

Personalized Medicine

The medicine of tomorrow is already a reality today, at least in some cases. The field of medicine is changing in a myriad of ways, such as through the use of genomic data,

new imaging systems, hybrid operating rooms, and robot-assisted interventions. To summarize recent trends, treatment will soon be more customized, interdisciplinary, and less invasive than ever before – making it easier to meet the exact needs of an individual patient and deliver the right form of therapy.

When President Barack Obama announced the Precision Medicine Initiative in a State of the Union Address in early 2015, he provided the political framework for a medical mega trend: The will to treat patients in a more targeted way based on their specific condition.[1] The idea of personalized medicine is not a new one. For the past hundred years, blood donors have been

selected based on matching a patient's blood type, which maximizes the safety of blood transfusions. The idea of more precise therapy, however, has long had a wider basis. The most important part of this is research into the human genome.

Genomic Testing Arises

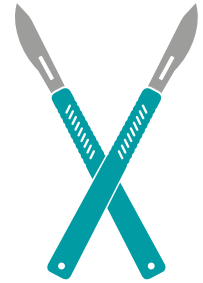
We are currently aware of over 80 million genetic variants in the human genome.[2] An individual's genetic code may soon be able to be decoded at the cost of an MRI scan in the United States.[3] This has catapulted genomic testing into the clinical arena. "The prospect of sequencing whole genomes for less than US\$1,000 reshapes our thinking about genetic testing," claims Larry Jameson and Dan Longo in a recent essay on precision medicine.[4]

Implementing special screening and treatment measures for breast cancer, based on evaluating a patient's genetic predisposition with analysis of the BRCA1 and BRCA2 breast cancer genes[5] is an example of how medicine can be personalized through gene analyses. If the patient develops a tumor in the breast, the genetic activity pattern can be determined in the tumor cells using gene expression tests. Chemotherapy may not be necessary depending on the result, as it is now possible to determine – with precision – the customized required dose for a wide range of pharmaceuticals, including anti-depressants and specific cardiovascular drugs, based on a genetic profile.[6]

Therapy Control System

Proprietary solutions are already available. For example, more than 20 test kits, or companion diagnostic devices, have been approved for use in the United States. These can determine whether, for example, a patient with breast or colon cancer would benefit from antibody therapy due to a specific mutation in the tumor.[7] Another example of personalized therapy is the number of patients with liver cancer who can be helped by irradiating the tumor internally. A range of diseases could be treated more precisely in the future. For example, quantitative MRI image analyses could be used to make better decisions on therapy and dose adjustments for patients with multiple sclerosis.[8]

The potential benefits of precision medicine are particularly obvious in the field of oncology, according to a recent analysis by the Director of the National Institutes of Health, Francis Collins, and his colleague, Harold Varmus.[9] One-size-fits-all medicine – with unspecific and often toxic chemotherapy treatments – is shifting to more selective, gentle, molecular-based tumor treatments.[10] Diagnostic tests are no longer just a means to diagnose the disease and give the subsequent treatment a general direction, but rather a way to control and optimize therapeutic success throughout the entire duration of treatment. Treatment becomes a continuously controlled process by integrating diagnosis and therapy.



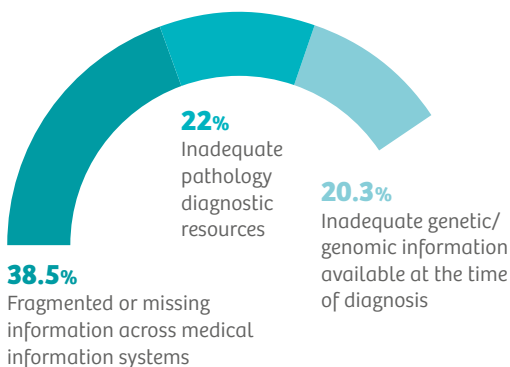
Strong growth of global operating room market expected[19]

The global operating room market is expected to grow from nearly US\$13.1 billion in 2014 to reach nearly

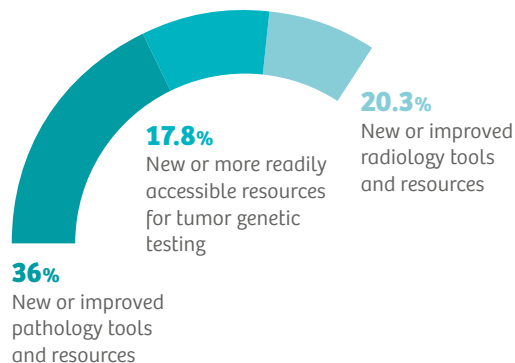
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billion in 2019.

