
Recent technological innovations have improved the translation of basic research to the clinic, enabling rapid response to the COVID-19 pandemic.

# The technologies that will transform health care

*Over the past two decades, scientists have helped doctors treat patients more effectively by equipping them with groundbreaking tools, such as gene editing, superresolution fluorescence microscopy, and next-generation sequencing.*

In early 2020, there was no delay in producing a precise illustration of the coronavirus particle that helped the world understand the nature of the public health problem it faced. The electron microscopy technology used to create the image was almost a century old in its origins (*1*). Since then, scientists have made rapid advances in developing ways to examine in exquisite detail how the human body operates.

The field of microscopy has flourished in the past two decades, according to Jennifer Lippincott-Schwartz, a senior group leader at the Howard Hughes Medical Institute's Janelia Research Campus in Ashburn, Virginia. As a cell biologist who's keen to see her research translated into clinical settings, she says the key to making the leap between lab and hospital is to have clinicians, scientists, and engineers working closely together.

"The doctors understand physical health problems at a high level, biologists see things at the cellular level, and the engineers help us work together by offering creative technical solutions," she says.

## Health care under the microscope

In 2014, Eric Betzig, Stefan W. Hell, and W. E. Moerner were awarded the Nobel Prize in Chemistry for the development of superresolution fluorescence microscopy (*2*). In developing a microscopic technique that allowed scientists to observe the workings of cells down to the nanoscale level, these researchers created unprecedented possibilities for understanding the nature of human diseases.

"We now have the ability to actually watch viruses invade cells. It's possible to watch them assemble and then leave," says Lippincott-Schwartz.

An example of the use of superresolution microscopy in health care has been as part of the search for a vaccine against the human immunodeficiency virus (HIV). Over the past 20 to 30 years, cell biologists have characterized how this virus behaves in our bodies.

"We now understand some of the reasons why it's hard to make a vaccine against HIV. One reason is that the virus has proteins sparsely distributed on its surface. This makes it hard to create antibodies that can tightly bind to the proteins so that a single vaccine can work against the virus," explains Lippincott-Schwartz.

Scientists used to think that the HIV viral assembly process was primarily protein-based. Now they understand that the virus relies on surface lipids to sort and assemble proteins into the viral

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particle, and this is critical for its release from one cell and for access to others.

"That's important because it gives you clues for how you might want to disrupt that process," says Lippincott-Schwartz.

Currently, she is working with a project team at Janelia called COSEM (Cell Organelle Segmentation in Electron Microscopy) that is using machine-learning and computer-vision techniques to automatically identify and quantify all intracellular substructures within isotropic EM data obtained from focused ion beam-scanning electron microscopy (FIB-SEM). This approach has the potential to help scientists better understand what pathways the coronavirus is using to replicate itself at a subcellular level.

"That's where I'm really excited. Using this microscopy platform allows you to get thousands of scanned electron-micrograph images serially collected through an entire cell," says Lippincott-Schwartz. "But it can take years to go through all the images manually and build the image."

To fix this problem, computer scientists in the COSEM team are developing machine- learning algorithms to automate this process, dramatically speeding up how fast she and her colleagues can analyze the data.

"It's the first time a whole cell has really been viewed in this fashion," she says.

Scientists in China are equally optimistic about how microscopy technologies could help us tackle diseases.

"Recent advances in optical imaging have changed how we traditionally diagnose disease," says Hui Li, a principal investigator at the Suzhou Institute of Biomedical Engineering and Technology of the Chinese Academy of Sciences, in China. "Pathology laboratories in hospitals will look completely different in the future as these technologies improve and are adopted into daily clinical practice. We may also see in-vivo imaging technology used in operating theaters."

