the Pathologist
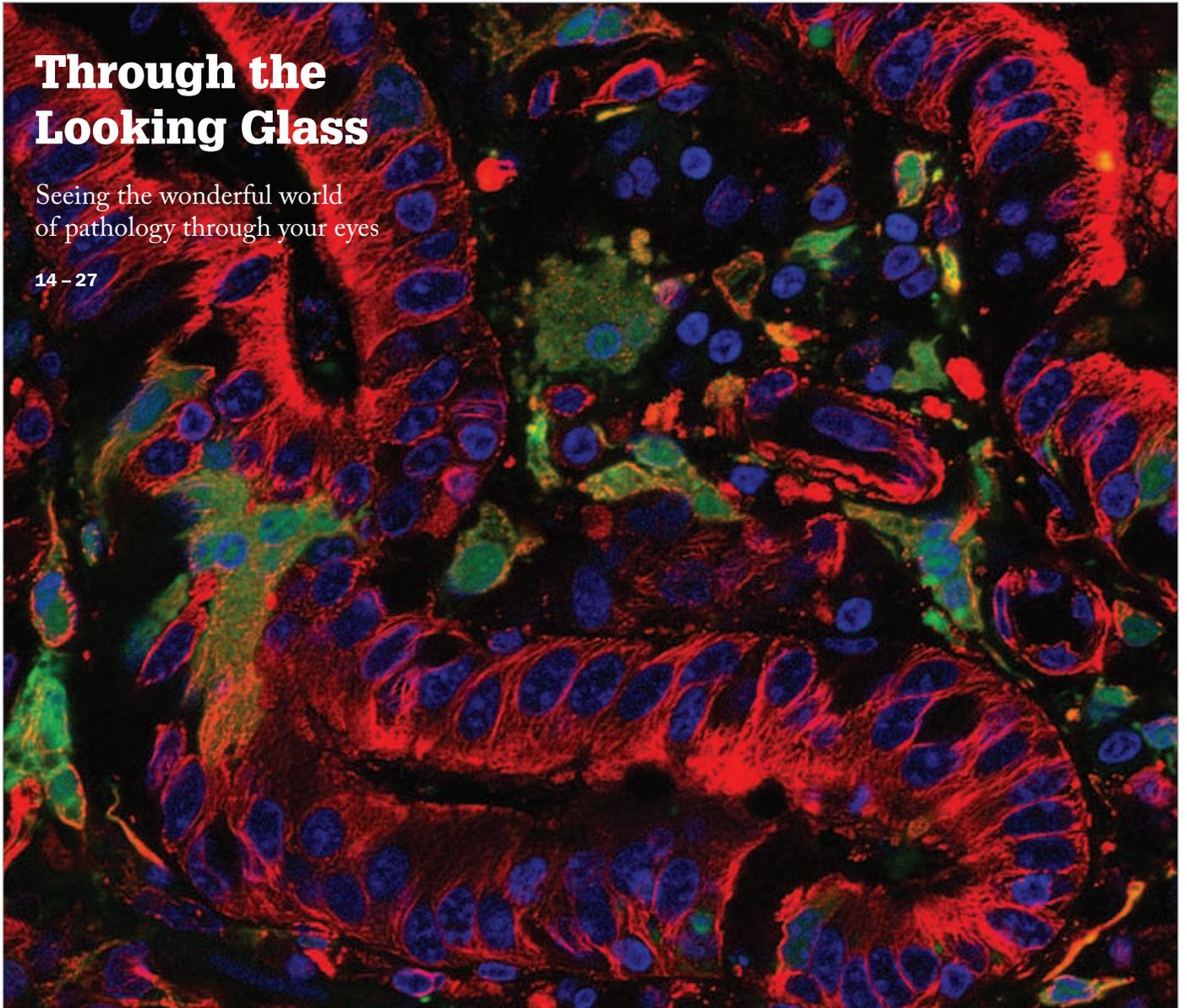
Through the Looking Glass

Seeing the wonderful world of pathology through your eyes

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Diagnosis Ex Machina

A new software tool may improve upon current infectious disease diagnosis methods to return faster, more accurate results

By Robert Schlaberg

When faced with an unidentified infection, doctors typically pursue two approaches – they apply treatment (for instance, a broad-spectrum antibiotic) based on the suspected cause of disease, or they can proceed with diagnostic testing to determine the cause of the infection, and therefore the best treatment. Both approaches have limitations. The former might result in inadequate treatment and risks prescribing antibiotics where none are needed. The latter is often time-consuming, delaying the patient's treatment, and may provide inconclusive results, hampering decisive action. This lack of good options becomes

