

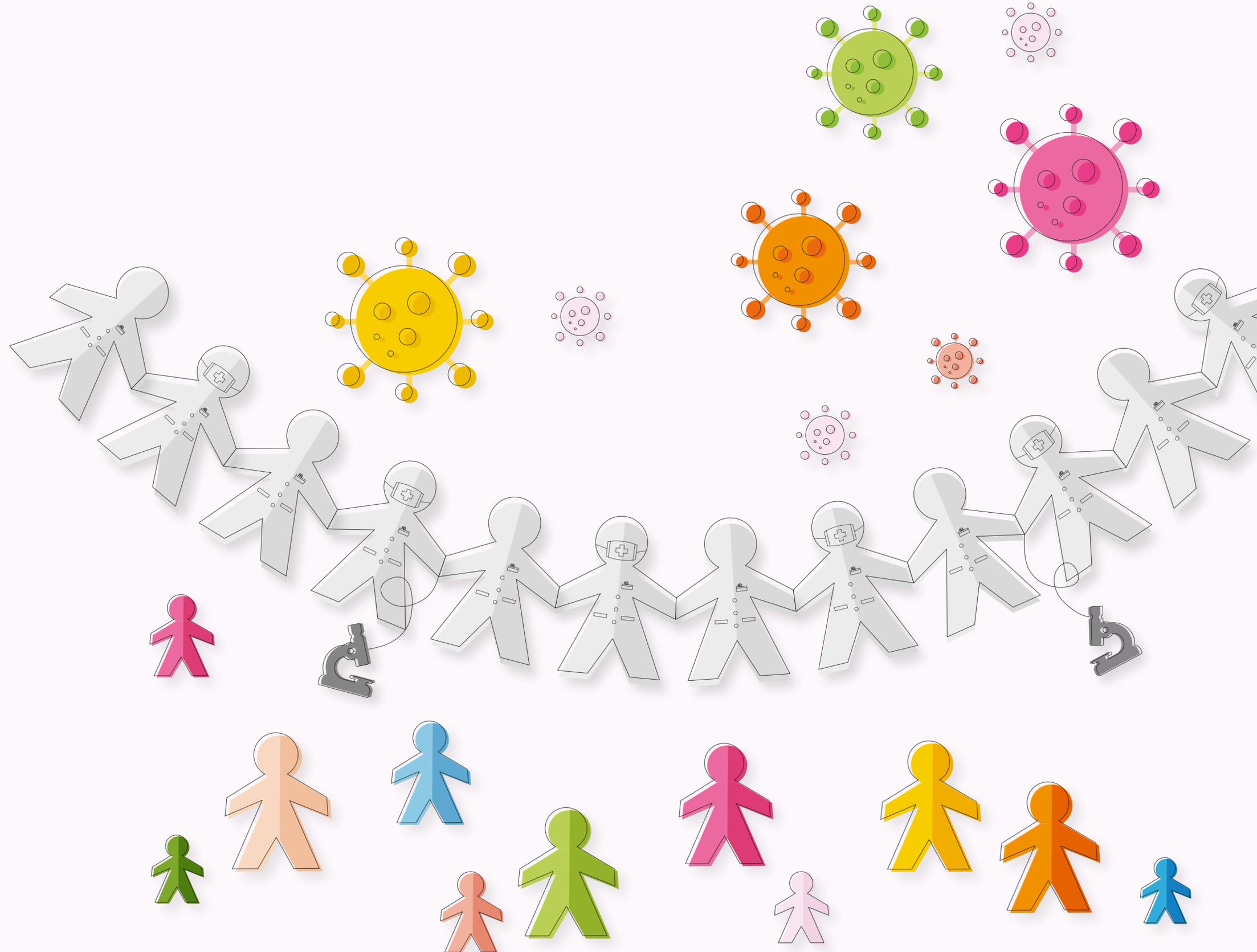
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IN MY VIEW

AI's Evolving Role

A veterinary pathologist's perspective on how AI can support pathology

Gillian Beamer is Assistant Professor, Department of Infectious Disease and Global Health, Tufts University's Cummings School of Veterinary Medicine, North Grafton, Massachusetts, USA.

I am excited that AI tools are becoming widely available to extract information from experimental histopathology samples. In research settings, AI has many advantages over visual scoring and manual annotation – in particular, eliminating some tedious and time-consuming tasks; reducing inter-pathologist variability; and offering greater capacity to analyze archived samples. I've started to train, validate, test, and use my own algorithms to rapidly identify and quantify regions of interest within *Mycobacterium tuberculosis*-infected lungs. AI can speed up data acquisition – and, unlike human pathologists, algorithms happily operate 24/7. This means that I can set data-extraction and low-level analytical tasks to run overnight.

AI cannot replace a pathologist's interpretation and intellectual contribution regarding mechanisms of disease or hypothesis generation and testing. However, the two – human intelligence and artificial intelligence – can certainly complement each other.

After training and validation, algorithms can detect, quantify, and spatially locate tissue, cell, and subcellular features. In research settings, pathologists often score, grade, or quantify visual changes in tissues *where the diagnosis*

is already known. Many research pathologists spend a substantial amount of time quantifying patterns, rather than establishing diagnoses. For example, in my own research laboratory we study host responses to *M. tuberculosis*. All samples come with a diagnosis: tuberculosis. Similar scenarios occur across many research fields each day. A major benefit of AI for research pathology is automatic recognition and *quantification* of visual information. Thus, AI algorithms can transform complex visual patterns into rich, quantified data sets that can be rigorously analyzed by statistical or machine learning methods. A second benefit is that AI doesn't need sleep or caffeine.

Like in human medicine, the emerging use of AI in veterinary medicine is a disruptive technology that needs early adopters to gather data and feedback in testing phases, critical evaluation of the pros and cons, and a rational path forward. All aspects of digital pathology, including AI, are now being examined by our professional organization, the American College of Veterinary Pathologists. We are engaging in discussions across many sectors: industry, academia, and diagnostic and research laboratories. We have challenges to be addressed and overcome. Some of those



challenges are physical or resource-related: access to equipment (scanners, servers, image-sharing software); hiring additional staff to perform and quality-control scans; and more. Other barriers are within our minds: fear of the unknown; fear of losing jobs; fear of becoming obsolete. These are scary concepts that have no easy solutions.

In our profession, we have realized that faculty who are training veterinary pathology residents need reliable information on digital pathology and AI. They need equipment and time to train themselves to become comfortable using it. And they need to understand the limits of this new tool. What I find interesting and exciting is that current trainees and recently boarded pathologists have found and adopted AI on their own through other resources. Some have produced and tested algorithms of their own; others are skilled coders who know more than their teachers (which I think is a great thing). The future of digital and computational pathology is bright, and education is the key. We must educate both ourselves and the next generation.