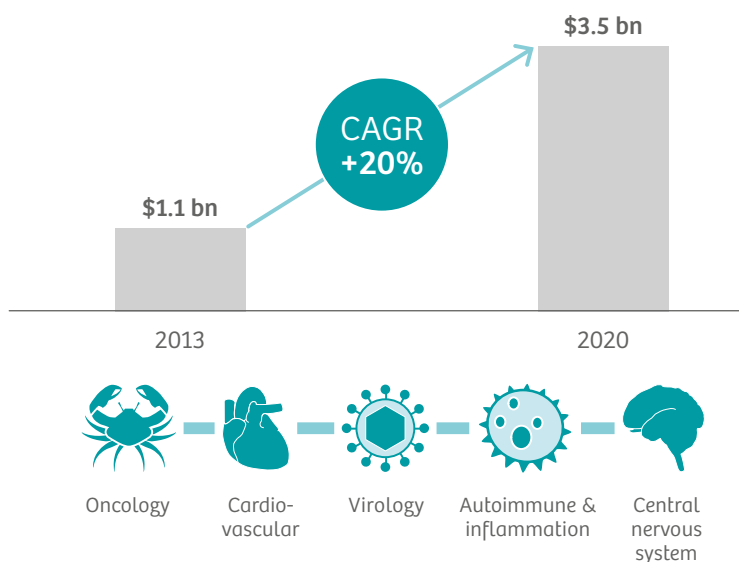
The top reasons are:



Possible ways to avoid misdiagnosis:



In the U.S., 28% of cancer is misdiagnosed[17]



Global companion diagnostic technologies market[18]

Companion diagnostics are in vitro diagnostics that provide information about therapeutic responses of patients for a specific treatment. The market is still nascent, the key drivers are the increase in the discovery of biomarkers and co-development of treatments and corresponding diagnostic tools. Companion diagnostics is segmented on the basis of its use for indications such as oncology, cardiovascular conditions, central nervous system indications, inflammation and virology.

Higher Flexibility

Other disciplines have used the flexibility of treatment in the hybrid operating room for some time. As neurosurgeon Karl Schaller and his colleagues at the University Hospital in Geneva describe, they can angiographically diagnose an emergency patient with a hemorrhaging brain aneurysm directly on the operating table. Using a surgical microscope, a 3D reconstruction of the cerebral vessels can be viewed in augmented reality, allowing the surgeons to easily find and close the aneurysm through an access point in the skull. Neuroradiologists can then immediately verify the success of the intervention.

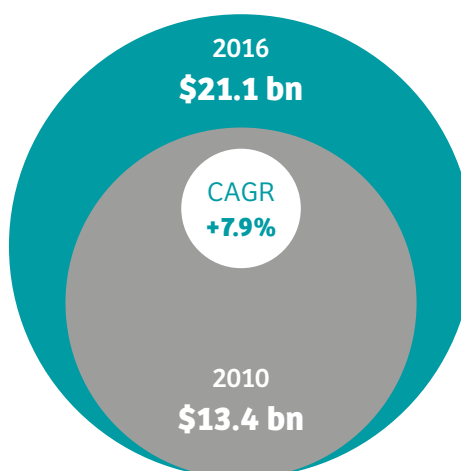
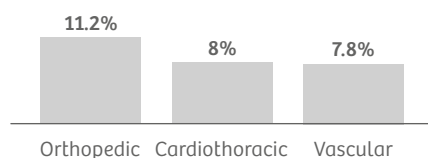
Schaller et al. explain that the previous diagnostic and treatment steps for surgical planning, which were performed across several hospital departments, are now no longer needed.[11] Of course, this development is not without conditions. Hybrid operating rooms not only have to be economically viable for hospitals, they also require a reorganization of internal work processes and the introduction of new specializations.[12] While radiologists have been performing interventions for a long time, even using their own wards for the purpose, hybrid surgeons are now becoming imaging specialists, which means the existing disciplinary boundaries in medicine are blurring.

Incisions with No Visible Trace

Shanghai-based surgeons Hai Hu and An-An Xu talked recently about the pinnacle of minimally invasive surgery.[13] In the 1980s, surgeons began removing gall bladders laparoscopically through small incisions in the abdominal wall. This invisible method has since been adopted for many other procedures around the world. Today, surgeons can even perform colon cancer surgeries laparoscopically. The procedure usually takes longer than an open abdominal operation due to the use of demanding technology, but on average patients lose less blood, have less pain afterwards, and can be sent home faster – with comparable long-term success.[14]

There have been new developments in this area, such as opening the abdominal cavity with a single incision and concealing the scar within the belly button. The technique, which is known as laparoendoscopic single-site surgery (LESS), uses novel access devices and flexible and/or articulating instruments.[15] A related procedure called natural orifice transluminal endoscopic surgery (NOTES) uses the body's natural orifices, such as making a small incision in the vagina to access the abdominal cavity and remove the gallbladder.[16] Endoscopic procedures can also be performed on the bladder through the urethra.

CAGR rate by surgery segment 2011-2016



The market for minimally invasive medical devices[20]

The global market for minimally invasive medical devices and instruments was worth an estimated \$13.4 billion in 2010. The market is expected to reach \$21.1 billion by 2016, a compound annual growth rate (CAGR) of 7.9%. Orthopedic surgery is the fastest-growing application segment, with a CAGR of 11.2% between 2011 and 2016, followed by cardiothoracic surgery (8%) and vascular surgery (7.8%).