## New model, new ideas

Cell biologists are also revolutionizing how we treat diseased organs and discover and test new drugs. In 2006, Japanese scientist Shinya Yamanaka discovered that he could take mature cells and turn back the developmental clock, inducing them to become pluripotent stem cells that could develop into body tissues. This breakthrough offered enormous possibilities for regenerative medicine, as researchers foresaw a clinical world in which they might take a person's skin cells, for example, reprogram them, and then use these to grow to healthy organs to replace damaged parts of the body. Organoids–tiny, self-organized 3D tissue cultures derived from stem cells–have started to have a practical impact on clinical practice with the development of immunotherapies against cancer.

"When it comes to screening drugs to use to treat cancer patients, there are lots of publications showing that organoids are very useful. You can take tumors from people and do almost personalized medicine. You can predict which drugs will work and which ones won't work," says biologist Christine Hale of the Wellcome Trust Sanger Institute, in Hinxton, United Kingdom.

Scientists are also working on developing organoid tissues that mimic how an organ works. Among the major projects were, for instance, the generation of liver organoids reported in 2013, and the generation of "mini-brains" in 2013 and 2015, says Volker Vogel, associate director of business development at Lonza Bioscience, headquartered in Basel, Switzerland.

"Organoids represent an ideal tool for research in developmental biology and related diseases," he says. "Furthermore, organoid-based technologies supported by stem cells and primary cells may lead to in vivo-like histology of microtissues with complex histology, such as brain, liver, kidney, or pancreas tissue."

Such microtissues, generated by organoid-based technologies, can be used to study normal and disease development, to discover new drugs, and to test a drug's toxicity.

"In the future, such microtissues generated by organoid technologies may be used for therapeutic organ repair. For instance, in liver diseases or diabetes," he adds.

## Life-saving detective work

Genetic tests to detect the presence of a virus have become routine, especially now during the coronavirus pandemic. Taking a simple swab from a person's nose and throat, scientists perform polymerase chain reaction (PCR) tests to determine whether that person carries the genetic material that causes COVID-19.

In recent decades, PCR technology has become increasingly sophisticated. With the advent of droplet digital PCR (ddPCR), scientists now have an exquisitely sensitive tool for investigating the behavior of tumors in patients undergoing treatment in real time, says George Karlin-Neumann, director of scientific affairs for Bio-Rad Laboratories in the United States.

Before ddPCR, methods for nucleic acid detection did not always have a low enough limit of detection to positively identify a target mutation by liquid biopsy, especially if a patient was in an early stage of cancer or had a residual tumor following treatment. Therefore, invasive tissue biopsies were relied on. Liquid biopsies are less invasive and can be done more frequently. Researchers have begun exploring additional ways to monitor patients for mutational biomarkers to better track disease progression and guide treatment.

"We've seen tremendous early uptake in liquid biopsy translational research, as it makes it easier to detect and monitor low

