SPECIAL REPORT

Pathogen Genomics in Public Health

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SUMMARY

Rapid advances in DNA sequencing technology ("next-generation sequencing") have inspired optimism about the potential of human genomics for "precision medicine." Meanwhile, pathogen genomics is already delivering "precision public health" through more effective investigations of outbreaks of foodborne illnesses, better-targeted tuberculosis control, and more timely and granular influenza surveillance to inform the selection of vaccine strains. In this article, we describe how public health agencies have been adopting pathogen genomics to improve their effectiveness in almost all domains of infectious disease. This momentum is likely to continue, given the ongoing development in sequencing and sequencing-related technologies.

An important transformation is under way in public health. Next-generation sequencing (also called "high-throughput sequencing") is reshaping communicable disease surveillance, allowing for earlier detection and more precise investigation of outbreaks. Next-generation sequencing helps characterize microbes more effectively and offers new insights into their ecology and transmission. The plethora of sequence data provides raw material for the research and development of new diagnostics and therapeutics. This article describes how pathogen genomics has been changing public health in the United States and globally.

ADAPTING NEXT-GENERATION SEQUENCING FOR USE IN PUBLIC HEALTH

The era of next-generation sequencing began with the commercial release of massively parallel pyrosequencing in 2005, the first fundamental advance in sequencing technology since the invention of Sanger sequencing in the 1970s.[1,2] In the early years, the efficiency of next-generation sequencing improved rapidly, with sequencing costs falling by as much as 80% annually.[1,3] In public health, these developments were both exciting, because of the myriad potential applications including bacterial whole-genome sequencing,[4] and intimidating, because of the barriers — implementing next-generation sequencing would require investment in sequencing equipment as well as high-performance computing infrastructure to move, store, and analyze large volumes of sequence data. Equally important was the need to integrate bioinformatics, a discipline new to public health.

Public Health England was an early leader in the use of next-generation sequencing on a national scale, particularly for tuberculosis[5,6] and surveillance for bacterial foodborne diseases.[7,8] In the United States, the Centers for Disease Control and Prevention (CDC) was a late adopter[9] but is now applying the technology broadly, largely because of the Advanced Molecular Detection program, a $30-million-per-year initiative established by Congress in 2013 to adopt next-generation sequencing and other innovative laboratory technologies — first at the CDC and then at state and local public health departments nationwide — to address infectious disease threats.

APPLICATIONS OF PATHOGEN GENOMICS

Today, pathogen genomics is part of almost every infectious disease program at the CDC.[10] Some applications of next-generation sequencing that serve specialized purposes, such as reference testing, are in use only at the CDC, while other applications drive entire domestic surveillance systems. Below, we provide examples to

highlight the value of next-generation sequencing technology for public health (Table 1).

BACTERIAL FOODBORNE ILLNESS

In the mid-1990s, U.S. foodborne disease programs first began applying standardized molecular subtyping by pulsed-field gel electrophoresis to bacterial pathogens as part of routine surveillance, leading to a fundamental change in how outbreaks were identified and investigated. The resulting national network, "PulseNet," now includes more than 80 public health laboratories.[24] Before PulseNet, outbreaks were difficult to detect and solve unless they were large or very geographically and temporally focused. For example, during the 20-year period before PulseNet, only 5 outbreaks of listeriosis (0.25 per year) were solved (i.e., a food source was identified),[25] with a mean of 54 cases per outbreak. In the 5-year period after PulseNet began, 11 outbreaks were identified (2.2 per year), with a median of 5 cases per outbreak.[25] Routine use of pulsed-field gel electrophoresis had a similar effect on the detection and response to other foodborne bacteria, particularly salmonella[26] and Shiga toxin–producing *Escherichia coli*.[11,27,28]

PulseNet has now transitioned from pulsed-field gel electrophoresis to whole-genome sequencing.[12,29] Partners in this effort include the Food and Drug Administration, which created the GenomeTrakr system[30,31] to perform whole-genome sequencing of food and environmental isolates, the Department of Agriculture, and the National Center for Biotechnology Information.