At a Glance
- *Infectious diseases are one of the world's biggest killers, but doctors still lack rapid, conclusive ways of identifying pathogens*
- *Current methods may be time-consuming, inconclusive, have limited scope, or require equipment and skills not available in all settings*
- *A new type of software, Taxonomer, may be able to speed up clinical diagnostics by examining pathogens' genetic material*
- *Unbiased pathogen detection combined with fast, accurate, and easy-to-use data analysis will, in the future, provide rapid answers to the question, "What's wrong with my patient?"*
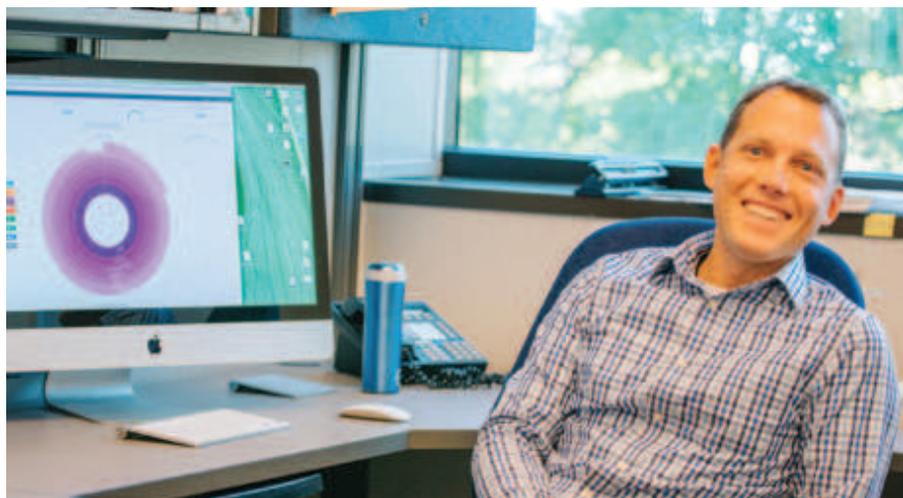
even more unconscionable when one considers the high morbidity and mortality from infectious diseases, especially in the elderly, young children, the seriously ill, and in resource-limited settings. My colleagues and I felt it was clear that a better solution was needed – so to tackle the problem, we developed methods that use next-generation DNA sequencing for the rapid, unbiased detection of all known pathogens. These efforts led to the development of Taxonomer (1,2), an ultra-fast NGS data analysis software package that can identify pathogens from millions of DNA sequences within minutes.
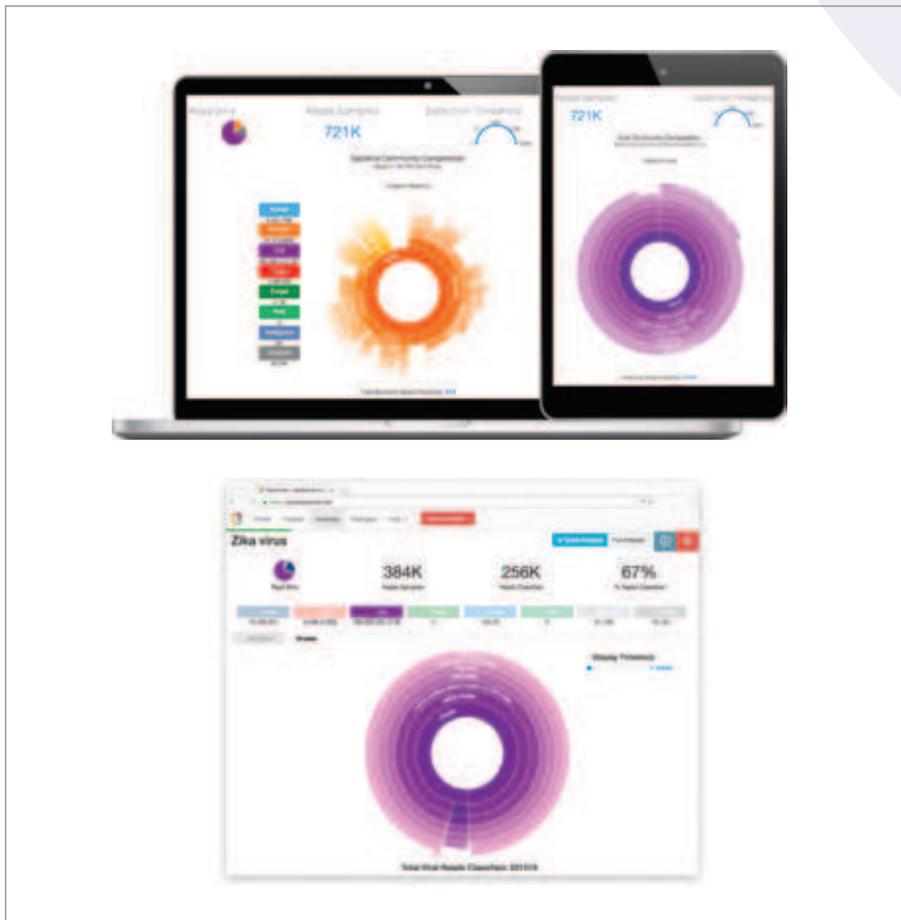
How does it work?