A Promising Scenario

All of these new approaches, however, will not make old procedures obsolete. Not every patient with colon cancer will be able to have minimally invasive surgery in the future, and not every patient with diabetes will have his or her genetic profile analyzed. Still, the

possibilities are considerably improved when clinical methods become more precise and more flexible. For many patients, less invasive methods offer gentler and more customized treatment options. For physicians, this means they can explore a wide variety of options and choose the right one for their patient – the perfect scenario for the therapy of tomorrow. ●

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Transforming Surgical Procedures for Lung Cancer

Text: Kathleen Raven | Photos: Thomas Steuer



“With the ability to look at the scan right in the OR, we can see the nodules ourselves, and immediately proceed to a resection.”

Mahesh Ramchandani, MD
Cardiothoracic surgeon,
Houston Methodist Hospital,
Texas, USA

With sophisticated image guidance, surgeons at the Methodist Hospital in Houston in the U.S. perform minimally invasive and highly precise interventions on patients’ lungs.

Mahesh Ramchandani, a cardiothoracic surgeon at Houston Methodist Hospital in Texas, USA, has devoted his career to searching for innovative methods for cardiothoracic surgery. Earlier this year, he asked his friend and colleague, Alan Lumsden, chair of the department, about the possibility of localizing a nodule or tumor in the lung with what Lumsden used every day: a CT-like angiography system in the hybrid operating room.

Trading toolboxes

By trading advice, “we get the opportunity to see what each other is doing – to sort of look into each other’s toolkit,” Ramchandani says. He is a specialist in operating on patients’ lungs. At the slightest puncture, the lung can collapse from an airy structure to something like a compact sponge. If possible, Ramchandani follows a minimally invasive approach called

“Combining the 3D imaging system and VATS might shorten a patient’s procedure by an average of four hours from start to finish.”

Alan Lumsden, MD
Cardiothoracic surgeon,
Houston Methodist Hospital,
Texas, USA



video-assisted thoracoscopic surgery or VATS, which consists of inserting a video camera along with special surgery tools through small incisions – forgoing the need to open up the whole chest. Because the surgeon works through small ports VATS provides less complications, less pain, a shorter recovery time and a better cosmetic outcome. However, the method has trade-offs, because the surgeon has limited sight and loses tactile contact to the surgery site.

About five years ago, Houston Methodist purchased a robotic-assisted angiography system, the Siemens Artis zeego, which delivers 3D CT-like images owing to a detector rotating around the patient in a flexible C-arm. Originally, the system was used mainly for cardiovascular procedures. Lumsden and his colleagues focused on the implantation of coronary stent grafts, trans-catheter valves and image-guided interventions on aneurysms of the aorta, for example. “We began using the system to place coils inside an aneurysm by going in with a needle through the back to treat endoleaks. In that situation it’s important that you are accurate,” Lumsden says. He quickly became an expert in navigating the system, while Ramchandani was an expert at VATS. Thus, the two colleagues made common cause.

Adopting a precision approach

With the VATS approach, nodules that are visible on the surface of the lung can be removed with relative ease. Since this approach

does not allow one to palpate the lung, deeper nodules need to be localized in advance. By combining the 3D imaging system and VATS, the physicians found they could pinpoint and remove such pulmonary nodules or tumor tissue with extreme accuracy using small chest incisions. The duo has already successfully performed the technique on several patients.

To understand how this method might improve lung cancer surgery, it helps to know what happens during a traditional VATS procedure, Ramchandani explains. On the day of surgery, a patient might arrive to the hospital at 7 o’clock in the morning. He or she then checks in at the radiology department, where a CT scan is performed. The radiologist localizes the tumor or nodule, for example by injecting blue dye to the targeted area based on CT images. By 8 o’clock, the patient enters the pre-operating area, by about 9 or later, the surgery eventually starts. “The patient ends up being shuttled from one part of the hospital to another, which is inconvenient,” Ramchandani says. During this time, the blue dye, if it is used, can dissipate from the targeted area. Further, CT scans taken in the radiology department do not always match the position of the patient on the operating table, Lumsden points out. Another important disadvantage of the traditional workflow is the risk of a pneumothorax during the needle procedure in the CT room. Such complications could be handled much safer in an OR environment.

With the new method, a patient enters the operating room without a visit to the radiologist.

“With the ability to look at the scan right in the OR, we can see the nodules ourselves, and immediately proceed to a resection,” Ramchandani says. Artis zeego, which delivers images with spatial resolution in the submillimeter range, has a virtual guidance system to apply a localization needle to the nodule or place a solid marker. Then, the surgeon can make small incisions to introduce his video camera and instruments and securely navigate to the targeted area under fluoroscopic control for removal of as little lung tissue as possible.

Improving procedures while lowering costs

Lumsden estimates that this precision technique might shorten a patient’s procedure by an average of four hours from start-to-finish. While he and Ramchandani are still gathering data, it is possible that patients will also have shorter recovery times, because of the quicker procedure and the lesser interventional trauma. The team plans to publish a cost-savings analysis that outlines the details of their protocol, Lumsden says. For example, the billing

process might be more simplified. “Normally you would get a billing from the radiology department, and a separate bill from the surgical side,” Ramchandani explains. “Theoretically, the cost of the procedure should also be lower to the patient and to the insurance company.”