Whole-genome sequencing offers a vastly finer resolution than pulsed-field gel electrophoresis — typically, a 3-million-to-6-million–bp sequence, in contrast to a gel pattern with 10 to 20 bands that reflect changes in small parts of the genome. Whole-genome sequencing data are inherently digital, standardized, and much less dependent on the choice of laboratory protocol. The results reveal evolutionary relationships between bacterial isolates, allowing a better understanding of transmission and links between cases (Fig. 1). Whole-genome sequencing can also predict phenotypic characteristics, such as virulence, serotype, and antimicrobial resistance.[11,13-15,17-19] Costs for whole-genome sequencing (approximately $200 to $250 per isolate, including consumables, labor, equipment, maintenance, and overhead, according to an unpublished analysis) are currently still higher than those for pulsed-field gel electrophoresis (approximately $100 according to the same analysis), although the higher costs may be partly or entirely offset by eliminating the need for traditional phenotyping assays. In addition, advances in sequencing technology and laboratory automation may further reduce the costs of whole-genome sequencing.

It is too early to know how the transition to whole-genome sequencing will affect U.S. surveillance for more common foodborne pathogens, such as salmonella and Shiga toxin–producing *E. coli*; however, early experience with surveillance for listeria, which was switched to routine whole-genome sequencing in 2014, has been encouraging. In the first 3 years of whole-genome sequencing (September 2013 through August 2016), 18 outbreaks of listeriosis were solved (6 per year), with a median of 4 cases per outbreak.[32] In the United Kingdom, where whole-genome sequencing has been in routine use for Shiga toxin–producing *E. coli* since at least 2015, the number of clusters detected has doubled.[33]

TUBERCULOSIS

Since the 1990s, several DNA fingerprinting technologies have proven useful for subtyping *Mycobacterium tuberculosis*.[34] Identifying closely related strains allows health department investigators to detect clusters of cases that may be linked to recent transmission — cases that require more-intense investigation and possible intervention.[35] Whole-genome sequencing offers subtyping at much finer resolution than was possible with older technologies and thus more confidence in the inferred relationships among cases. After using whole-genome sequencing selectively for several years, investigators in U.S. tuberculosis control programs have now scaled up the process to sequence isolates from all culture-confirmed cases nationwide. In California, whole-genome sequencing has allowed public health workers to refute more than half of suspected outbreaks initially identified by conventional genotyping, thereby saving time and resources (Shaw T, California Department of Public Health: personal communication). Early experience in U.K.,[5] Canadian,[36,37] and Dutch[38] tuberculosis programs has also confirmed that whole-genome sequencing supports more effective investigations by more accurately defining outbreaks,[5,36,38] providing insights into transmis-

Table 1. Attributes of Next-Generation Sequencing That Drive the Adoption of the Technology in Public Health.

High-resolution subtyping of pathogens

Examples:

Bacterial enteric illness: improves detection of and response to outbreaks.

Tuberculosis: allows better targeting of interventions to stop transmission.

Legionella: provides a new tool to understand the ecology of the pathogen in water systems.

Potential agents of bioterrorism: allows for improved forensics.

Caveats: Legacy technologies often need to be continued during a transition period, since older subtyping characterizations often cannot be reliably predicted from nucleic acid sequence data; pulsed-field gel electrophoresis patterns, for example, usually cannot be predicted from routine whole-genome sequencing.

Efficient inference of phenotypic traits

Examples:

Serotyping: In U.S. public health laboratories, influenza viruses are now subject to a "sequencing-first" approach, in which antigenic type and subtype can be inferred from the sequence; only a subgroup of viruses undergoes traditional typing and subtyping. For pathogens such as *Escherichia coli*,[11-13] salmonella,[14,15] or pneumococcus,[16] the serotype can usually be inferred from sequence data, without the need to acquire and maintain serum panels.

Antimicrobial resistance: for bacterial pathogens such as salmonella,[17,18] *E. coli*,[19] streptococcus,[16,20] *Mycobacterium tuberculosis*, or gonococcus[21] (to name but a few), antimicrobial resistance is increasingly inferred from genomic data.

Virulence: known virulence factors, such as the presence or absence of Shiga toxin genes in an *E. coli* strain, can also be inferred from genomic data.

Caveats: There will probably always be a need for traditional phenotyping. The ability to predict a phenotype from a genome generally relies on known correlations between the phenotypic characteristics and specific genetic sequences. Particularly in rapidly evolving species such as influenza, those correlations will need constant updating. In addition, the consistency of those correlations is variable. The reliability of inferred antimicrobial resistance, for example, is highly dependent on the type of antibiotic, the mechanism of resistance, and the species of bacteria. This reliability should improve over time as more data become available and algorithms for predicting phenotype improve. The capability of inferring phenotype from genotype means that fewer traditional tests will need to be done in the future and that fewer laboratories (i.e., reference laboratories) will need to maintain the capacity to perform them.