After DNA from a patient's sample is converted to millions of short sequences, the user simply uploads the data to Taxonomer, which can be accessed through a web browser without the need for the large computers and programming skills usually needed to analyze NGS data. It even works from mobile devices, empowering physicians and scientists to analyze their NGS data interactively and in real time. Users can analyze DNA sequences that are stored on their own devices, in the cloud, or use public data by simply selecting the files they want to access. All the heavy computing happens on a server that can be located anywhere

in the world – which frees physicians and scientists of the need to invest in expensive computers and bioinformatics resources and lets them interact with their data immediately and directly.

How does Taxonomer analyze the information? By using search algorithms to compare short DNA sequences from patient samples to millions of reference sequences. The software classifies each sample sequence to the organism from which it most likely originated – but it completes the task automatically and within minutes, rather than requiring extensive input and hours or days of time as would have been needed only a few years ago.

Taxonomer compares DNA query sequences to both DNA and protein reference sequences. This makes it possible to identify new organisms more effectively, because there is usually greater sequence conservation at the protein level. The end result is a catalog of all known viruses, bacteria, and fungi detected in a given sample; not just their presence, but also their relative abundance. And it's not only a tool for identifying pathogens – it can also identify which of the patient's genes are turned on. This helps determine the way a patient reacts to an infection. When combined with the right interpretive information, this may be a method that laboratory medicine professionals use in

Taxonomer's interactive display presents the vast genomic data extracted from pathogens found in a patient.

their data to the program's server for analysis and view the results in real time. It's my hope that, by providing accessible and easy-to-use software, we can speed up the adoption of NGS for improved diagnosis of infectious diseases.

Getting the clinic on board

I'm convinced that unbiased pathogen detection combined with fast, accurate, and easy-to-use data analysis is heading rapidly toward widespread adoption for infectious disease testing. Sample preparation workflows are still challenging to perform in diagnostic laboratories, but improvements are made continuously. Our vision for Taxonomer's development was to provide rapid, accurate, and complete answers when doctors ask, "What's wrong with my patient?" – and to achieve that without having to first assume a suspected pathogen. I wouldn't be at all surprised if multiple laboratories offered tests based on Taxonomer or similar tools within the next few years.

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References

1. S Flygare et al., "Taxonomer: an interactive metagenomics analysis portal for universal pathogen detection and host mRNA expression profiling", Genome Biol, 17, 111 (2016). PMID: 27224977.

2. EH Graf et al., "Unbiased detection of respiratory viruses by use of RNA sequencing–based metagenomics: a systematic comparison to a commercial PCR panel", J Clin Microbiol, 54, 1000–1007 (2016). PMID: 26818672.

the future to differentiate patients who need antibiotics from those who don't – among other things.

Benefits of unbiased detection

Patients whose symptoms may be caused by any one of a long list of pathogens, or in whom an infectious disease needs to be ruled out, will benefit most from unbiased pathogen detection. This includes cases of suspected pneumonia, encephalitis, meningitis, or sepsis, especially in transplant and other immunocompromised patients, the elderly, infants, the severely ill, or patients with unusual symptoms. Often, we're not sure what to test for. Unbiased pathogen detection lets us explore all of the possibilities without having to guess.

Many diagnostic laboratories now have access to next generation sequencers within their departments, in core facilities or through commercial laboratories. Sequencing itself is only the first step, though. Quickly, accurately, and consistently analyzing NGS data is still a challenge, especially for diagnostic laboratories. We believe we've developed software that can help physicians and scientists close this gap. And with next generation sequencers becoming ever smaller and even portable, the software holds great promise for unbiased pathogen detection in remote locations and in outbreak settings. The technology's interactive web interface enables access from a smartphone, tablet computer, or laptop, which means laboratories around the world can stream