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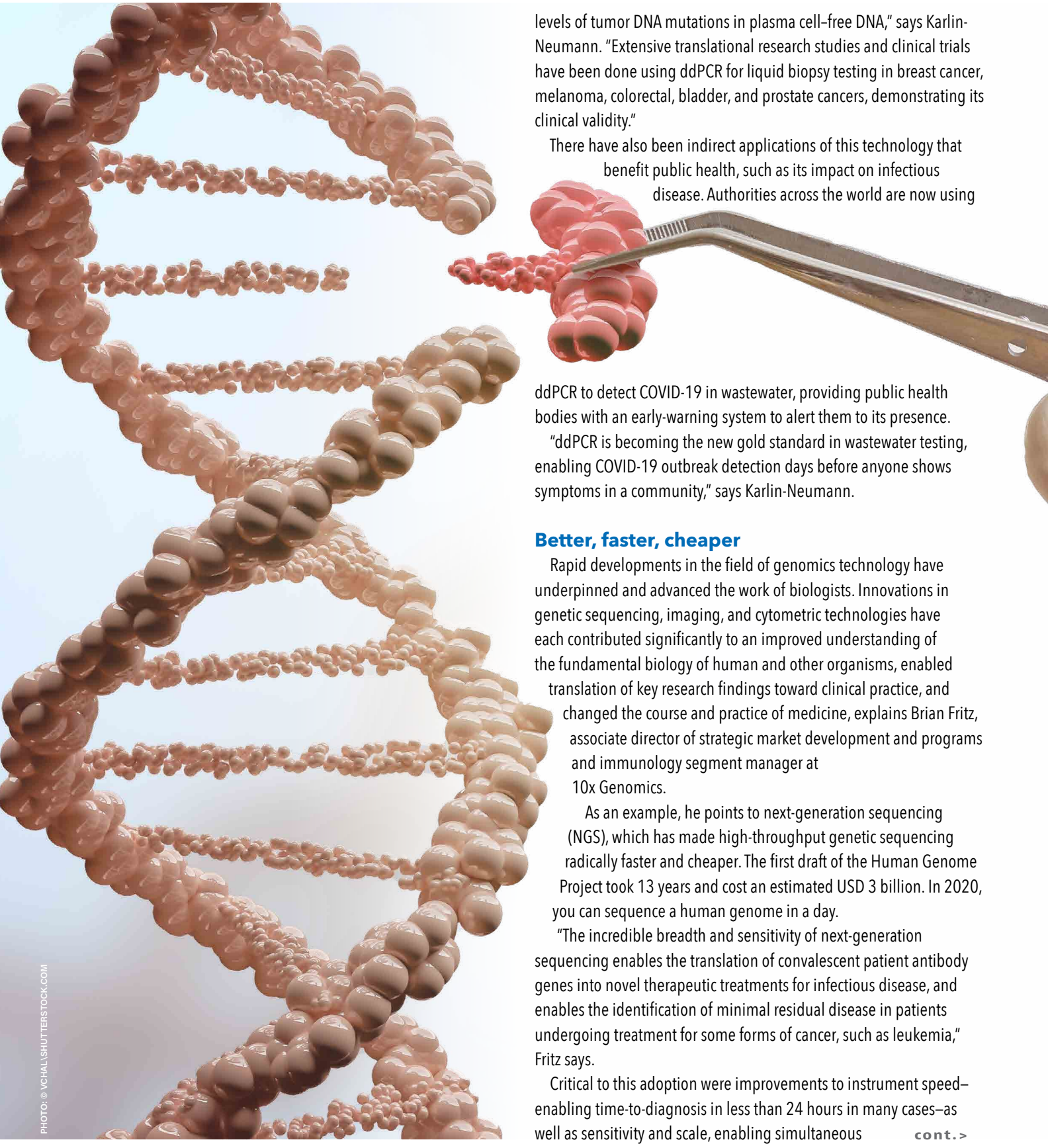

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levels of tumor DNA mutations in plasma cell–free DNA," says Karlin-Neumann. "Extensive translational research studies and clinical trials have been done using ddPCR for liquid biopsy testing in breast cancer, melanoma, colorectal, bladder, and prostate cancers, demonstrating its clinical validity."

There have also been indirect applications of this technology that benefit public health, such as its impact on infectious disease. Authorities across the world are now using ddPCR to detect COVID-19 in wastewater, providing public health bodies with an early-warning system to alert them to its presence.

"ddPCR is becoming the new gold standard in wastewater testing, enabling COVID-19 outbreak detection days before anyone shows symptoms in a community," says Karlin-Neumann.

## Better, faster, cheaper

Rapid developments in the field of genomics technology have underpinned and advanced the work of biologists. Innovations in genetic sequencing, imaging, and cytometric technologies have each contributed significantly to an improved understanding of the fundamental biology of human and other organisms, enabled translation of key research findings toward clinical practice, and changed the course and practice of medicine, explains Brian Fritz, associate director of strategic market development and programs and immunology segment manager at 10x Genomics.

As an example, he points to next-generation sequencing (NGS), which has made high-throughput genetic sequencing radically faster and cheaper. The first draft of the Human Genome Project took 13 years and cost an estimated USD 3 billion. In 2020, you can sequence a human genome in a day.