This type of lung cancer surgery could become popular for removing pulmonary nodules that are caught early through low-dose CT screening. Screening has recently proven to help reduce mortality in heavy smokers, and is endorsed by new U.S. guidelines on screening and reimbursement. As the guidelines gain traction, then surgeons may find themselves in even greater demand for imageguided biopsies as well as for minimally invasive resection of small pulmonary nodules.

Of course, hospitals will need to invest in hybrid ORs first, Lumsden points out. Typically, hybrid operating rooms have been considered necessary for cardiac or endovascular procedures, but not for thoracic ones. That could change. “People will start thinking about the possibility that CT-like scanning in the OR could help,” Ramchandani agrees. “Only by using it can one learn the possible applications of this important technology.” ●


Kathleen Raven has covered lung cancer clinical trials for Biopharm Insight, consumer health for Reuters Health and biomedical news for Nature Medicine. She is a freelance writer in New Haven, Connecticut, USA.





Performing Art in Interventional Oncology Therapy

Text: Robert L. Bard | Photos: Jock Fistic



Sylvester Comprehensive Cancer Center at the University of Miami in the U.S. provides more accurate diagnosis and specialized treatments. New imaging technologies allow specialists Govindarajan Narayanan, MD, Riccardo Lencioni, MD, and their team to provide successful, less invasive therapies.

Staffed with clinicians specializing across the entire spectrum of procedures, the Department of Interventional Radiology (IR) at the University of Miami Miller School of Medicine is a well-known and respected institution. Sylvester Comprehensive Cancer Center, part of UHealth – the University of Miami Health System, is a center of excellence for cancer treatment and research that provides the full scope of available treatment models. The IR department at the Miller School of Medicine relies on a fleet of high-end equipment to cater for a high volume of patients and support highly proficient clinical staff. Leading this operation is Govindarajan Narayanan, MD, Chairman of Interventional Radiology at Sylvester Comprehensive Cancer Center, in a unique collaboration with Riccardo Lencioni, MD, FSIR, EBIR, Vice-Chair of Clinical and Translational Research at Sylvester.

Lencioni is a world-renowned interventional oncologist from the University of Pisa in Italy. He is considered one of the pioneers in interventional oncology and was greatly involved in defining the field. He served for six years as Chairman of the European Conference of Interventional Oncology (ECIO) and later the World Conference of Interventional Oncology (WCIO). Lencioni explains that the full name for this field as proposed years ago was in fact “image-guided interventional oncology” and later came to be known simply as interventional oncology; Lencioni, however, still stresses the “key role of imaging in oncology.”

Narayanan was inspired by Lencioni’s innovations and successes with less invasive treatments for liver cancer. Sylvester was fortunate enough to lure Lencioni to the United States to help expand the treatment options for its patients.



Govindarajan Narayanan, MD
Chairman of
Interventional
Radiology Sylvester
Comprehensive
Cancer Center

“Our patients is given a treatment option based on what is the best choice for them, not based on what the center is best at performing.”

Convincing Lencioni to join the division at Sylvester is just one of Narayanan's recent successes. Since Lencioni's appointment, the program has grown from a team of just four to 16 interventional radiologists and now ranks among the largest fellowship programs in the country. Narayanan explains, “Our program is unique in that you get general IR, the entire gamut, along with trauma and a very high-quality interventional oncology program. Most sites in the country are for one or the other.”

Narayanan continues, “We deliberately built the program from the initial stages to offer all transcatheter and ablation options available”. The most common procedures of these are transarterial chemoembolization (TACE), radioembolization (Y90), along with irreversible electroporation (IRE), microwave (MWA), radiofrequency (RFA), and cryoablations. Sylvester Comprehensive Cancer Center not only has the equipment to perform all procedures currently offered, they also offer skilled specialists who routinely perform these procedures as well as engaging in research. Therefore, as Narayanan says: “A patient here is given a treatment option based on what we

think is the best choice for them, not based on what we are best at.”

Radiopaque beads and syngo DynaCT

While TACE has been around for over 30 years, a dedicated embolic particle for TACE was only introduced 10 years ago. “The introduction of drug-eluting beads basically revolutionized the treatment of some tumors, particularly primary and metastatic liver cancer,” Lencioni explains. However, unlike Lipiodol used for conventional TACE, the drug-eluting beads themselves are not visible on X-ray. This means that during the procedure, the treating physician has only indirect feedback on the extent of embolization and exact location of the delivered drug.

The team at Sylvester Comprehensive Cancer Center is one of the first globally to use a new type of embolic beads, which are radiopaque. The visibility of these new radiopaque beads during the embolization procedure enables real-time adjustments to optimize patient treatment. “During the procedure, you have feedback that was not available with the standard beads,” Lencioni explains.

The new bead technology works in concert with cone beam computed tomography (CBCT) and Narayanan depends on the Siemens application *syngo DynaCT*. “In the past, we relied solely on conventional angiography where you see images without the cross-sectional 3D view and a lot of times you don't get the entire information,” says Narayanan. “Vascular anatomy of the tumor is usually the most important aspect and it determines whether your procedure is going to be successful or not. So if you have the option of additional information which otherwise may have been missed, it improves your outcome. *syngo DynaCT* gives you an extra layer of information which initially was not available with conventional angiography,” he explains.