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FEATURE

The Evolution of the Lab

How a grassroots movement is positioning the laboratory at the forefront of healthcare

Khosrow Shotorbani is President and Executive Director of Project Santa Fe Foundation, CEO and founder of Lab 2.0 Strategic Services, LLC, and a Clinical Laboratory 2.0 industry advocate.

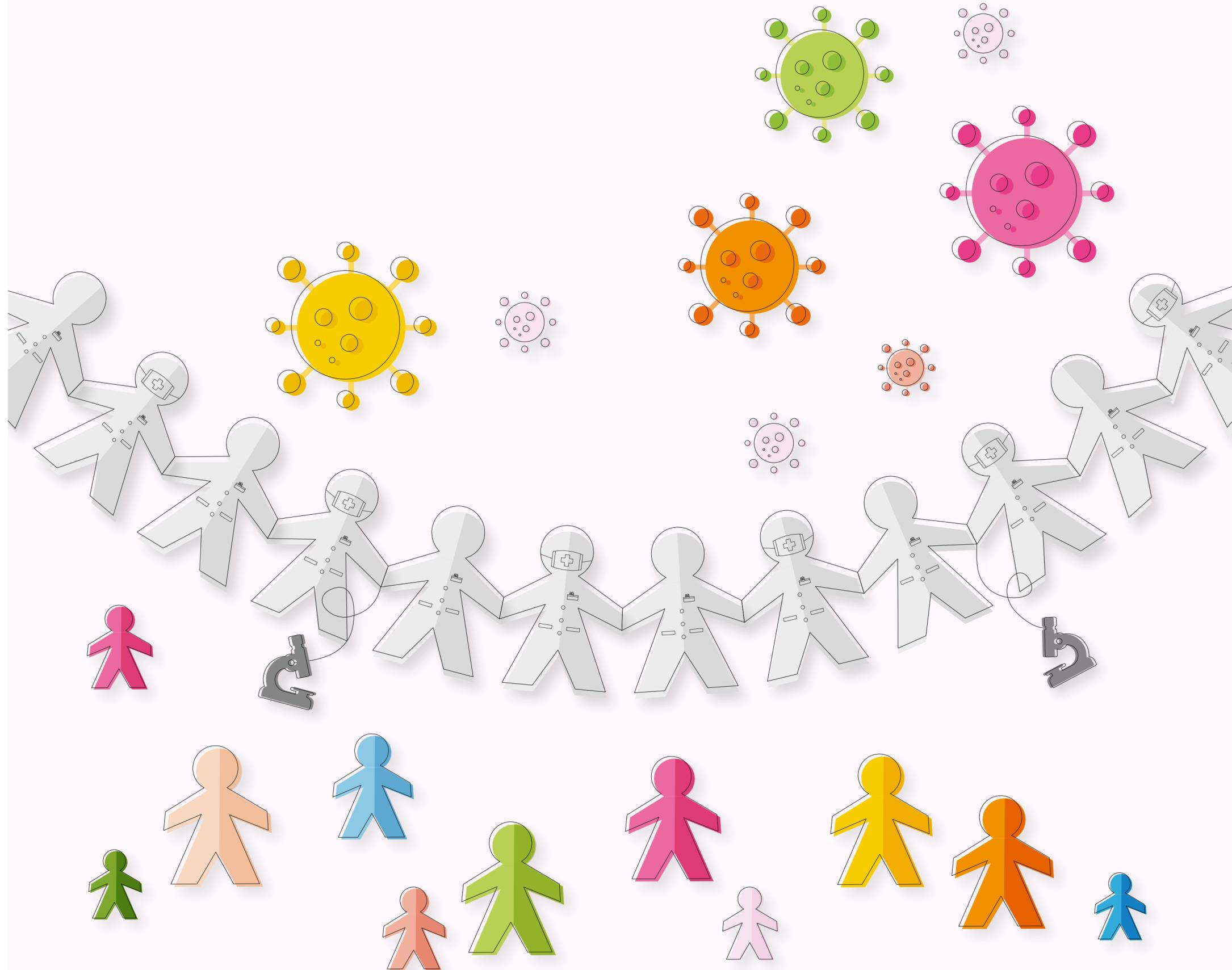
Jeremy Orr is a practicing, board-certified family physician and Chief Executive Officer and Chief Medical Officer of Medial EarlySign, Aurora, Colorado, USA.

Keren Landsman is a public health specialist. She is a member of Mida'at, a public health non-governmental organization, and works as an epidemiologist in the Israeli Ministry of Health and as a physician in the Levinsky Clinic, Tel Aviv, Israel.

With an increasingly global society – not to mention a growing pandemic – the idea of population health is at the forefront of many medical minds. But who is responsible for population health? Is it the epidemiologists, the sociologists, or the politicians? A new movement, termed “Clinical Lab 2.0,” suggests that the laboratory is an integral part of population health – and that laboratory medicine professionals can be leaders in the move from volume- to value-based healthcare. But what is Clinical Lab 2.0, and how does it position the laboratory at the apex of population health?

The meaning of Clinical Lab 2.0

An initiative of the Project Santa Fe Foundation, the Clinical Lab 2.0 movement is a grassroots effort to transform the role of the diagnostic laboratory to better support the objectives of population health and value-based healthcare. The effort, launched in 2016, is designed to



promote more effective utilization of laboratory data in pursuit of the lab's enormous potential for improving patient and population outcomes, reducing the total cost of care, and strengthening the patient and clinician experience.

The movement was born from a realization among a select group of laboratory leaders that our industry had reached a major inflection point. In other words, the past was no longer reflective of the future. We understood that the diagnostic lab's value proposition needed to evolve dramatically to align with, and support, healthcare's transition from volume to value. At the same time, it was clear that longstanding business models and conventional industry wisdom had not provided much room for innovation. Finally, as the commoditization of clinical testing has accelerated, it has become evident that hospital-based laboratories are at increasing risk of being sold or replaced by outsourced laboratory providers. And that's why developing ways to add value to the lab have become critical.

In the simplest terms, Clinical Lab 2.0's mission is to position the lab as the center of value-based care by promoting new strategies, models, and ideas to empower laboratory leaders – pathologists and management alike – to harness the data we collect in pursuit of population-level initiatives. These efforts can lead to substantial improvements in both outcomes and the cost of care. Underpinning this mission is a recognition that, although in vitro diagnostics account for just two cents of every dollar spent on US healthcare, lab results serve as the basis for over two-thirds of all medical decisions. Given the ubiquity of clinical testing, we believe the laboratory can positively impact virtually all aspects of healthcare and 100 percent of spending.

It has been four years since those laboratory leaders first met in Santa Fe (hence the name of the organization), and our message continues to gain traction both in the US and globally. We've created a nonprofit organization, launched four multi-institutional demonstration

projects, hosted three additional closed-door colloquia, and produced three public workshops (all of which have been sold-out events) – and there is more to come. Our meetings continue to be critical to our movement by providing forums for a range of stakeholders to discuss the opportunities presented by the Clinical Lab 2.0 concept.