"Deep sequencing" rather than "consensus sequencing"

Whereas Sanger sequencing generally provides a single "consensus" sequence from a sample, next-generation sequencing typically provides many (often hundreds, thousands, or more) "reads" of the gene or amplicon.

Examples:

Malaria: In areas where malaria is highly endemic, infection with multiple strains of malaria is common. In such cases, Sanger sequencing usually reflects only the most dominant strain in the individual patient and can miss the presence of other strains, which may have differing resistance to antimalarial agents. In areas where malaria is endemic, deep sequencing can also be used to quantify the number of strains in an individual patient, a correlate of the intensity of transmission that can also be of potential use in evaluating the effectiveness of community interventions.

Hepatitis C: Hepatitis C virus mutates rapidly in individual patients, resulting in a "swarm of quasispecies." Data on the diversity of quasispecies in two patients provides a reliable means of inferring whether they are part of a single outbreak.[22,23]

Influenza: High mutation rates in influenza virus can also lead to minor variants with resistance to oseltamivir or other antiviral agents, which could be missed by consensus sequencing.

Caveats: Sequencing errors, which are more common with next-generation sequencing than with Sanger sequencing, can create the illusion of rare variants. Careful analysis of potential sequence variants is needed to prevent this.

More efficient workflows

Characterizing pathogens by means of sequencing is sometimes but not universally less laborious and less expensive than traditional typing.

Examples:

E. coli: Shiga toxin–producing *E. coli* is a common cause of foodborne illness. A standard workflow for characterizing Shiga toxin–producing *E. coli* involves determination of the serotype, traditionally accomplished by means of a panel of antiserum specimens to determine O antigen and, if indicated, H antigen, as well as detection of Shiga toxin or Shiga toxin genes by, for example, polymerase chain reaction. All these characteristics, as well as susceptibility or resistance to several antibiotics, can be reliably inferred from whole-genome sequencing.

Influenza virus: The United States is now using a sequence-first approach to influenza virus characterization.

Caveats: Sequencing, for the time being, is often more expensive than traditional subtyping alone. For bacterial pathogens, for example, whole-genome sequencing is typically twice as expensive as pulsed-field gel electrophoresis alone. However, if pulsed-field gel electrophoresis for a particular pathogen needs to be accompanied by traditional phenotyping such as serotyping, virulence typing, or antimicrobial resistance testing, and the features found on such phenotyping can be reliably inferred from the genome, then the sequencing approach is often less expensive.

