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Martin Wiedmann[1*] and Melanie J. Neumann[2]

[1]Department of Food Science, Cornell University, Ithaca, NY 14853, USA
[2] Neumann Advisory Services, LLC, Lansing, NY 14882, USA

Whole Genome Sequencing for Food Safety: Opportunities, Benefits and Challenges

ABSTRACT

Whole genome sequencing (WGS) is increasingly used by public health and regulatory agencies to detect foodborne disease outbreaks, identify outbreak sources, and, less commonly, to assess food industry's regulatory compliance status. WGS application appears most prevalent in US, Canada, many parts of Europe, Australia and New Zealand, as compared to other countries and specifically most low and middle income countries. The use of WGS by the food industry is more limited and typically focuses on very specific applications where benefits have been determined to outweigh potential risks of WGS use, including regulatory, legal and reputational risks due to use and sharing of WGS data and attribution of WGS data to a specific firm. Broader industry adoption is further hampered by hurdles such as lack of trained personnel to properly interpret WGS findings and/or the ability to put the findings into context of enterprise risk. Ultimately, global public health will benefit from the use of WGS and the sharing of normalized and standardized data provided that (i) the risks to the private sector can be appropriately and reasonably identified and mitigated and that (ii) global WGS infrastructure is enhanced and further harmonized.

INTRODUCTION

This paper is intended to (i) enhance the understanding of how the food industry, regulatory and public health agencies use whole genome sequencing (WGS) to identify and characterize foodborne pathogens, and (ii) highlight key technical, regulatory, legal and business risks and benefits in using and sharing WGS data. Further, this paper aims to raise awareness of certain adoption challenges, particularly in the private sector, and offer practical risk mitigation considerations to help set the stage for further discussions between the public and private sectors across the globe to foster increased and effective use of WGS and sharing of WGS data to improve food safety.

Specifically, this paper aims to:

1. Define key terms and overarching principles related to WGS to enhance industry understanding and help set the stage for further discussions between the public and private sectors.

*Author for correspondence: Martin Wiedmann; Email: mw16@cornell.edu

2. Provide a technical overview of the use of WGS by the food industry, regulatory authorities, public health agencies and academia in the United States and selected countries where WGS has been adopted to notable levels.
3. Summarize key benefits of WGS use and data sharing in enhancing food safety.
4. Summarize key challenges and risks of WGS use and data sharing (with a focus on the private sector) and discuss possible risk mitigation considerations.
5. Provide recommendations for future consideration by both public and private sectors for fostering greater industry adoption of WGS testing and data sharing.

Metagenomics use in food safety and application of next generation (gen) sequencing (NGS) methods for metagenomics (including metagenomics based testing approaches) were considered outside the scope of this paper as these tools are currently less commonly used in food safety as compared to whole genome sequencing (see *Table 1* for descriptions of NGS and metagenomics).

Whole genome sequencing (WGS) is increasingly used by public health and regulatory agencies to detect foodborne disease outbreaks, identify outbreak sources, and, less commonly, to assess food industry's regulatory compliance status. To date, use of WGS does not appear to be a common legal or regulatory requirement, despite headlines and promotional statement that may give the appearance of regulation (e.g., a headline that read *"European Union Reference Laboratories support the National food, feed and veterinary Reference Laboratories with rolling out whole genome sequencing in Europe"* [32]). However, a EU regulation published on January 31, 2025 *(13)*, specifically includes the following language *"Where available, food and feed business operators shall submit to the competent authority, upon its request, the isolates of the pathogens referred to in paragraph 1 and the related results from WGS from their own investigations when associated or suspected to be associated with an outbreak, together with the associated data"*. This suggests that requirements for industry to submit WGS data under specific circumstances may become more likely and more common.

While WGS adoption is occurring by public health and regulatory agencies across the globe, it is most prevalent in the US, Canada, parts of Europe, Australia and New Zealand, and to a lesser degree in other countries and regions *(11)*. WGS is most commonly used by public health and regulatory agencies to characterize specific priority foodborne pathogens, including *Listeria monocytogenes*, *Salmonella* and pathogenic *E. coli*, as well as foodborne viruses. In some countries (e.g., Denmark, US, Canada), however, a broader range of foodborne pathogen isolates (e.g., *Vibrio*, *Yersinia*) obtained from humans and foods may be characterized by WGS, either routinely or during outbreak investigations. By comparison, use of WGS by the food industry (abbreviated as "industry" for the rest of this paper) is more limited, often involving attorneys to provide legal protection, e.g., from requests for WGS data (i.e. "attorney client privilege"). Industry use of WGS typically focuses on very specific applications where benefits have been determined to outweigh the risks (e.g., complex root cause analysis cases, identification of lab cross-contamination, confirmation of pathogen positive tests, surveillance of bacterial and viral populations in the pre-harvest supply chain). While a few predominantly large companies may have substantial in-house expertise in WGS, this appears to be the exception. When WGS expertise is available, it is frequently siloed with technical experts who may not have the exposure to their firm's broader enterprise risk management (ERM) strategy to effectively understand the risks and benefits WGS use or sharing presents to their companies. In some situations, technical experts and company leadership may also differ in their interpretation of the relative benefits and risks associated with WGS use.