Extending the laboratory

Clinical Lab 2.0 represents an extension of the laboratory's existing transactional model (Clinical Lab 1.0) to incorporate and reflect quantitative value around the total cost of delivery and cost avoidance. Whereas 1.0 is reactive and focused on “sick care” and de-escalation, 2.0 concentrates on early detection, early escalation, intervention, and prevention (see Tables 1 and 2).

In 2017, we authored an article that we hoped would change the conversation about the potential of the clinical lab (1). We asserted that, in traditional business and care models, the clinical lab has been viewed primarily as an ancillary and increasingly commoditized departmental function. In the 2.0 model, the lab's aggregated data provides vital longitudinal touchpoints to support the full spectrum of integrated health care. Because the lab generates data regardless of where, when, or how the patient receives care, we can serve as a repository of actionable information across the entire care continuum.

Clinical Lab 2.0 can support pre-diagnostic identification and closure of care gaps, as well as deliver post-diagnostic computations of aggregated longitudinal data to enable a range of insights and actions. These include clinical prevention, programmatic clinical interventions, and optimization of diagnostic and therapeutic management. Our goals? Improved patient and population outcomes and management of population risk.

In effect, Clinical Lab 2.0 views lab personnel as “first responders.” They're the first to see these critical important data and the best-

Labs, Population Health, and COVID-19

By Khosrow Shotorbani

The question you may be asking is: as guardians of public health, what is the lab's role in the COVID-19 pandemic? Obviously, our ability to serve as leaders goes beyond our duty to provide timely, accurate testing.

The four points we need to highlight – and illustrate by our actions – are:

- The laboratory is the first to know with real-time results.
- Laboratories are the first responders providing recommendations and developing new strategies.
- Laboratories are the “epicenter of informatics.” with insights around disease patterns and predicting outbreaks.
- Laboratories should serve as the “command center” managing this pandemic by developing guidance as to who should be tested and when.

A Clinician's Perspective: COVID-19 and the Lab's Evolving Role

By Jeremy Orr

During the early part of the pandemic, laboratorians mobilized to provide timely, accurate testing for individual patients. In places where testing was limited, lab personnel sometimes enforced prioritization criteria. Fortunately, in many (though not all) parts of the world, tests are now available in greater quantities and rationing is no longer an issue. So it's natural to ask: what lies ahead for the lab as the next stages of the pandemic unfold?

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“Although in vitro diagnostics account for just two cents of every dollar spent on US healthcare, lab results serve as the basis for over two-thirds of all medical decisions.”

equipped to understand the implications. As such, they’re optimally positioned to manage population health in value-based care.

My Clinical Lab 2.0 story

Clinical Lab 2.0 has no borders – it’s truly a global movement. I’ve been excited to see the level of interest and engagement our efforts have elicited in diverse healthcare settings around the world. I’ve heard about the concerns and challenges faced by healthcare systems globally – and what I’ve learned is that, regardless of the setting, the fundamental principles of Lab 2.0 are universal in their application. Labs can play a critical role by providing population risk stratification relative to the known prevalence of chronic conditions, identifying care gaps and predicting clinical risk, identifying high-risk patients before they are admitted into emergency room or hospital, and facilitating early intervention between care providers and patients. These capabilities and their implications resonate globally.

The Lab 2.0 integrative model cannot exist without a solid Lab 1.0 foundation. The models are iterative and interconnected. In envisioning the lab as the first responder, we’re saying that the lab is the first to become aware of a clinical need and therefore in the best position to provide

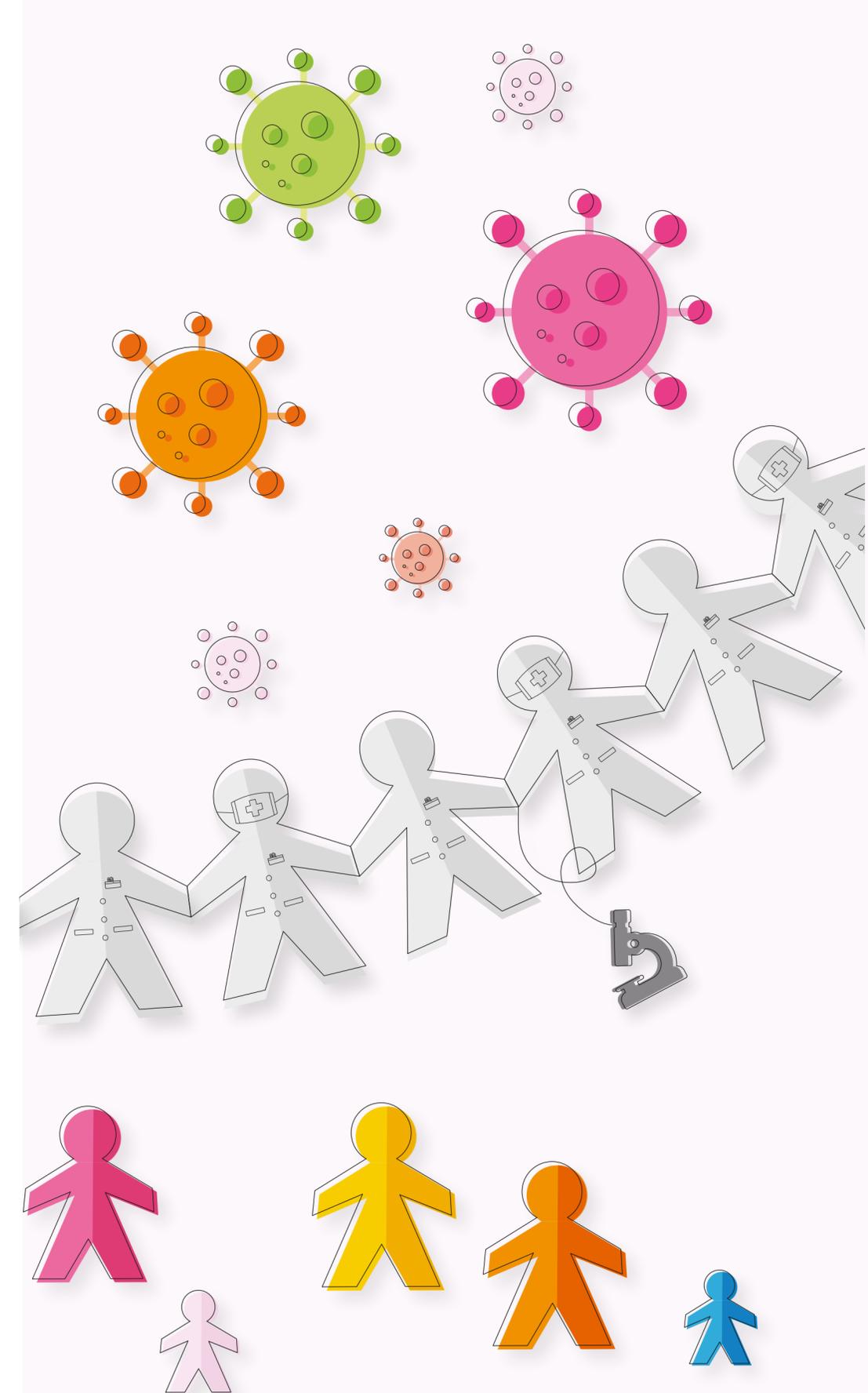
leadership in addressing that need. Reducing the time to diagnosis can help with diagnostic optimization and appropriate laboratory test utilization, which, in turn, leads to care optimization, therapeutic optimization, and appropriate screening and surveillance.