Lencioni adds, “during the procedure you have feedback that was not available with the standard beads, and we have already seen how in action this translates into fine tunings,



Govindarajan Narayanan, MD, and his team working at Sylvester Comprehensive Cancer Center.

adjustment in the position of the catheter, going more distal or proximal. This becomes a truly 'manicured' embolization."

Searching for a predictor

Currently, the first indication of tumor response comes only weeks after the intervention, in the patient's follow-up imaging results. Lencioni found that there was room for improvement: "With the current protocols, basically, you often wait for the tumor to send a signal of activity and follow the tumor. We are not first; the tumor is ahead. Then, we try to deal with it. This may not be the best way to treat the cancer: You want to be ahead of the tumor, rather than behind it." He continues:

"The way to be ahead is to understand that because you didn't get a particular feeder, this indicates that the tumor will reoccur."



Riccardo Lencioni,
MD, FSIR, EBIR
Vice-Chair, Clinical
and Translational
Research Sylvester
Comprehensive Cancer
Center

*"Imaging has a key role
in oncology."*



Combining *syngo* DynaCT with radiopaque beads could make it possible to look deeper into the state of the tumor immediately after treatment and identify predictors of tumor recurrence at that time. Lencioni, who developed the currently adopted follow-up criteria known as the modified RECIST (mRECIST) criteria, envisions a potential change: “The mRECIST criteria have been supported by several studies including meta-analysis. It’s ok, but the tumor is still ahead of us. If we want it to be the other way around, we need to change the paradigm. So, if we were truly able to predict the outcome based on information that wasn’t available before, even the mRECIST criteria, which I developed, could become obsolete. Of course, this is something that we first need to understand. But this is the area we are currently focusing on.”

Beyond cancer treatment

Research opportunities go beyond cancer as Sylvester Comprehensive Cancer Center also operates a prostate artery embolization (PAE) program led by Shivank Bathia, MD.

This relatively new procedure is clinically beneficial for patients with benign enlargement of the prostate, a condition from which many men suffer but one without sufficient treatment options. PAE involves stopping blood flow to the prostate, thus positioning of the catheters is vital. Narayanan emphasizes: “Precision is of paramount importance here because if the particles get to other branches that feed the bladder or the rectum, you could have disastrous complications.”

To tackle such procedures with confidence requires having the right set of tools at hand. Narayanan explains using a simple analogy: “The driver (interventionalist) has to have good knowledge of the anatomy but the car that you drive, or the machine that you use needs to be a high-quality machine that gives you excellent images and resolution.” In addition, he relies on helpful software applications for both 2D and 3D guidance, such as *syngo* Embolization Guidance to plot the vessel path on the *syngo* DynaCT images and overlay it with the fluoroscopy images for real-time guidance during the catheterization. He is also particularly pleased with the ability to overlay reference images with contrast for 2D guidance using the Overlay Reference functionality, known by many users as “Fluoro fade”. “These are all additional tools that are available to make your catheterization better, easier, and give you a higher level of precision and control,” he says.

Specialized training

Narayanan stresses the need for good driving skills to get the most out of the equipment: “Without a good driver, the car is not nearly as useful. The equipment alone is not enough.” Narayanan is leading efforts to make specialty training mandatory, providing his technicians with a week of Siemens Healthineers training to become “super users” of the system. He explains that many institutions put money up front for the capital investments but shy away from training because it is often viewed as an “add-on.” However, Narayanan firmly believes this investment in training is critical for the best results.

Quality, innovations, and the solid service back-up which minimizes downtime are important factors that led to the decision

to install that equipment at Sylvester Comprehensive Cancer Center.

The union of man, machine, and medicine is being optimized at the University of Miami. Interventional radiologists’ cutting-edge treatments and research along with the optimal use of imaging equipment by well-trained technicians provide a synergistic approach with an eye toward innovation. With the current setup, Sylvester Comprehensive Cancer Center patients and the entire region served by UHealth are benefiting from these innovations – now and for the foreseeable future. ●

Robert L. Bard

is a freelance medical writer who specializes in clinical cardiology, heart failure and exercise, and imaging. Bard also conducts clinical research at the University of Michigan’s Division of Cardiovascular Medicine.



“We receive excellent imaging which supports guidance into the vessel.”

Shivank Bhatia, MD
UHealth – the University
of Miami Health System

Professor Oscar Di Paolo and his team at Hospital Provincial del Centenario in Rosario, Argentina, are successfully trying out a blood test for the HER2/neu biomarker. It may help to determine, at a very early stage, whether or not a treatment is working.

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Quality of Life and More Certainty for Breast Cancer Patients

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Wouldn't it be great to be able to determine via a blood test whether a breast cancer patient was developing metastases after removal of a tumor? Is the postoperative treatment working or should the doctors start looking for alternatives?

Text: Karin Naumann | Photos: Thomas Steuer



More than 50 breast cancer patients have been observed so far.

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HER2/neu* is an important biomarker for targeted breast cancer therapy.

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Professor Oscar Di Paolo and his team focus on targeted therapy for HER2/neu positive breast cancer patients.