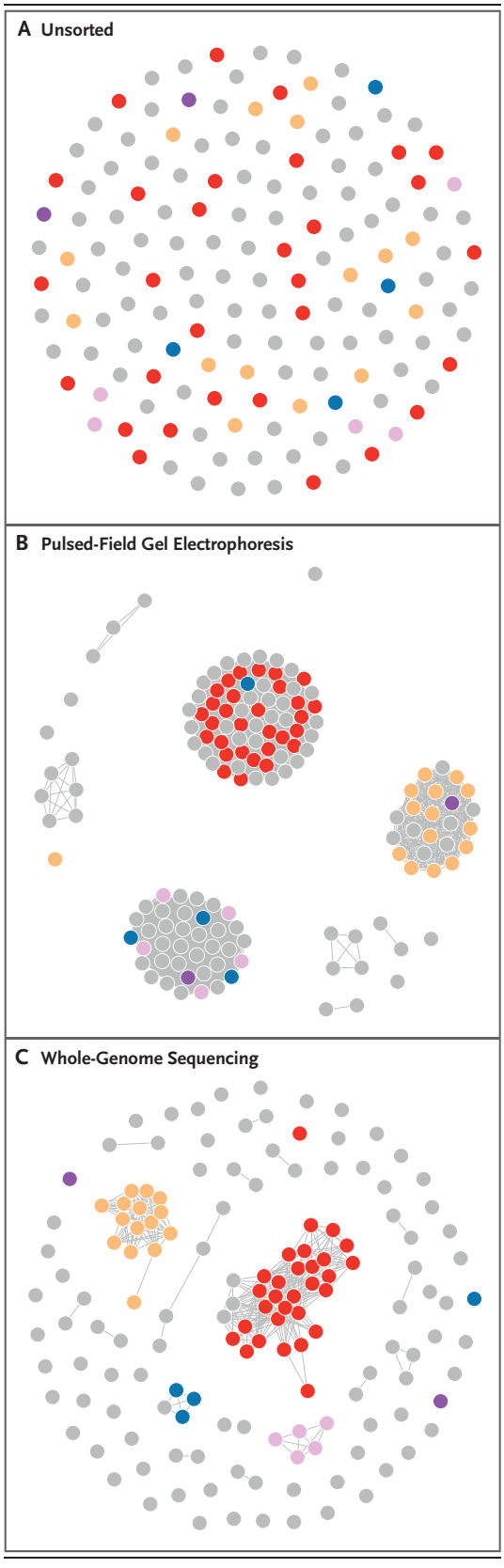

Figure 1. Example of Sequencing for Outbreak Detection and Investigation.

An important purpose of surveillance for infectious diseases is to identify outbreaks for investigation and intervention. Discovering patterns in the epidemiologic data (i.e., finding common exposures among cases that cluster in time and location) can help distinguish outbreaks from the often much larger background of sporadic cases. Molecular subtyping has played an increasingly central role in this process through the detection of cases with isolates that share a common molecular "fingerprint."

In this figure, we schematically represent surveillance data for a foodborne pathogen, *Salmonella enterica* serovar Enteritidis, reported from one region of the United States in 2018; in that year, some states in the region were already sequencing salmonella isolates in real time, and others had not yet started. In the three panels, each dot represents a case of gastroenteritis due to *S. enterica* serovar Enteritidis. Gray dots represent cases that were later determined to be "sporadic" (i.e., not linked to outbreaks), and colored dots represent cases that were eventually linked to outbreaks. The largest of these outbreaks (red dots) began as two distinct clusters of disease associated with restaurants in two different states. Whole-genome sequencing linked these two clusters together and to several other cases outside the region.

Panel A displays cases randomly, without regard to molecular subtyping. Panel B represents a grouping of cases based on results of pulsed-field gel electrophoresis, a molecular subtyping technology that U.S. public health agencies have used since the 1990s. In this example, pulsed-field gel electrophoresis was mostly successful at grouping cases from the largest (red) outbreak; however, the group includes many cases unrelated to the outbreak, which complicates the investigation and reduces the likelihood of finding the food source. Panel C shows that the finer resolution afforded by whole-genome sequencing was more effective in segregating the red outbreak cases from others. This gave investigators more confidence in the cluster definition and allowed them to focus on cases that were more likely part of the same outbreak. In this outbreak, epidemiologic investigation identified shell eggs as the likely source, which was quickly confirmed by isolating *S. enterica* serovar Enteritidis from the implicated eggs and showing that its whole-genome sequence matched that from the outbreak cases. In addition to the outbreak in red, this panel shows four additional outbreaks. Cases in blue were part of a restaurant-associated outbreak linked to chicken in a single state. Two cases (purple) were linked to live poultry exposure as part of a much larger, multistate, multistrain outbreak that occurred mostly outside the region shown here. The 5 cases in light pink were investigated as an outbreak, but no food source was identified. The 15 cases in light orange occurred in a state where real-time whole-genome sequencing had not yet been implemented; their isolates were not sequenced until a later date, after the apparent outbreak had ended. This figure summarizes the relationships identified by whole-genome sequencing with the use of a simplified graph; in practice, however, the data would be represented as a phylogenetic tree, which contains additional detail that more precisely represents the relationships among sequences.

sion dynamics,[39] and sometimes suggesting the presence of previously unidentified cases or possible "super-spreaders" that should be prioritized for isolation and treatment.[5,36] Whole-genome sequencing may also indicate whether recurrent cases are due to reactivation or reinfection, information that is useful in the evaluation of a program's effectiveness.[40]

The ability to prioritize case investigations may also be of use in high-incidence, low-income

and middle-income countries that carry the world's heaviest burden of tuberculosis.[41] In these countries, however, a different application of next-generation sequencing — sequencing of *M. tuberculosis* directly from sputum — could have an even more important role.[42] Direct sequencing of *M. tuberculosis* from smear-positive sputum samples is already feasible in research settings[43-45] but is too expensive and cumbersome for routine clinical and public health use. If the approach can be made practical and cost-effective, it will enable rapid inference of drug susceptibility, which is already quite accurate for most first-line drugs and will improve as more data become available.[42,46] In addition to supporting prompt treatment with appropriate drugs, next-generation sequencing will reduce the need for routine phenotypic testing, which is complex, slow, and difficult to maintain in resource-limited laboratory settings.