If we don’t get the first step – identifying actionable clinical information at the point at which it is generated – right, the entire continuum of care becomes suboptimal, and that can cause significant patient harm. The lab can be the catalyst for improving population health outcomes, reducing the overall cost of care and, importantly, empowering health systems to successfully manage the financial risk of providing value-based care. The central advantage we possess is the ability to produce scientifically measured, structured data at each touchpoint on the care continuum. That means the information we generate is clinically actionable with zero latency.

From obstacles to opportunities

We’ve identified a number of barriers or obstacles that can impact the transition to Lab 2.0. These include:

- Lack of a common language among providers, data analysts, health systems, and payers with respect to certain clinical conditions and lab results



- Lack of models for comparison and benchmarking
- The inability of existing laboratory information systems to integrate data or provide information for clinical decision support; current systems tend to support only revenue cycle and contract pricing data
- Lack of outcomes-based evidence for laboratory-led innovation
- Difficulty integrating laboratory insights into the existing clinician workflow
- Lack of aligned incentives
- Inadequate leveraging of laboratory data into actionable information, including the absence of detailed data-sharing agreements
- Lack of access to capital for in-system laboratories versus the for-profit sector of laboratory industry
- Lack of access to new and necessary skill sets
- Limited understanding of the laboratory's potential among health system leaders and inadequate engagement of same
- No playbook for providing Lab 2.0 leadership

The Lab 2.0 initiative helps the industry overcome these barriers by emphasizing three fundamental pillars of transformation:

- *Leadership*: Helping clinical lab leaders embrace a new leadership mindset that extends beyond the four walls of the laboratory.
- *Standards*: Measuring what matters – that is, the development of new measurements and benchmarks that support a new clinical value proposition.
- *Evidence*: Developing multi-institutional demonstrations to show how laboratory medicine and pathology affect population health and align with the drivers of value-based care. Our projects focus on providing outcomes-based evidence and producing roadmaps

that all labs can follow.

Our Project Santa Fe colleagues and participants have encountered many of the opportunities generated by a more engaged and integrated lab. Here are just a few that have been presented in the recent literature:

Diabetic patients (with comorbidity): In most countries, attempts to de-escalate the impact of diabetes don't occur until morbidity is severely advanced, typically when the patient's A1C level is over 9 and the kidney function (EGFR) is below 60. Generally, this means irreversible stage 3 kidney failure. However, if at-risk patients are identified early – when their A1C is 5–7 and EGFR is between 90 and 60 – we can manage their care to improve outcomes and reduce downstream cost. The ability to identify at-risk patients in the pre-diabetic stage can help avoid the progression of the disease which, if uncontrolled, can cost an average of US\$10,970 per case (2).

Urinary tract infections: Laboratory-provided insights into urinary tract infections managed in the emergency room (ER) not only diagnose the acute condition, but also offer clues to improving treatment and identifying patients with recurrent infections. These insights “could result in more appropriate drug treatment, improved resource allocation, and decreased ER costs for integrated health systems (3).”

Cost-effective drug therapy regimens for chronic disease: Laboratories are beginning to understand the value of having pharmacists on their staff. These experts can help with antibiotic stewardship and identify appropriate treatments for chronic diseases – especially those that, like rheumatoid arthritis and chronic reoccurring

Protecting the Population

How “behind the scenes” workers are safeguarding the world's health during the COVID-19 pandemic

Michael Schubert interviews Keren Landsman

Can you tell us a little bit about your work?

I'm a doctor specializing in epidemiology and public health. Ordinarily, I work in two places – in the epidemiology department of the Israeli Ministry of Health and in the Levinsky Clinic, a free sexual health clinic where we test and treat people from all kinds of socioeconomic backgrounds. At the moment, the clinic is closed and I'm working full-time at the Ministry of Health to deal with the COVID-19 pandemic.

What is the current COVID-19 situation in Israel?

We're doing pretty well on a global scale. The Ministry of Health moved very quickly to decide on a curfew, stop all flights abroad, and initiate social distancing protocols. But that's not to say we aren't facing issues here; we have over 9,000 confirmed cases and over 50 deaths to date – but we studied the curves and tried to learn from the events in other countries. We had China, South Korea, and Italy to learn from before COVID-19 hit Israel, so we worked around the clock to purchase and produce supplies, source ventilators, and prepare special sections in each hospital for COVID-19 care. New cases are still being diagnosed everywhere, but Israel's upward trajectory is slow compared with other countries, so I am cautiously optimistic.

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“We don’t have to boil the ocean to add new value – just getting out of the lab and telling a different story is mission-critical.”

infections, require long-term, high-cost therapy. “To manage these diseases, the cost of drug treatment, monitoring of drug therapy regimens, and treatment adjustments for empiric therapy require post-analytic interpretation of laboratory results, along with drug therapeutics knowledge (3).”

Pregnancy: For women who don’t receive routine care – for instance, those on low incomes or without insurance – laboratories can identify pregnancies early, avoid treatment options that could present a pregnancy risk, and monitor prenatal testing patterns and results to identify high-risk pregnancies and women in need of more intensive prenatal care (3).

Opioids and benzodiazepines: We need innovative approaches to tackle the ongoing opioid crisis. “As stewards of health analytic data, laboratories are uniquely poised to approach the opioid crisis differently,” says one study (4). The pilot study aimed to “bridge laboratory data with social determinants of health data, which are known to influence morbidity and mortality of patients with substance use disorders.” The study found that co-use is largely determined by the patient’s providers, with increasing age and geographic area also predicting co-use. “The prominent geographic distribution of co-use suggests that targeted educational initiatives

may benefit the communities in which co-use is prevalent. This study exemplifies the Clinical Lab 2.0 approach by leveraging laboratory data to gain insights into the overall health of the patient.”