Professor Oscar Di Paolo and his team at Hospital Provincial del Centenario in Rosario, Argentina, are convinced that this is possible.

Life-saving Biomarker

Di Paolo has been heading up a research project since 2010 in which he and his staff regularly ask HER2/neu* positive breast cancer patients for blood samples. HER2/neu is a gene that promotes cell growth and produces an onco-protein and HER2 positive breast cancers tend to be more aggressive than other types of breast cancer.

“We believe we can determine whether or not the treatment is working by checking the HER2/neu levels in these patients’ blood samples.”

Early Recognition of Therapy Success

“Approximately 20% of all breast cancer patients are HER2/neu positive. We believe

we can determine whether or not the treatment is working by checking the HER2/neu levels in these patients’ blood samples,” says Oscar Di Paolo. Our theory is that if the concentration remains below a threshold, then everything is okay. If the HER2/neu level exceeds the threshold, then the therapy may not be working. Our goal is to spare the patient a treatment that has no benefit for him or her – and an effective alternative can be tried instead. Moreover, the researchers have so far discovered that metastases were found sooner or later in all patients whose HER2/neu* level increased again after removal of the tumor.

Research Focus on the Patient

At first glance, the University Hospital does not appear to be a hotspot of international cancer research. The plaster on the walls is crumbling, students scribble on the hallway walls without fear of repercussions. Oscar Di Paolo and his team, however, are well known in the region. Even patients from expensive, private facilities come to them to participate in the study. “The patients proactively ask: ‘How are my levels?’ as they are monitored. “They are very interested in being engaged in their care and want the optimal treatment with the least side effects,” says Di Paolo. He is one of those doctors who always focuses on the patient. He is passionate about their care and quality of life. The warmth

*The clinical utility of the measurement of HER2/neu in serum as a prognostic indicator for early recurrence and in the management of patients on immunotherapy has not been fully established.

with which patients are greeted at Hospital Centenario is very apparent. The doctors sometimes even pay the bus fare for poorer patients or pick them up from home.

The Study is Far from Over

Early on, the researchers examined 200 healthy women from the Rosario area to determine a threshold for HER2/neu in the blood. In the second phase, they have

so far observed the course of the disease and measured the HER2/neu concentration in more than 50 breast cancer patients. “We must continue our research,” Di Paolo emphasizes. In the long term, Professor Di Paolo believes that it should not just be about determining whether or not a therapy is working. Di Paolo and his team want to know whether the biomarker can be used effectively in the early detection of metastases, which may improve survival chances and save money because patients would need fewer biopsies or even diagnostic imaging. “There is a lot to discover,” says Di Paolo. ●

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Trastuzumab: A Blessing with Possible Side Effects

Breast cancer patients who have a high level of HER2/neu in their blood have a slim chance of survival without a targeted therapy. HER2/neu stands for “Human Epidermal Growth Factor Receptor 2.” Treatment with trastuzumab – a monoclonal antibody that blocks the receptor for this growth factor – can prevent the growth and proliferation of cancer cells.

Unfortunately, the side effects are troubling. The drug can induce cardiotoxicity particularly when combined with anthracyclines although their mechanism is different. Doctors need to keep an eye out for cardiological effects of the therapy – even years after treatment with trastuzumab. In particular, this drug is used in women with a high risk of relapse or when the tumors exceed a certain size. Taking beta blockers and ACE inhibitors as a preventive measure can possibly prevent heart damage.[1]

The team of researchers working with Oscar Di Paolo at Hospital Provincial del Centenario in Rosario, Argentina and the hospital’s cardiology department are planning to observe the effects of trastuzumab on HER2/neu positive patients. Since the side effects of trastuzumab are considerable, it is important to know as soon as possible whether the therapy is really working, and the HER2/neu biomarker can provide an indication of this. If the therapy is not working, heart damage can quite possibly be prevented and the treatment tailored to the patient’s individual needs.

