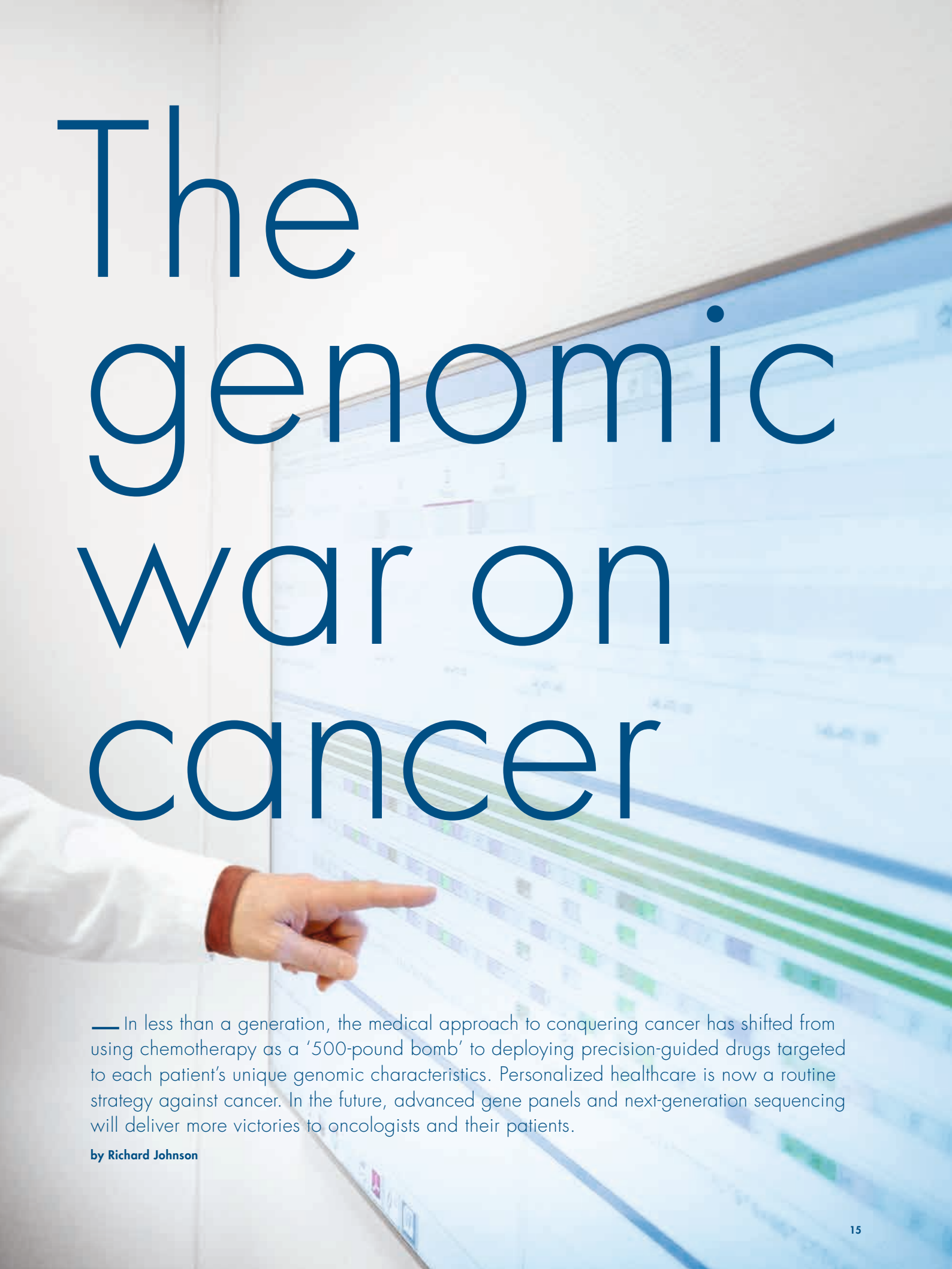
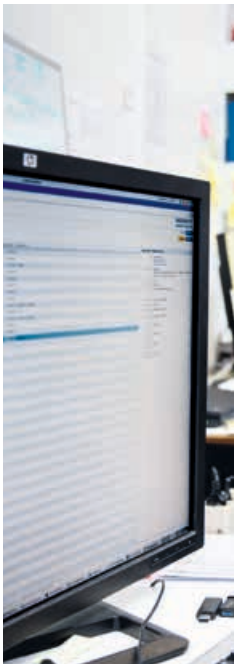
The genomic war on cancer



— In less than a generation, the medical approach to conquering cancer has shifted from using chemotherapy as a '500-pound bomb' to deploying precision-guided drugs targeted to each patient's unique genomic characteristics. Personalized healthcare is now a routine strategy against cancer. In the future, advanced gene panels and next-generation sequencing will deliver more victories to oncologists and their patients.

by Richard Johnson



The Center of Genomic Medicine is located right above the main entrance, overlooking the flow of visitors entering the hospital.