In the meantime, an intermediate strategy is already practical in high-income countries: whole-genome sequencing directly from early positive cultures, a procedure that provides information on drug susceptibility weeks before the results of traditional tests are available.[43] Laboratories in both the New York State Department of Health and Public Health England[42] have received regulatory approval to forgo traditional drug-susceptibility testing of isolates predicted by whole-genome sequencing to be susceptible to all four first-line drugs (approximately 70 to 80% of all isolates).[42]

Another promising strategy is amplicon sequencing, an approach that involves targeted polymerase-chain-reaction (PCR) amplification of selected mycobacterial genes or marker sequences, followed by sequencing of the resulting amplicons.[47] To remain relevant over time, any sequence-based method for inferring drug susceptibility must rely on the continuous updating of databases with correlated genotypic and phenotypic data.[42]

INFLUENZA

The selection of seasonal influenza vaccine candidate strains is a complex, global undertaking, involving massive surveillance efforts from dozens of countries and contributing organizations. The World Health Organization (WHO) convenes international experts twice yearly to review information on circulating influenza strains and, on the basis of that information, to recommend components of the Northern and Southern Hemisphere influenza vaccines.[48] The CDC contributes to this process by overseeing the characterization of 4000 to 10,000 influenza specimens each year.[49]

The traditional method for characterizing influenza strains begins with viral culture, which is increasingly challenging for certain strains, particularly H3N2.[50] Two or more passages through culture are often required, during which some adaptation of the virus may occur. Next, a few viral isolates are selected for phenotyping, which previously included antigenic characterization and consensus (Sanger) sequencing of selected genes. These steps are time consuming and labor intensive.

Next-generation sequencing now enables a more efficient "sequence-first" approach, in which original specimens are subjected directly to whole-genome reverse-transcriptase PCR, followed by sequencing.[50-52] These sequence data provide a highly granular view of viral emergence and allow for a more parsimonious selection of viruses for phenotypic characterization, including antigenic analysis and susceptibility to antiviral agents. This approach is not only faster but also more informative. For example, detailed phylogenetic information on all viral segments provides a richer picture of how influenza viruses are diversifying to evade existing immunity, and deep sequencing (sequencing many copies of the genome from the same sample) can reveal the presence of drug-resistant minor variants not reflected in the consensus sequence. Sequencing cannot completely replace traditional phenotyping, but the strategy of sequencing directly from clinical specimens allows for phenotyping to be performed more selectively.

Next-generation sequencing data on influenza are now routinely reviewed at the biannual WHO consultations, and the review of such data has already affected decision making about vaccines in at least two major instances, most recently contributing to a change in the A(H3N2) vaccine component to target a newly emerging clade.[50,53,54] Next-generation sequencing data are also used to forecast the relative importance of emerging strains and assess risk,[55-57] characterize viruses used in vaccine effectiveness studies,[58] and inform treatment for patients infected with viruses that have high pandemic risk such as H7N9.[59,60]

PARASITIC DISEASES

Diagnosis of many parasitic diseases continues to rely on microscopy, a 19th-century technology that is operator dependent and resistant to automation. PCR and other diagnostic techniques (e.g., serology) have been developed for many common parasites but require separate tests for each suspected pathogen.

The parasitic diseases laboratories at the CDC are developing a new type of diagnostic test based on the targeted amplification and next-generation sequencing of eukaryotic housekeeping genes. This approach enables the accurate detection of all known potential human parasitic agents present in a blood sample with a single test. Early validation data suggest that this new assay is at least as sensitive as standard PCR for parasites found in blood.[61] Further validation and development is ongoing, with plans to add more targets and to adapt the assay to more complex samples, including tissue and stool.