The future of Clinical Lab 2.0 is somewhat academic, but with a sense of agility and urgency. Our vision is to share knowledge through publications and key partnerships, to continue to build the evidence base with expanded multi-institutional demonstration projects, and to continue to host annual scientific colloquia and produce educational workshops. Project Santa Fe Foundation is a member-driven organization. Obviously, our movement cannot achieve its objectives alone – so key partnerships are a critical component of our future activities. These relationships will help us broaden our reach, engage industry partners in the in vitro diagnostics and informatics space, and potentially help influence policies that determine the direction of healthcare. Ultimately, our goal is to create a tipping point that elevates the value of the clinical lab, domestically and globally, as healthcare transitions from volume to value and from sick-care to well-care.

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IN PRACTICE

Spreading the Word: Molecular Diagnostics for Infectious Disease

What role can cutting-edge assays play in the diagnosis of infectious diseases – and how do we maximize their potential?

Bobbi Pritt is Director of the Clinical Parasitology Laboratory in Mayo Clinic's Department of Laboratory Medicine and Pathology, Rochester, Minnesota, USA

Molecular diagnostics have an increasingly important role to play across all areas of pathology, but their importance in infectious disease cannot be underestimated. Thanks to a simple, widely available technique – the polymerase chain reaction (PCR) – molecular techniques now serve a variety of applications in routine clinical laboratories, with real-time PCR allowing the rapid detection of various infectious microorganisms.

But are these cutting-edge assays too easy? Often, pathologists perform them even when there is no prior evidence of infection. It's true that there are many circumstances where molecular diagnostics can be valuable, but we need to educate our surgical pathologists on what the tests can do – and when they might not be the best option.

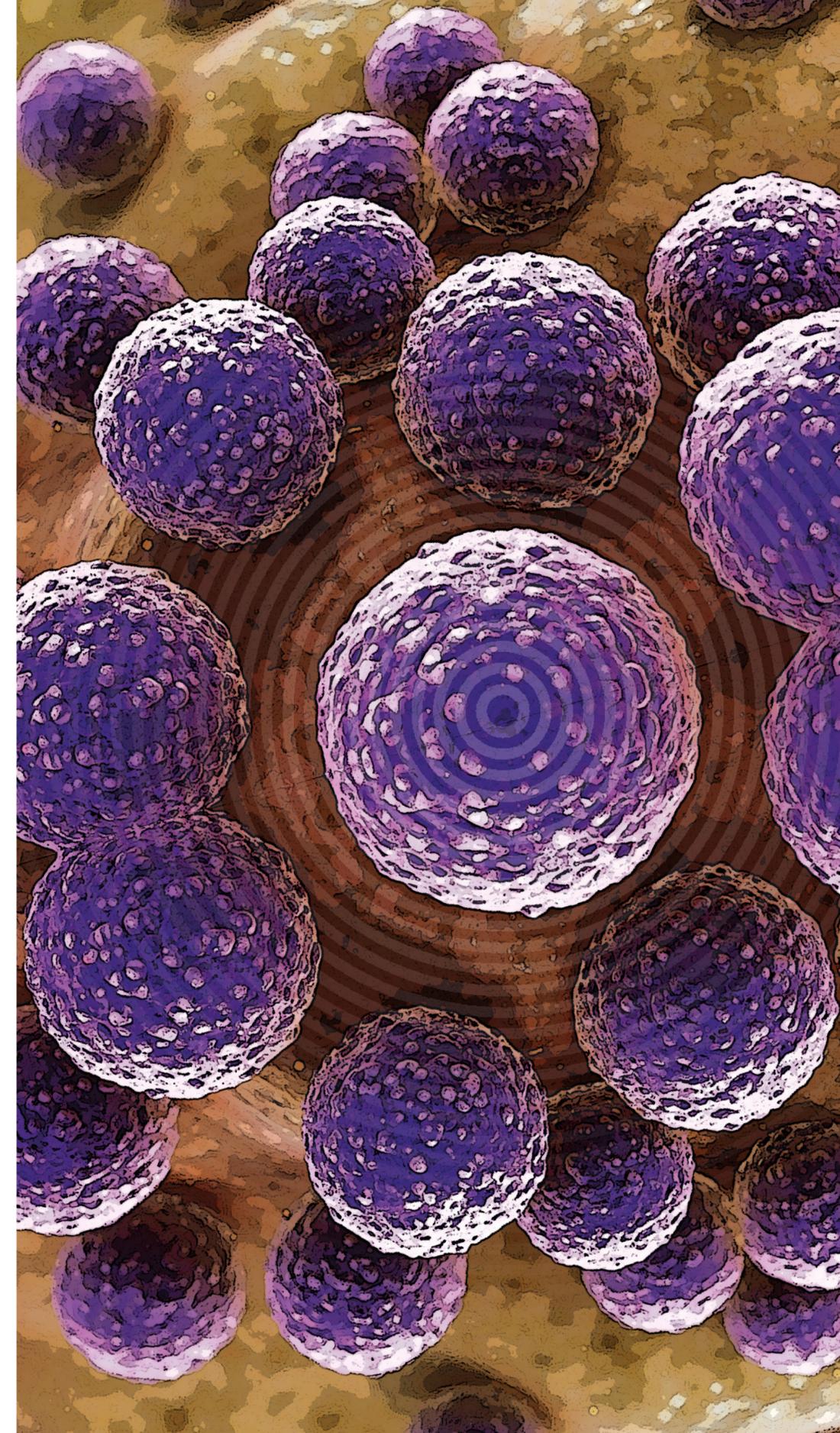
As our clinical colleagues become more familiar with the molecular diagnostic tests that are now widely available, surgical pathologists can expect to receive more frequent requests for them. But we cannot blindly follow these requests; we are also diagnosticians and need to be prepared to turn down tests that aren't suitable or suggest more appropriate alternatives. Pathologists are physicians who are ultimately responsible for the tissue we work on, so we must play an active role in making these decisions. And to do so, we need to fully understand the applications and limitations of

molecular diagnostic assays so that we can use them properly.

Target-specific or broad-range?

In the context of infectious disease, the strength of molecular diagnostic tools lies in identifying specific organisms. For example, a lymph node may be consistent with cat-scratch disease (CSD), but the pathologist wants to rule out any other potential causes. A PCR test for *Bartonella henselae*, the specific bacterium that causes CSD, would be entirely suitable – and a conclusive result would either rule in or rule out CSD.

However, now that we can increasingly use broad-range assays that can detect multiple organisms simultaneously, things aren't so straightforward. The use of 16S ribosomal RNA gene sequences – present and highly conserved in nearly all bacteria – has opened new doors in terms of detecting multiple bacterial species in a single sample. The molecular amplification method can be applied to a number of different samples, including cerebrospinal fluid and both fresh and formalin-fixed surgical pathology specimens. Because it's essentially a PCR test, once you've amplified the 16S gene in a sample, you can sequence it to identify the specific bacteria that are present. ➔



“Pathologists can also work with treating physicians to ensure that any tissue that might be used for molecular testing is sent without any type of media, as this could contain unwanted DNA.”