Walking into Copenhagen's Rigshospitalet, the leading specialty hospital in Denmark, a visitor feels the mixture of hope and apprehension that vast institutions tend to inspire. Sixteen stories of concrete-and-glass functionality, the building stacks floor upon floor of hospital rooms, each packed with high-tech equipment and, intermittently, staff working to save the lives of patients.

Through the windows of the Center for Genomic Medicine, looking out on Rigshospitalet's main entrance from one floor up, it is the patients and their families that you notice.

"Many of the patients coming into the hospital are already very sick," says Professor Finn Cilius Nielsen, head of genomic medicine for Rigshospitalet. "As a regional center, we tend to see cancer patients and others who are difficult cases. They may have failed treatments at other hospitals, or relapsed after treatment, so they come here for a higher level of specialized care."

The Center for Genomic Medicine brings 21st Century weapons into this battle.

For patients and doctors, fighting cancer has shifted to the molecular front: Life's building blocks, DNA and RNA, have emerged as critical for diagnosing and treating cancers. And so this war on cancer has become a genomic war. In the century to come, genomic medicine will undoubtedly conquer other frontiers – but today that battle is mostly being fought in cancer.

QIAGEN works hand-in-hand with scientists in universities and life science companies advancing the understanding of cancer – and with doctors deploying companion diagnostics, novel sequencing technologies and advanced bioinformatics to make personalized treatment decisions based on each patient's genomic data.

Bridging the continuum

Rigshospitalet exemplifies the continuum of healthcare in large, research-based institutions that are leading the war against cancer.

Across the street, the University of Copenhagen is deeply engaged in research into the causes and pathways of cancer, the basic science of how the disease works. In the hospital, the focus is on patients and how to apply the best treatment to reverse the disease or prolong survival. Many of Rigshospitalet's staff members serve dual capacities, in the university and the hospital.

Molecular biologist Dr. Christina Westmose Yde focuses on exploring new treatment options for cancer patients.

14 million

people are newly diagnosed with cancer every year, accounting for more than 8 million annual deaths.

Viewing cancer as a genomic enemy

Each year, more than 14 million people are newly diagnosed with cancer, and the disease takes more than 8 million lives, according to the World Health Organization. Authorities expect the number of new cases worldwide to grow by about 70 % over the next two decades.

The threat is exacerbated because cancer is not one disease, but many. Cancer can take hold in any of more than 100 parts of the body and is often named by its site of origin – lung cancer, breast, colorectal and so on. That was the historical approach to fighting the war on cancer.

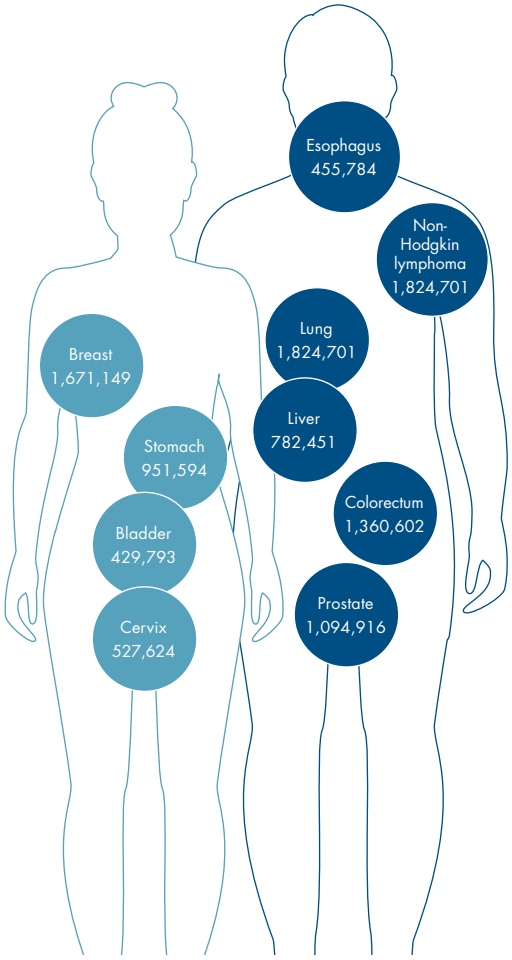
Less visibly, cancer wreaks its havoc in the body at the molecular level. As gene mutations disrupt the normal growth mechanisms of cells, uncontrolled cell division forms tumors in one place or begins to disseminate cancer cells through the body. The problem is a molecular "variant" in DNA, its RNA messenger system, or proteins they use to maintain body functions.