PCR amplification and next-generation sequencing of specific genes is an effective means of identifying drug resistance in malaria parasites.[62] Because such testing takes 2 to 3 days and is still somewhat expensive, its use in routine patient care remains limited. For surveillance at the country or regional level, however, it is a cost-effective and efficient way to assess drug resistance and to target treatment recommendations more precisely. Protocols based on next-generation sequencing may also be useful for assessing the intensity of transmission by gauging multiplicity of infection among residents in areas in which malaria is endemic.[63]

Cyclospora cayetanensis causes outbreaks of foodborne diarrheal disease in the United States every year. The limited genotypic variability of the organism and its inability to be propagated in the laboratory have confounded the development of effective genotyping methods for surveillance. The CDC has developed a method to extract *C. cayetanensis* directly from stool and has used the extracts to produce whole genomes of multiple isolates.[64] Several promising genotyping targets have been identified, and their translation into a functional and discriminatory genotyping tool is showing promise.[65]

OTHER APPLICATIONS

Next-generation sequencing is applicable across the spectrum of important pathogens in public health. For Legionnaires' disease, for example, finer subtyping has been useful for investigating and responding to outbreaks.[66,67] Eventually, insights from next-generation sequencing into ecology and persistence of legionella in water systems could improve prevention.[68] For hospital-acquired infections, next-generation sequencing is proving to be an invaluable tool for identifying and investigating outbreaks[69,70] and also provides a better understanding of transmission at both the hospital[70] and the community[69,71] level. For human immunodeficiency virus, genetic-sequence data generated for clinical purposes can be analyzed to identify potential clusters for early intervention[72,73]; user-friendly tools[74] now allow state and local health departments to make use of these data. Community-level molecular surveillance for hepatitis C clusters has also proven useful.[75] Other applications for next-generation sequencing in public health include tracking the emergence of antimicrobial resistance and new resistant pathogens such as *Candida auris*,[71,76] tracking insecticide resistance in mosquito vectors of disease,[77,78] monitoring streptococcal pathogens,[20,79] and investigating potential clusters of meningitis.[80]

SEQUENCING TO SUPPORT OUTBREAK RESPONSE

An important subgroup of next-generation sequencing applications in public health involves outbreak response.[81] With respect to bacterial foodborne disease, for example, sequencing is now central to the detection of outbreaks, investigation of cases, and confirmation of the implicated food and then tracing it back to its source. A very different example comes from the latter phases of the 2014–2016 Ebola outbreak in Guinea, in which sequencing was useful in ascertaining the likely source of infection in "outlier" cases (i.e., those with no known connection to other cases). Each outlier raised troubling questions: Did the case represent another introduction from an animal reservoir? Was it attributable to sexual transmission? Had a long chain of transmission been missed, which would suggest serious gaps in surveillance? Each of these questions would require a different response. Fortunately, in this outbreak, sequences from outliers were consistently closely related to those in the known outbreak zone, and the response team was able to remain focused on stopping transmission there.[10,82]

In contrast, sequencing Zika virus during its emergence in the Americas was not useful for responding to individual cases. However, sequence data were critical in developing diagnostic procedures and vaccines, gaining a better understanding of the evolution of the epidemic,[83] and recently, supporting evidence of an undetected outbreak in Cuba.[84] An analysis of Ebola virus genomes after the West Africa outbreak also provided useful insights into the spread of the virus.[85]

WHERE TO GO NEXT?

Six years into the Advanced Molecular Detection program, next-generation sequencing is now central to U.S. public health programs for monitoring, controlling, and preventing infectious diseases. Progress is currently needed in several areas.

METAGENOMICS

Sequencing, particularly bacterial whole-genome sequencing, often requires pure cultures of the organisms, which are increasingly difficult to obtain as clinical laboratories expand the use of highly multiplexed, syndrome-based, culture-independent diagnostic tests.[86,87] Most immediately, this trend is adversely affecting enteric disease surveillance as clinical laboratories move away from the use of cultures.[88] One solution may be to bypass culturing and to sequence pathogen genomes directly from specimens.[43,89] Although the methods are already feasible for selected organisms in particular specimens, they are not yet practical for routine use.