This broad-range test is ideal in a number of scenarios. For example, if a patient has received antibiotics, the bacteria may not grow in standard microbiology culture – which means that the surgical pathologist might be the only one who can provide insight by using the 16S test. This is particularly important for patients who have diseases such as infective endocarditis. These patients will almost always receive broad-spectrum antibiotics before surgery, so the 16S test can help determine which bacteria are present and therefore which specific antibiotics to use.

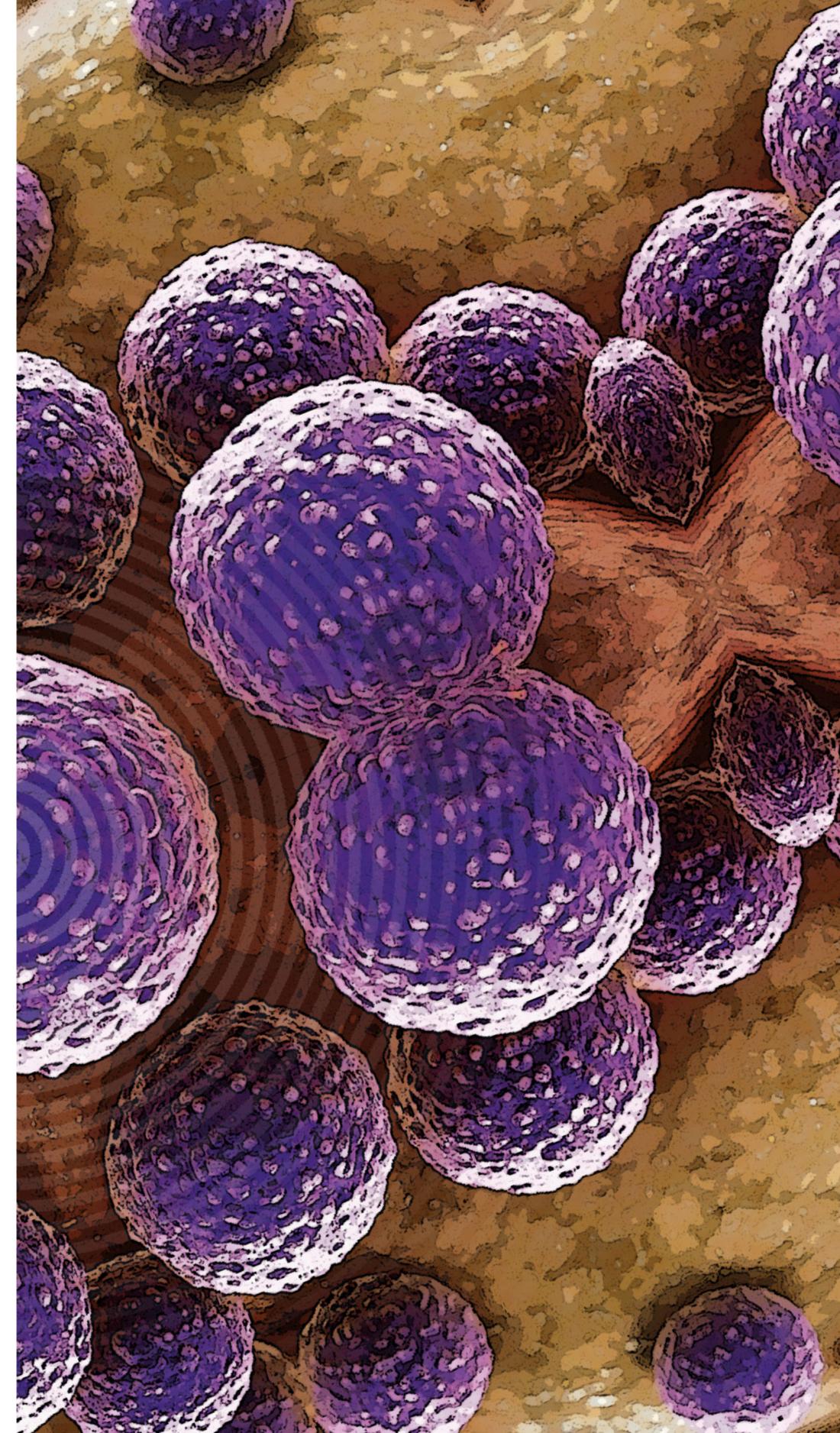
No magic bullet

But don't mistake the test for a magical, detect-all assay. The first thing to bear in mind is that a 16S test is only for bacteria; it won't detect parasites, viruses, or fungi. And when a sample doesn't show signs of any organisms, there's little reason to carry out the test, because the sensitivity plummets if you don't see anything that looks like inflammation or the presence of organisms. When a case that does require a 16S test arises, it's important to remember that the results will only be as good as the assay. Factors such as the extraction method, the gene region targeted, and the database used for analysis can all impact their accuracy.

Another caveat to the test is that we don't live in a sterile world; bacteria are all around us. That's why it's important to familiarize ourselves with all of the ways that exogenous DNA can be introduced to tissue samples, so that we can account for any contamination. The journey that a sample takes from tissue biopsy to glass slide is long and convoluted. From the cutting block in the grossing room, to the reagents used during tissue processing, to the staining process when transferring a paraffin ribbon section onto a slide, exogenous DNA contamination is inevitable at some point.

The risk of contamination is simply a side effect of having a highly sensitive assay that can detect every single bacterium – and there's not much that can be done to prevent it. Ultimately, contamination means that the 16S test will detect bacteria with no clinical correlation to the patient. To combat this, it's important to know what you do – and don't – expect to find; for example, the presence of a species commonly found on skin has probably been introduced during the histologic process, rather than being an infective agent.

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IN PRACTICE

Tackling a Triple Threat

The potential impact of deworming on tuberculosis treatment

Adil Menon is a fourth-year medical student at Case Western Reserve University School of Medicine, Cleveland, Ohio, USA. He is a recipient of the ASCP's Gold Medical Student Award and holds a Master's of Bioethics from Harvard Medical School.

Helminthic infections and tuberculosis (TB) – not only do these represent two of the most significant global public health concerns (present pandemic excepted), but there is also notable geographic and population overlap between them. Recently, researchers have begun to gain a better understanding of this geographic concordance and the commensurately high rates of coinfection. A new hypothesis states that helminthic infection may deleteriously impact the management of TB. To clarify their potential interactions, I have examined studies conducted in South Africa to establish the current state of evidence and offer a perspective on the impact that anthelmintic interventions may have on TB control.