Molecular variants and their combinations are highly individualized – so that one lung cancer patient in a hospital can differ in critical ways from a lung cancer patient in the next bed. In fact, no two patients have exactly the same disease. Their genomic profiles can dramatically influence the development of the disease and the efficacy of potential treatments.

Personalized healthcare – also called precision medicine – employs molecular diagnostics to test each patient's genomic variants as a guide to the best treatment. The tests find biomarkers for changes at the molecular level known to either cause the cancer or affect the usefulness of potential drugs in treating it.

↗ *Center for Genomic Medicine*
www.genomic-medicine.dk

↗ *GeneReader NGS System*
www.genereaderngs.com



10 most common cancers worldwide by annual incidence and main associated mutations.

Breast	**Non-Hodgkin lymphoma**
1. PIK3CA p.H1047R	1. TP53 p.R43H
2. ESR1 p.K303R	2. TP53 p.R175H
3. PIK3CA p.E545K	3. TP53 p.G154V
Stomach	**Lung**
1. APC p.T1556fs*3	1. CDKN2A c.1_471del471
2. PIK3CA p.H1047R	2. EGFR p.L858R
3. KRAS p.G12D	3. EGFR p.E746_A750del
Bladder	**Liver**
1. FGFR3 p.S249C	1. TP53 p.R249S
2. CDKN2A c.1_471del471	2. HNF1A p.G292fs*25
3. HRAS G12V	3. CTNNB1 p.A5_A80del
Cervix	**Colorectum**
1. PIK3CA p.E545K	1. BRAF p.V600E
2. KRAS p.G12D	2. KRAS p.G12D
3. KRAS p.G12S	3. KRAS p.G12V
Esophagus	**Prostate**
1. TP53 p.R43H	1. PTEN c.1_1212del1212
2. TP53 p.R175H	2. HRAS p.Q61L
3. TP53 p.G154V	3. BRAF p.V600A

Source: GLOBOCAN 2012, QIAGEN Knowledge Base 2016.

The genomics center, a long, narrow strip of offices and laboratories jammed with instruments, test kits and patient samples, bridges these worlds – connecting the laboratory bench to the patient's bedside. From the research end, the latest advances continually create potential new strategies to deal with genomic influences on cancer, its pathways and treatment. On the clinical side, the laboratory works closely with oncologists to provide insights into the hospital's patients and how to address their urgent needs for approaches to fight the disease.

The Rigshospitalet lab has a full range of technologies, from standard tests to screen for individual cancer-causing gene mutations to sophisticated next-generation sequencing (NGS) algorithms for more complex cases. The center runs about 3,500 tests a year.

"In running these tests, the goal is to provide the most promising treatment for each patient," Professor Nielsen says. "We have access to a large number of targeted therapies for cancer, whether approved or in clinical trials, and our research role allows us to use deep sequencing to suggest clinical trials of more experimental treatments for patients who fail standard therapies."

A lung cancer patient, for example, came into Rigshospitalet already very ill. Next-generation sequencing on a sample of his tumor revealed a mutation of the BRAF gene, a cancer-causing variant active in about 50 % of melanoma skin cancers – but not usually seen in lung cancer.

3,500

samples, mostly from cancer patients, are processed by the Center of Genomic Medicine a year.

"There is an approved drug for BRAF, but normally the patient would have melanoma to receive this drug," says Dr. Lars Joensen, head of the center's NGS core unit. "This lung cancer patient was offered a drug that acts against the BRAF-activating mutation, and he responded well to the drug. The patient is alive today, almost a year later, so it's a very good and happy story."

The bench-to-bedside continuum uses the same kinds of tools from cancer research to clinical diagnostics: instruments, kits and software to prepare samples, to sequence genes and detect variants, and to sort the results for a clear interpretation. So diagnostic methods migrate from university and industry laboratories, through regulatory processes, into hospitals and clinics.

From the early days of biotechnology, QIAGEN has offered an ever-broadening portfolio of the latest and best genomic tools to its customers in life science research and molecular diagnostics. The company's tools are instrumental in thousands of research studies, relied upon in drug development, and used by physicians around the world in the war against cancer.