DATA INTEGRATION AND DATA SCIENCE

In public health settings, laboratory and epidemiologic data are often stored and managed separately. Until recently, these data could be brought together for analysis without loss of information: laboratory data such as a positive or negative result, a titer, or even a pulsed-field gel electrophoresis pattern identifier could be imported into an epidemiologic database and analyzed with the use of traditional statistical tools. With pathogen genomic data, this is no longer true: laboratory and epidemiologic data need to be integrated to realize the full value of both.[36,90,91]

Fortunately, academic researchers are addressing this challenge,[92] producing tools, such as Microreact (https://microreact.org),[93] Nextstrain (https://nextstrain.org),[94] and the Interactive Tree of Life (https://itol.embl.de), for visualizing and analyzing epidemiologic and phylogenetic data together.[95] More broadly, the emerging field of data science offers new approaches for integrating, analyzing, and visualizing increasingly diverse public health data.[31,96]

SOFTWARE TO FACILITATE NEXT-GENERATION SEQUENCING WORKFLOWS

Complex workflows are required to manage the sequencing process, analyze raw sequence data, store processed data and integrate it with epidemiologic data, and share information securely. In a single academic laboratory, it is feasible for a bioinformatician to accomplish this, but in a network of public health laboratories, it can be more practical to manage much of this centrally. Bioinformatics tools are available to accomplish the basic steps of assembling raw sequence data into genomes, and "pipelines" that make use of these tools are available to automate core processes, such as validating quality, assembling a genome, and inferring phenotypes. However, user-friendly tools for managing workflows and integrating data are often lacking. In other instances, too many tools exist, and it is not clear which ones will survive the test of time.

CHALLENGES

Workforce transformation among both microbiologists and epidemiologists, although perhaps the most obvious hurdle, is in some ways the least challenging because of the enthusiasm about genomics. Even recruiting and retaining bioinformaticians has not been as difficult as initially anticipated. Among the first 27 recruits into the Association of Public Health Laboratories–CDC Bioinformatics Fellowship, 19 (70%) are still working in public health, despite a competitive marketplace. Those who stay in public health often cite the opportunity to have positive social impact as a key motivator.

Costs represent a more difficult issue. At present, sequencing is often more expensive than traditional subtyping. In addition, to minimize per-sample costs, sequencing technologies such as the MiSeq platform (Illumina) may require batch sizes of 15 samples or more, which