Coinfection is common

Most TB and helminthic endemicity occur in the same settings, and coinfection is common. A broad range of countries with high helminthic burdens, such as Malawi and India, have Bacillus Calmette–Guérin (BCG) vaccination results inferior to those seen in regions with lower parasite prevalence (1). A study comparing infant BCG vaccination success demonstrated that “three months post-BCG, 100 percent (51/51) of UK infants made an IFN γ response to *M.tb* PPD compared to 53 percent of Malawian infants (1).” In the literature, the primary explanation for BCG's reduced efficacy in lower-income settings is differences in environmental mycobacterial exposure. However, another study offers a compelling alternative explanation: the interaction between helminths

and TB. The researchers demonstrate that helminth coinfection correlates with diminished levels of IgM and IgG factors critical in the immune response to TB vaccination (2). The association of helminth infections with the modulation of B cell function in TB is further underscored by post-treatment data from the same paper – following successful anthelmintic treatment, the diminished levels of both IgM and IgG increased. These results support the hypothesis that BCG confers the least protection in areas with high endemic helminth prevalence because the baseline immunity in individuals living in these areas is perturbed by coinfection.

South Africa is a natural context in which to explore the interplay of helminth and TB infection. Although TB represents a serious health problem across the globe, South Africa possesses “the highest TB incidence in the world (3)”. Even discounting the mortality stemming from TB/HIV coinfection, TB represents the top “natural” cause of death in the nation (4). Under these circumstances, progress toward better comprehending and responding to co-pathogens in South Africa's context may promote better health and health outcomes. Additionally, the association of helminth infections with AIDS and TB in South Africa has been recognized since the nation's independence, particularly with respect to the triple disease burden borne by the 36.4 percent of the population living below the poverty line. Despite the awareness of their potential interrelatedness, “studies of helminth coinfection with HIV/TB and their deleterious effects are lacking (5)” in South Africa to the detriment of efficient management of a significant public health issue. ➔



A triple threat

If addressing helminth infection positively affects the treatment of TB in South Africa, it will be primarily in terms of its consequences for immune response to TB infection itself – and, due to the high rates of triple infection, its impact on HIV progression.

Let us first consider the impact of helminth coinfection on immune response to TB. Almost two decades ago, researchers suggested that, based on findings in Cape Town, “it is plausible that helminthic infections and Th2 dominance (reflected by IgE, IL-4, IL-13, IL-10) contribute to the high incidence of TB in Third World populations (6).” The potential import of Th2 bias in the context of TB control stems from the fact that, in conjunction with innate immunity, protection against the pathogen requires “an effective adaptive cellular immune response characterized by robust T helper cell type 1 (Th1) T-cell immunity and relative weaker T helper cell type 2 (Th2) T-cell immune responses (6).” Using the tuberculin skin test as a proxy for Th1 response and, consequently, functional immune reaction to TB, a second study underscored this hypothesis by documenting an inverse relationship between *Ascaris* infections (as reflected by IgE response) and tuberculin skin test-positive status in children from high-risk, poor, urban South African communities (7); that is, the children with intestinal roundworm infections had fewer positive TB skin tests than those who were free of worms.

Though such data could imply that helminths carry a protective effect against TB, that does not seem biologically plausible. It’s far more likely that “helminth exposure/infection may reduce the immune response following *M.tb* exposure (7).” If this is the case,

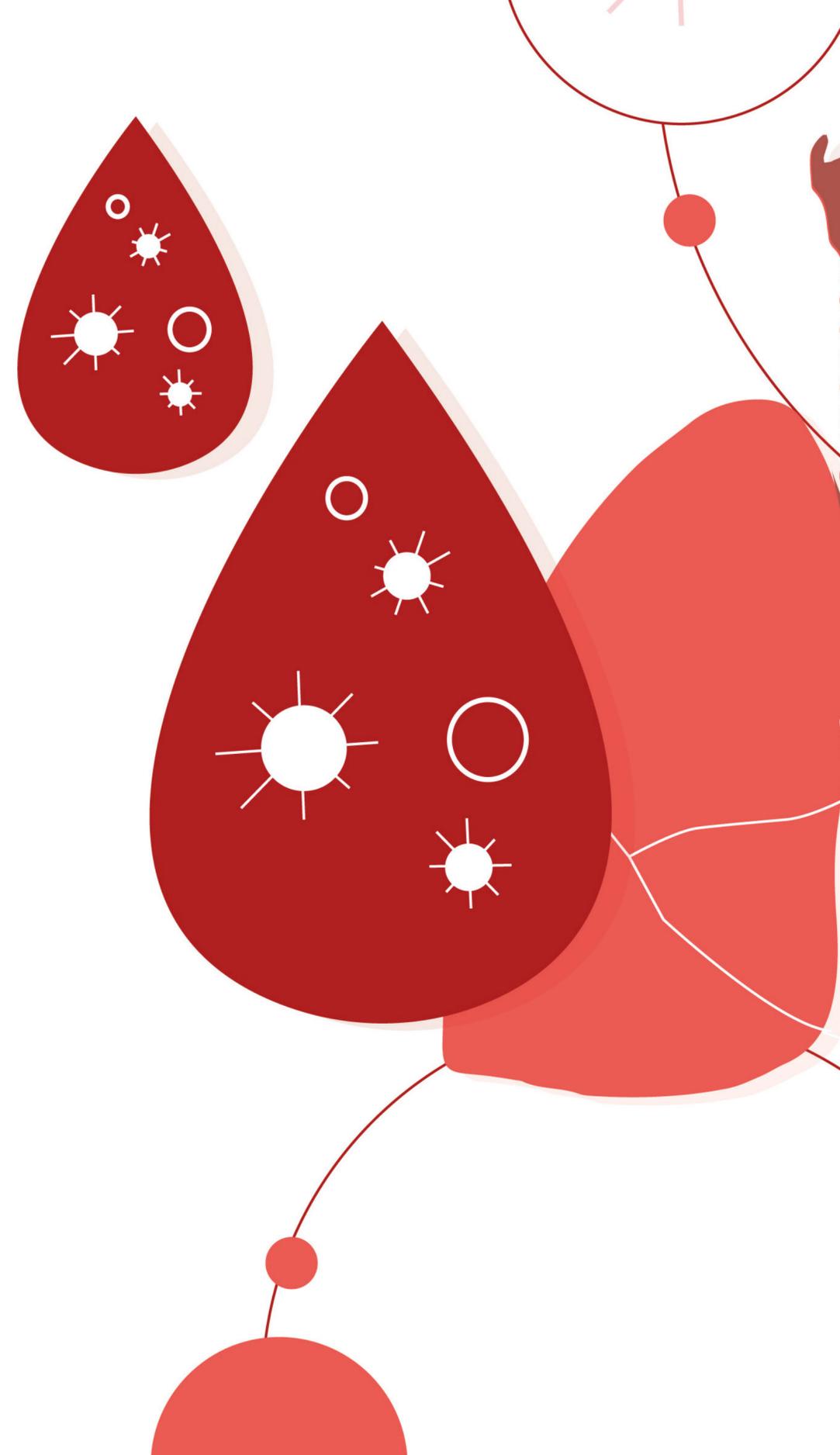
then there are two potential advantages of deworming:

1. *The possible reversal of the demonstrated Th2 bias.* A Th1-focused immune response is well-established as critical for an optimal immune response to TB.
2. *Improved diagnosis.* According to the government of South Africa’s Western Cape Province, “testing for children is done using skin tests and chest X-rays (8).” Given the high prevalence of pediatric TB in South Africa and the methods used to diagnose it, there is enormous potential for undiagnosed TB due to helminths – especially if Western Cape Province’s diagnostic approach is the norm throughout the nation.