Making personalized medicine routine

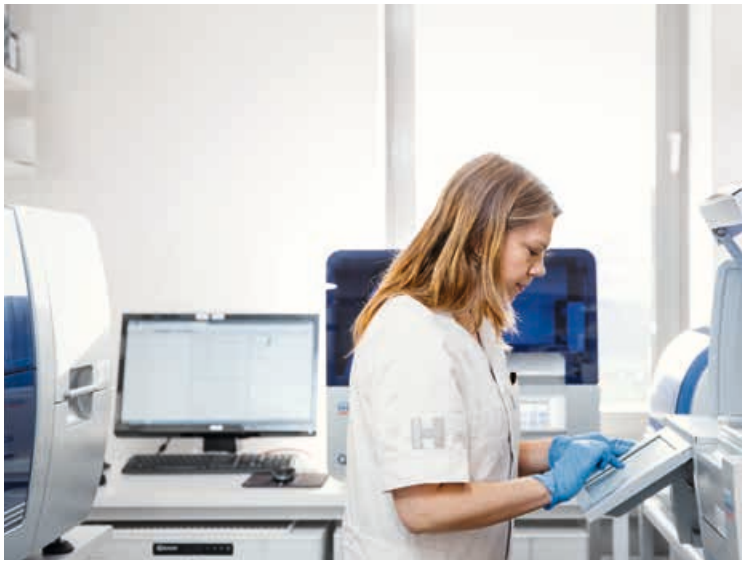
Since the first companion diagnostics emerged in the 1980s, detection of genomic mutations to guide treatment has expanded to the point where personalized medicine has become standard medical strategy for a number of cancers – routine, and yet continuing to evolve rapidly.

"A lot has happened in the field of genomic profiling in the last few years," nods molecular biologist Dr. Christina Westmose Yde, who focuses on genomic profiling of patients for whom no approved treatment options are yet available. "Instead of putting a cancer into a certain box based on the initial diagnosis, personalized medicine now enables us to take a deep look into the tumor to find out what's driving its growth and then to target the specific disease."

Typically, treatment follows clinical guidelines that provide for testing to detect one or more genetic biomarkers to match patients with targeted therapies that act upon their variants. These protocols amount to decision trees, with each step guided by a single-purpose test.

A patient with non-small cell lung cancer (NSCLC), for example, would be tested for alterations of the epidermal growth factor receptor (EGFR) gene. Testing "positive" indicates the patient's tumor growth could be slowed or halted by one of the innovative drugs designed to block the EGFR receptors on cells from binding with enzymes that lead to uncontrolled growth.

"Companion diagnostics based on insights like the EGFR link to lung cancer have come into routine use by oncologists around the world. QIAGEN provides about half of the kits targeting EGFR mutations, and our tests for other cancer biomarkers are disseminating as we steadily gain regulatory approvals," says Dr. Tadd Lazarus, chief medical officer of QIAGEN. "The emergence of reliable, standardized tests is making a great difference for patients. Before genomic testing



The Center of Genomic Medicine has been an early tester of the GeneReader NGS System and plans to use it for several applications that require fast turnaround times.

enabled personalized medicine, cancer treatment was often trial-and-error."

As the knowledge of cancer continues to expand, the number and type of biomarkers are growing rapidly – as are the treatments targeting those mutations. About 50 genomic variants are now targeted by drugs offering potential benefit in different cancers. So research-driven clinicians like those at Rigshospitalet are broadening their genomic testing to cast a wider net.

"Cancer is complex. Some cases are easy, but some are very difficult," Professor Nielsen says. "When it comes to many solid cancers, you find a pattern of mutations, so we need to be able to look into a combination of variants and potential treatment approaches. What you are looking for, and therefore the kind of tests to run, depends on the individual patient."

The trend is to move from tests for individual biomarkers toward gene panels that analyze dozens or hundreds of gene variants in a particular type of cancer. For different needs, laboratories can access a variety of technologies from PCR to multimodal instruments to next-generation sequencing.

Taking sequencing to the next generation

In clinical research and healthcare applications, time constraints are driving a shift to ever-faster platforms that can analyze more and more variants simultaneously. Testing a patient with cancer or a rare disease for a single variant at a time – or, at the other extreme, sequencing the patient's whole genome – is simply too slow in many cases.

"Turnaround time is really important for the patients. You want to avoid delaying the treatment too much," Professor Nielsen says. "Some of the patients are very ill to start with, or children who have already been through a diagnostic odyssey. So we need to get answers."

Leading institutions like Rigshospitalet are deploying next-generation sequencing and multiplex gene panels to accelerate the process of precision diagnosis and treatment.

"For a cancer patient, any delay in treatment seems like double time. If you have to wait and the cancer continues to progress, then by the time you have results it may be too late to do the patient any good," says Dr. Maria Rossing, a physician and staff specialist with the Center for Genomic Medicine. "If we could run a gene panel that looks at the most likely muta-

Liquid biopsies from blood and other body fluids hold great promise to improve the diagnostic process and treatment monitoring of cancer patients.