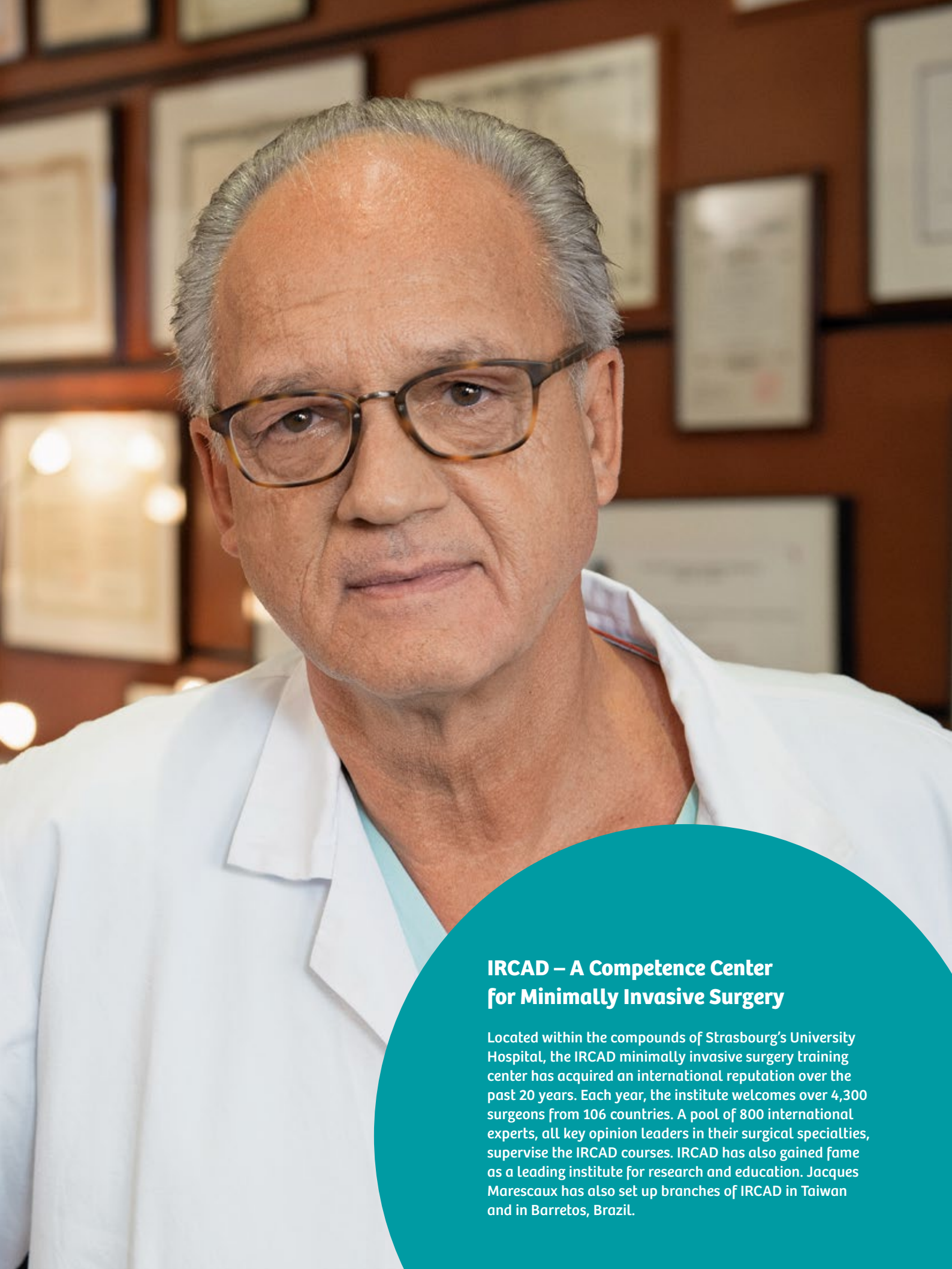
Shaping the Hybrid Future

Text: Andrea Lutz

Since founding IRCAD (Institut de Recherche contre les Cancers de l'Appareil Digestif – Research Institute against Digestive Cancer), a center for original research and training for surgeons in partnership with industry, Professor Marescaux has always geared his work toward integrating 3D patient data with the operating rooms of tomorrow. He thus encouraged the development of virtual and augmented reality combined with robot-assisted surgery.

In September 2001, Professor Marescaux revolutionized the global surgical community by performing the first robot-assisted operation between New York and Strasbourg, known as Operation Lindbergh. In July 2012, as part of the IHU program, his team performed a world-first in robot-assisted liver surgery: using augmented reality intraoperatively. He believes that augmented reality is the most important improvement for treating patients. That is why he is counterbalancing the idea of controlling healthcare spending with the idea of prioritizing research and innovation.





IRCAD – A Competence Center for Minimally Invasive Surgery

Located within the compounds of Strasbourg's University Hospital, the IRCAD minimally invasive surgery training center has acquired an international reputation over the past 20 years. Each year, the institute welcomes over 4,300 surgeons from 106 countries. A pool of 800 international experts, all key opinion leaders in their surgical specialties, supervise the IRCAD courses. IRCAD has also gained fame as a leading institute for research and education. Jacques Marescaux has also set up branches of IRCAD in Taiwan and in Barretos, Brazil.



Hybrid ORs can help to improve patient care in the future.
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Professor Jacques Marescaux, France, has revolutionized surgery and continues to push the envelope with unprecedented research and training ideas. He believes that hybrid ORs and augmented reality in surgery can improve patient care in the future.

How would you define a hybrid operating room?

Marescaux: You always have a treatment to propose to your patient. Especially in the case of cancer. We can propose flexible endoscopy, laparoscopic surgery, or interventional radiology. During the operation, surgeons want every possibility to take a closer look inside the patient. Using flexible endoscopy plus surgery, or flexible endoscopy plus 3D image guidance, or interventional radiology plus surgery – that is the idea of the hybrid operating room.

How can we optimize patient care in the future?

Marescaux: One core topic in optimizing patient care is the availability of all patient data from before, during, and after surgery, along with the option of combining this data. Several projects are underway that aim to superpose image data from different imaging modalities. The fusion of image data from an endoscopic camera with DynaCT data, and the fusion of ultrasound images with preoperative CT data are both particularly valuable for minimally invasive procedures.

How will surgery evolve from now?