But an exploration of the interplay between helminth infection and tuberculosis treatment in the South African context is incomplete without considering a third pathogen: HIV. South Africa ranks among the worst-afflicted countries in the world for both HIV infection and TB. Half of all new TB cases in South Africa are diagnosed in HIV-coinfected patients (9). Given these statistics, any factor that worsens HIV prognosis and progression almost certainly plays a deleterious role in TB prevention and treatment.

The high prevalence of coinfection between helminths and HIV is well-established in South Africa. One study demonstrated a 24.7 percent HIV/helminth coinfection rate, with 42 percent of these patients hosting *Ascaris lumbricoides*, the “large roundworm” (10). Crucially, the study authors observed a statistically significant association between a CD4 count below 200 cells/ μ L and a helminth infection.

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IN PRACTICE

The Problem of Filarial Disease

A systematic review of filarial disease

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The term “filariasis” may seem remote to some – but for others in the medical field, it is far too close to home. Filariasis refers to a group of neglected tropical diseases caused by nematodes of the superfamily Filarioidea, transmitted through arthropod vectors. These diseases are classified as lymphatic or cutaneous/ocular filariasis based on which tissues are the primary home of adult worms (1). It is estimated that over 120 million people are infected worldwide, 40 million of whom are disfigured or incapacitated by the disease. The social, psychological, and economic burden of filariasis – amounting to a loss of 2.8 million Disability Adjusted Life Years annually (2) – is clear. The World Health Organization has committed to eliminating lymphatic filariasis as a public health problem by 2020 – and river blindness, a cutaneous/ocular form of the disease by 2025 – by i) mass drug administration in endemic regions and ii) targeting the vectors to halt transmission (3, 4). However, even regions that have eliminated filariasis may see its re-emergence due to travel in and out of the area (5).

How and where

Parasitic nematodes responsible for human lymphatic filariasis include *Wuchereria bancrofti* (which causes over 90 percent of lymphatic

filariasis), *Brugia malayi*, and *Brugia timori*. Nematodes causing cutaneous and ocular filariasis include *Onchocerca volvulus*, *Loa loa*, *Mansonella perstans*, *Mansonella ozzardi*, and *Mansonella streptocerca*. Transmission of lymphatic filariasis occurs through the *Culex* (in urban and suburban areas), *Anopheles* (in rural areas), and *Aedes* (Pacific islands) mosquitoes. Black flies are vectors for *M. ozzardi* and *O. volvulus*, and deer flies for *L. loa*. Biting midges transmit *M. ozzardi*, *M. perstans*, and *M. streptocerca* (1,2,6).

To make an accurate diagnosis, the geographic distributions of these parasites are key.

- *W. bancrofti* has widespread distribution, mainly in the tropics and subtropics including Asia, Pacific islands, Africa, South America, and the Caribbean basin.
- *B. malayi* is concentrated in southeast Asia, including India, China, Philippines, Malaysia, Indonesia, Korea, and Vietnam.
- *B. timori* is limited to some islands of eastern Indonesia including Timor (2).
- *O. volvulus* is endemic to west and central Africa, as well as parts of eastern Africa and Yemen. ➔



- *L. loa* is found only in the tropical regions of west-central Africa; exercise caution in diagnosing loiasis outside Africa. *Dirofilaria* causes ocular infections clinically similar to loiasis in Europe and Asia (7,8).
- *M. perstans* is distinctive to Africa south of the Sahara, Central and South America, and some Caribbean islands.
- *M. ozzardi* is distributed from Central to South America and in the Caribbean.
- *M. streptocerca* is native to tropical areas of western and central Africa (9).

The circle of life

Filarial nematodes need two hosts to complete their life cycle: mosquitoes or flies as intermediate hosts for development and maturation, followed by humans as definitive hosts for reproduction (10,11). Humans have adult worms localized to lymphatics (*W. bancrofti*, *B. malayi*, *B. timori*), subcutaneous tissues or eyes (*L. loa*, *O. volvulus*, *M. streptocerca*, *M. ozzardi*), and body cavities (*M. perstans*). Adult worms can survive for years in human hosts. When they undergo sexual reproduction, female worms release millions of larvae (microfilariae) into the skin or blood. These motile microfilariae stay in pulmonary vessels during the day and migrate to peripheral blood at night, reaching peak peripheral blood concentration – and thus ideal sample collection time – around midnight in parasites with nocturnal periodicity (*W. bancrofti* and *Brugia* spp.).

How does it work? A vector picks up microfilariae circulating in blood or cutaneous tissue during a feed. The development stages, which occur in the vector and take 10–14 days, are L1 (inactive), L2 (pre-infective), and L3 (infective). Finally, the vector bites a human host and releases L3 larvae that migrate to their respective localization site.

Studies have demonstrated the presence of *Wolbachia* bacteria as endosymbionts in some filarial nematodes. This association is implicated in disease pathogenesis, and host immune response, and adult worm

viability and development. However, when the nematode dies, these bacteria are released and can initiate an immunologic reaction (12) – which is why it may be effective to accompany antifilarial treatment with antibiotics targeting *Wolbachia*.

Clinical manifestations

The spectrum of disease differs between patients living in endemic regions and those who have traveled or recently migrated to those regions. In general, filarial disease has a severe, acute presentation in recent travelers or newly exposed individuals, whereas people native to endemic areas experience a more chronic and debilitating disease course.

Lymphatic filariasis

In lymphatic filariasis, asymptomatic or subclinical microfilaremia is the most common presentation. In endemic areas, this begins in early childhood (13). Patients may exhibit lymphangiectasis or dilated lymphatics (including scrotal lymphatics), microscopic hematuria, and proteinuria (1).

In acute filarial lymphangitis, patients present with high-grade fever, retrograde lymphatic inflammation, lymph node enlargement, and transient edema. Genital lymphatic involvement in *W. bancrofti* filariasis leads to funiculitis, epididymitis, and scrotal pain. Acute dermatolymphangioadenitis is characterized by fever, chills, myalgia, red tender edematous inflammatory plaques, and vesicles or ulcers. Ongoing lymphatic inflammation and subsequent obstruction leads to elephantiasis: brawny edema, thickening of subcutaneous tissue, and hyperkeratosis. Hydrocele, scrotal lymphedema and chyluria may be noted, and obstructive lymphedema may involve other organs. Recently exposed individuals present with short-lived lymphadenitis, followed by retrograde lymphangitis (1,5,14).

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