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Dr. Lars Joensen
Biochemist, Center for Genomic Medicine, Copenhagen, Denmark.

tions, coming up with a preliminary answer in five days rather than weeks, that would be a good thing."

In late 2015 QIAGEN introduced a novel solution that promises to address this need for clinical research labs: the GeneReader NGS System and the platform's first application, the Actionable Insights Tumor Panel. This multiplex assay targets 12 clinically actionable genes implicated in prevalent cancer types, including breast, ovarian, colorectal, lung and melanoma. While not yet approved for diagnostic use, this platform will soon be the solution sought by many labs.

The Actionable Insights panel can detect up to 1,250 different genetic mutations in a sample. The assay integrates with QIAGEN Clinical Insight, a cloud-based bioinformatics solution that helps to identify important genetic variants – including those that are in approved drug labels, professional guidelines and active phase III clinical trials.

The Rigshospitalet genomics center, which uses a wide range of NGS technologies, put the GeneReader NGS System and Actionable Insights panel through their paces this winter in carefully controlled tests – and the reactions from the staff involved were positive.

"We managed to have a turnaround time of around five days, from sample to answer," says Dr. Joensen. "It's very helpful to have a small panel, where you cover all of the clinically relevant variants and can quickly deliver actionable insights."

For understanding the biology behind a disease, researchers use whole genome or exome sequencing to capture every possible bit of genomic evidence – but when a patient is in the hospital, the doctors' focus is on getting to the right decision on treatment. "There are some practical obstacles to sequencing full genomes, including a longer time to result and more challenging data analysis," Dr. Yde explains. "But

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Prof. Dr. Finn Cilius Nielsen
Head of the Center for Genomic Medicine, Copenhagen, Denmark.

the main question is what you're adding in terms of actionable insights. As of today, I believe that targeted sequencing approaches cover most of what you're looking for to guide treatment decisions."

Professor Nielsen says the QIAGEN focus on clinical relevance and fast turnaround, combined with GeneReader's automated handling from sample to final report, will allow any laboratory without research-level NGS expertise or bioinformatics staff to begin to take advantage of NGS. The integration of QIAGEN Clinical Insight, drawing on continually updated, expertly curated knowledge bases, also provides a powerful interpretive tool to determine the relevance of genetic variants found in a sample with the latest information in the rapidly developing field of cancer research. "It's a democratization of the process," Professor Nielsen says.

Working toward tomorrow's victories

The struggle against cancer is a war of insights – with medicine striving both to understand the mechanisms of the disease and to find the best treatments for each individual patient. The victories are adding up, and the campaign is gaining momentum.

The Rigshospitalet team embraces increasing standardization and automation of genomic testing, including NGS, to save money and to drive the growing use of precision medicine. Professor Nielsen sees a future of expanding reliance on molecular diagnostics for clinical insights – both earlier in the process and later in the course of treatment.

"There is no doubt that we should do genomic tests as early as possible. When we come in very early, we know that we can actually change the course of disease for the patient," Professor Nielsen says. "If you ask me, I would like to have the first biopsy available and do all the tests then – the gene panels, the NGS sequencing. The earlier it's done, the better the outcome."

The emergence of relatively inexpensive, minimally invasive "liquid biopsies" will also benefit the diagnostic process and enable the monitoring of outcomes while treatment progresses, Professor Nielsen says. Liquid biopsies use easily collected samples of blood or other fluids to detect circulating tumor cells or genomic molecules shed by cancer anywhere in the body, and these patient-friendly tests can replace difficult and sometimes risky surgical biopsies.

"Every day in the newspaper, people discuss the increasing cost of using cancer drugs," Professor Nielsen adds. "If we can reduce those expenses by monitoring how the treatment is working with an easy test and by tailoring the use of the drug to the patient's precise need, it's good for the patient but it's also very good for society."

Medicine has advanced in the war on cancer. There is wide variation among cancer types and patient circumstances, but most cancers have become more survivable. Across all varieties, 68 percent of U.S. patients survive more than five years, up from 49 percent two decades earlier. Other countries also have seen dramatic improvements. With early diagnosis, innovative therapies plus targeting through genomic medicine, the blunt news "You have cancer" is giving way to a systematic, personalized process aimed at curing or managing the disease.

"The patients we see are in advanced stages, but even if they do not get complete remission, they are gaining some good additional time to live, where they are feeling much better," Dr. Rossing says. "Not to be personal, but had it not been for the good successes we have seen in our patients, I could not function as an M.D. in this setting. That makes it worthwhile."