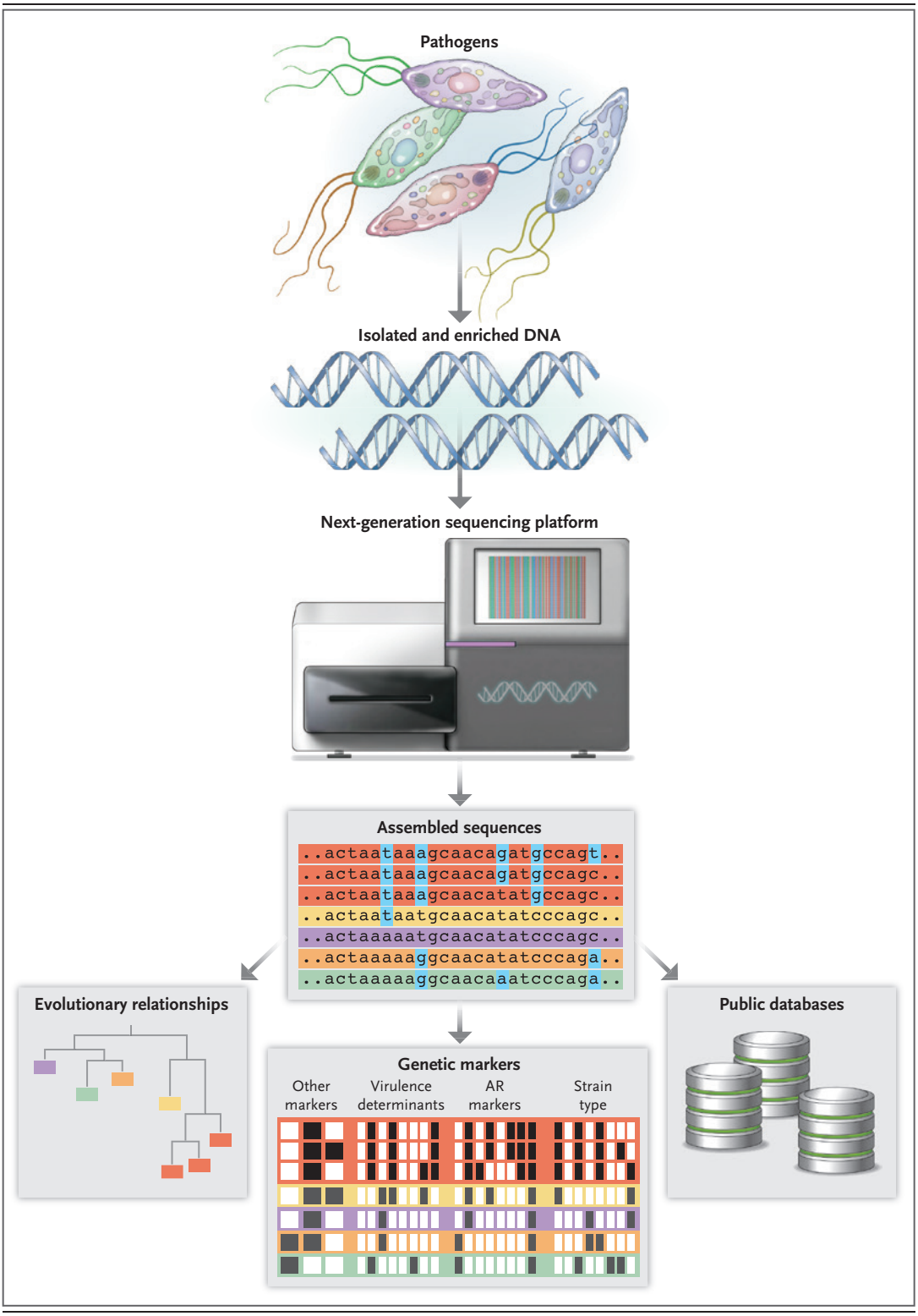

Figure 2 (facing page). Typical Pathogen Genomics Workflow.

Shown is the typical pathogen genomics workflow. From the pathogens collected in the course of disease surveillance, genomic DNA or RNA are extracted, shorn into shorter segments, labeled, and subjected to next-generation (high-throughput) sequencing. The raw data from the sequencer are sorted, reassembled, and aligned to other genomes for comparison. The assembled genomes are used for several purposes, including the determination of relatedness and the prediction of phenotypic traits such as virulence, antimicrobial resistance, and serotype. The data are increasingly being made publicly available in real time for use by researchers and for the development of diagnostics and therapeutics and vaccines.

can extend turnaround times beyond the 36 hours needed for the sequencing itself. Clearly, during a fast-moving outbreak, such delays are undesirable. Single-molecule, long-read sequencing technology, most notably the MinION (Oxford Nanopore Technologies), already has niche uses within public health because of its portability but also has the potential to reduce batch sizes and turnaround times.[82]

DATA OPENNESS

In both academia and public health, pathogen genomics is ushering in a new era in data openness. In the United States, local, state, and federal agencies are uploading data on bacterial foodborne pathogens,[31] influenza,[50] and other pathogens to public databases hosted by the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/pathogens), making these data available in near real time. These groups also contribute to other global databases, such as the Relational TB Sequencing Knowledgebase (ReSeqTB) data platform (www.reseqtb.org) and the Global Initiative on Sharing All Influenza Data (GISAID; www.gisaid.org), established to promote international exchange of sequence and other data. In addition to enabling secondary uses of data, openness also encourages collaboration among public health organizations, academia, and industry. Nevertheless, openness can never be complete and unconditional: public health agencies have always been vigilant guardians of confidentiality, and pathogen genomic data are released only after careful consideration of risks.[91,97,98]

CONCLUSIONS

Next-generation sequencing and bioinformatics are transforming the response to infectious disease outbreaks, providing new insights into disease emergence and transmission, expediting pathogen characterization, and promoting data sharing (Fig. 2). In public health, sequencing is already routine in many core domains, including foodborne bacterial pathogens, tuberculosis, influenza, and antimicrobial resistance. These developments are taking place within a rapidly evolving technology landscape: next-generation sequencing is becoming more automated, efficient, and accurate, and related technologies, such as systems for highly multiplexed DNA amplification, are advancing.

Development of the public health workforce is central to this process. Microbiologists need a strong knowledge base in microbial genomics. Epidemiologists need the skills and tools to translate genomic data into public health action. Both groups need to grasp the basic vocabulary of bioinformatics. Public health should strive to attract professionals with broadly applicable data-science skills. For anyone considering a career in public health, this is an exciting time to jump in.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC) or the Agency for Toxic Substances and Disease Registry. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Office of Advanced Molecular Detection, National Center for Emerging and Zoonotic Diseases, the CDC, the Public Health Service, or the Department of Health and Human Services.

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