Marescaux: A few years ago, all the companies developing imaging technology were focusing on the radiology department. Today, it is totally different. Surgeons want to look at all the details of the picture. They no longer depend on the radiologist's interpretation. For surgeons, the Artis zeego is a fantastic tool. You have everything you want in real time. But in the future, many surgeons still might not have access to a hybrid room. So they will need to have at least an intraoperative ultrasound system – that will be a good first step.



Marescaux believes that surgeons will be more specialized in the future.
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Benefits and efficiency of a hybrid OR have now to be proved.
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IHU Strasbourg – Developing a New Medical Discipline

IHU Strasbourg is a leading research center for biomedical research, medical-technology research, patient care, training, and technology transfer in the healthcare sector. IHU's mission is to develop a new medical discipline that brings together minimally invasive surgery, gastroenterology, and radiology to provide every patient with care tailored precisely to his or her needs. A central aspect of this mission is the inclusion and optimization of image guidance in hybrid surgery. With this in mind, Siemens and IHU Strasbourg have entered into a cooperation agreement.

What is the role of 3D patient data in that respect?

Marescaux: Virtual reality is one of our institute's most important tools. It translates real data into digital data, thus allowing us to turn a medical scan into a virtual 3D clone of the patient. The surgeon can then prepare the procedure on the patient's virtual clone, as these simulations are becoming increasingly realistic. During the intervention, augmented reality provides a transparent view that should soon allow for the automation of complex surgical movements. This automation will only be possible with developments in the field of surgical robotics.

What opportunities do you see for augmented reality?

Marescaux: To me, augmented reality is the most important improvement for treating patients. One example is complex pelvic surgery, in which surgeons must see the different structures they have to preserve: the urethra, the vessels, and the nerves. In some complex cases, it is impossible to see these three elements. Therefore, we want to have the best image of each structure before the operation. The concept of augmented reality makes everything transparent. We need to have an intraoperative imaging system that allows us to see all details, even if the organ moves. I'm sure that if we can show that it is an additional benefit for both the patient and the surgeon, it will be mandatory for a hospital to have a hybrid OR. What we have to prove now is its efficiency.

Can you give us an example of how you could prove that efficiency?

Marescaux: Today, a lot of money is still paid out in the event of complications. If we prove that a surgeon has a better view during the operation and that we can thus decrease the complication rate, then paying two or three million euros for a hybrid room is not too much. You will never be the "gold standard" in the future without this new OR concept.

What advice would you give to decision-makers planning an operating room?

Marescaux: The most important thing is to have enough space for all the devices and to give the team access



to the patient. It is impossible to know what kind of equipment we will need for each surgical discipline in the future. But for general surgeons, it is important to collaborate with several disciplines on the same platform. If you can perform several steps in one operation, you don't need two or three anesthetics for the patient.

What skills will surgeons of the future need?

Marescaux: In the USA, there is a lot of specialization, but the majority of surgeons are generalists working in smaller hospitals. I think that surgeons in Europe are more specialized today. One example is that we have "hepatobiliary surgeons" working with surgeons who only do transplants. And the future will probably bring even more specialization.

So what will be the real challenge?

“I’m sure that if we can show that it is an additional benefit for both the patient and the surgeon, it will be mandatory for a hospital to have a hybrid OR.”

Professor Jacques Marescaux
has revolutionized surgery.

Marescaux: All surgeons like new technologies – and the operating room of tomorrow, with all its robotics, will look like the cockpit of an airplane. You will have the robotic system, the 3D visualization, and a lot of screens. You will push the button and the technology will work for you. It will be very easy. But it will be a challenge for surgeons to know everything about radiation protection. Today, surgeons don’t have enough knowledge of radiation. We want to organize courses to help them understand how best to manage the new kind of OR. WeBSurg is a platform for that.

To what extent do robots change operating rooms?

Marescaux: We are still in the prehistory of robotics. At the moment, the robot just improves a surgeon’s abilities. Sure, it is more precise, but that is really just “peanuts.” However, there is another advantage that will change everything: A robot interface can analyze 1,000 signals per second. When you combine the preoperative image and 3D image guidance with the skill of the surgeon, it will be a huge benefit for the patient.

So are we on the way to the ideal operation?

What is WeBSurg?

WeBSurg is a virtual surgical university. The concept was developed by Professor Jacques Marescaux and his team at the European Institute of TeleSurgery (EITS) in Strasbourg, France. The goal is to provide the surgical community, scientific societies, medical teaching centers, and industries with the first worldwide online surgical training, information on the latest surgical breakthroughs, and a platform for chatting with experts all over the world.

Marescaux: Today, the 3D image that we take from the CT scan gives us the option of doing the operation before the operation. It is like producing a movie. You do one minute of the operation, then you stop. Then you do another minute, stop again, and then cut the best parts together. The mixture of the imaging and the abilities of the robotic system could really lead to the ideal operation. Maybe we will have automatic surgery in 20 or 30 years’ time.

What is your wish for the future of surgery?

Marescaux: The real success for surgery will be the day when you really don’t need surgery anymore in some cases. My wish is that imaging progresses and that targeted therapy continues to develop. ●

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