"The incredible breadth and sensitivity of next-generation sequencing enables the translation of convalescent patient antibody genes into novel therapeutic treatments for infectious disease, and enables the identification of minimal residual disease in patients undergoing treatment for some forms of cancer, such as leukemia," Fritz says.

Critical to this adoption were improvements to instrument speed–enabling time-to-diagnosis in less than 24 hours in many cases–as well as sensitivity and scale, enabling simultaneous

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### Featured participants

**10x Genomics**
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**BGI Genomics**
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**Bio-Rad Laboratories**
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**Integrated DNA Technologies**
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**Janelia Research Campus, Howard Hughes Medical Institute**
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**South China University of Technology**
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**Wellcome Trust Sanger Institute**
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sequencing of many individuals. The past decade has seen this technology widely adopted and used among clinicians, from diagnosing rare disorders in children to testing for COVID-19 infection.

According to Xin Jin, a director of the Institute of Precision Heath at BGI Genomics in Shenzhen and a professor at South China University of Technology (SCUT) in Guangzhou, China, we have witnessed in the past 10 years how NGS has changed health care, not only in terms of clinical practice but in making the idea of precision medicine a potential reality. Jin is talking about an approach to health care that uses a genetic understanding of disease to enable doctors to select treatments most likely to help their patients. He uses screening tests for Down syndrome during pregnancy as an example.

"Scientists developed a noninvasive prenatal test that can diagnose this genetic condition by identifying chromosomal abnormalities. It is now used worldwide for millions of women each year," he says. "It has changed the path of prenatal health, forever."

Jin hopes that health care will move from a model of diagnosis and treatment to one of prevention.

"Today, the majority of technology developed is used for after the disease has spread. But by employing many different, yet complimentary advanced molecular techniques, the idea of curing a disease before its onset may become a reality," he says.

Fritz agrees that research activities in the fields of cell biology and genomics are coalescing. "Sequencing is merging with advanced imaging, and principles of cytometry are being combined with both sequencing and imaging," he says. "The confluence of these technologies will ultimately enable the discovery of novel biomarkers, which will subsequently enable redefinition of canonical disease states, refine therapeutic decision-making, and propel the concepts of precision and personalized medicine forward even further than next-generation sequencing has demonstrated on its own," he adds.

## Knockout health care

Eight years ago, the introduction of CRISPR, a simpler, faster, cheaper, and more accurate alternative to older genome-editing methods, led to an explosion of research into gene editing.

The invention of CRISPR/Cas 9 gene-editing technology was awarded the 2020 Nobel Prize in Chemistry, rightly recognizing the tremendous impact that this innovation is having today in basic and applied research, says Mark Behlke, chief scientific officer of Integrated DNA Technologies.

Academics across the world recognized that gene editing had the potential to permanently change the DNA content of cells, repairing disease-causing mutations or replacing nonfunctional genes. Behlke says that in theory, this could offer a "one-and-done" treatment option, where treatment is done once and the results last forever. Of course, he cautions, this adds potential risk, since any errors in editing are also permanent. To make the final step toward personalized medicine a reality, scientists must successfully find ways to deploy gene-editing tools in clinical settings, says Behlke. And yet there are no gene-editing therapies on the market, only certain forms of gene therapeutics, such as for B-cell lymphomas and ocular diseases. Without any FDA approval of gene-editing therapeutics, however, this new therapy modality has not yet had a practical impact on clinical practice, he says.

But research is moving in the right direction. There are currently ongoing clinical trials to treat sickle cell disease using ex-vivo genome-editing approaches to modify autologous CD34+ hematopoietic stem cells with reinfusion back into the patient. Behlke says that the greatest medical benefit of gene editing so far has occurred in the basic research and translational research setting. Here, cell and animal disease models can be treated and potentially cured of diseases that heretofore were deemed to be untreatable.

"This gives rise to the vision of our ability to cure 'incurable' diseases," he says.

## The road ahead

The advancement of biomedical technologies is integral to the rapid translation of academic research into medical therapies. In the age of COVID-19, the quest to develop better ways to protect our health has never been more pressing.

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