However, in many food companies, regulatory, food safety and quality personnel may lack the expertise needed to properly interpret WGS findings (whether generated in-house, by third-party laboratory partners or by government agencies) and/or the ability to put the findings into context of enterprise risk. Despite substantial outreach and training efforts, including a number of white papers and review articles (e.g., references *6, 15, 50-52*), concerns about method standardization are still occasionally raised *(1)*. On the technical side, these concerns however have largely been addressed to a point where even different WGS methods (e.g., Illumina sequencing with different platforms) provide comparable results. In addition, publication of a relevant ISO standard (ISO 23418:2022) *(22)*, entitled *"Microbiology of the food chain - Whole genome sequencing for typing and genomic characterization of bacteria - General requirements and guidance"* also should have alleviated some of these concerns. However, interpretation of similarity metrics between isolates (e.g., X Single Nucleotide Polymorphisms [SNPs], Y core genome Multilocus Sequence Typing [cgMLST] alleles; see *Table 1* for definitions) remains a area of concern and confusion, which is addressed and further discussed in the section below entitled "Current Uses of WGS in food safety".

Another major challenge with application, use and further adoption of WGS by industry is the regulatory and legal uncertainty with regard to use and attribution of WGS data. A factor contributing to this challenge is that non-WGS data (e.g., epidemiological data, supply chain data), which can be essential for interpretation of WGS data, are often not clearly detailed in reports of public health and regulatory findings, contributing to uncertainty as it is difficult assess how these data informed regulatory decision making. As additional challenge, there typically is no clear (regulatory) guidance on how public health or regulatory agencies use WGS data. Specifically, there is little guidance on how WGS data would constitute an appropriate burden

TABLE 1. Key terms, definitions and abbreviations related to Whole Genome Sequencing (WGS)

Abbreviation/Name	Definition and Explanation
Allele	Allele refers to a different form of a gene. For example, *Listeria monocytogenes* has approx. 3,000 genes (with a gene typically being about 1,000 nucleotides long); if two *Listeria* isolates are identical, except for one gene (which differs between the isolates by 1 or more nucleotides), then these two isolates differ by one allele. See also entries for MLST, cgMLST, and wgMLST.
Base pair (bp)	Base pair (bp) is a unit that is used to measure the length of DNA. While base pair and nucleotide (nt) can be used interchangeably (in *"gene X is 600 nt long"* or *"gene X is 600 bp long"*), the term nt refers to a single letter (i.e., A, C, T, or G) and hence a single strand of DNA, while the designation of "bp" emphasizes the fact the DNA is made of two strands of letters ("pairs") where an A on one strand means there is T on the other strand and where a C on one strand means there is a G on the other strand.
Centers for Disease Control and Prevention (CDC)	The US CDC leads and coordinates WGS characterization of human isolates in the US; the actual sequencing of human isolates is however typically conducted by state health departments. CDC guidance on WGS may often be adopted internationally.
Core genome Multilocus Sequence Typing (cgMLST)	In cgMLST, only those genes that are found in all subtypes of given bacterial species are analyzed to characterize the differences between two isolates. For example, while *L. monocytogenes* has about 3,000 genes, only the approx. 1,700 genes found across all *L. monocytogenes* are included in a cgMLST scheme
DNA	DNA (Deoxyribonucleic Acid) is the genetic material, which is the blueprint for all molecules that make up a cell (bacterial, human, etc.). DNA is made up of four "nucleotide bases" (A, C, T, and G); an easy way to think about this is a language of four letters. Genomes (except for some viral RNA genomes) are made of DNA and only contain these four letters; bacterial genomes typically range from 2 to 10 million "letters" (nucleotides). For example, the *Listeria* genome consists of about 3 million A, C, T, and Gs.
Genome	The term genome refers to the entirety of the DNA that makes up an organism; bacterial genomes typically range from 2 to 10 million bp. Bacterial genomes are organized into distinct genes (if a genome is a book with letters, then genes may be described as individual pages). An average gene is made up of about 1,000 nucleotides ("letters").
Illumina	Illumina is a company that develops and sells Next Generation sequencing products, such as the MiSeq and NextSeq 2000. Other prominent companies that provide sequencing technologies include, but are not limited to, Oxford Nanopore Technologies (ONT) and PacBio (see separate entries for both).
Long Read Sequencing	Next generation sequencing (NGS) can be performed using a number of different methods, including (i) Short Read Sequencing and (ii) Long Read Sequencing (which also is often referred to as "Third generation sequencing"). In Long Read Sequencing, the individual part of the DNA sequenced is much longer (typically >10,000 nucleotides) as compared to the part of the DNA sequenced in widely used Short Read Sequencing systems (which typically sequence 75 to 300 nucleotides); in both methods, genome sequences are determined by assembling the individual DNA pieces via bioinformatics methods.
Multilocus Sequence Typing (MLST)	MLST can be described as a data analysis approach that characterizes the difference between bacterial isolates by analyzing each bacterial gene separately (see https://pubmlst.org/multilocus-sequence-typing); with MLST the genetic differences between isolates are expressed as the number of "allele" or "allelic" differences (see entry on "Allele" above). In contrast, if the overall genome is analyzed, the differences between two isolates are expressed as "SNP" differences (see entry on "SNP"). For WGS data, both cgMLST and wgMLST approaches (see separate entries) are used for data analyses.

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TABLE 1. Key terms, definitions and abbreviations related to Whole Genome Sequencing (WGS) *(cont.)*

Abbreviation/Name	Definition and Explanation
Metagenomics	Metagenomics is the study of the genetic material (DNA) recovered directly from environmental or other (e.g., food) samples, allowing analysis of entire microbial communities. "shotgun metagenomics" characterizes essential all DNA in a sample, while 16S rDNA metagenomics (or more correctly "16S rDNA amplicon sequencing") specifically targets characterization of bacteria present in a given sample. Both shotgun metagenomics and 16S rDNA amplicon sequencing are typically performed with NGS methods.
National Center for Biotechnology Information (NCBI)	NCBI is a center that is part of the US National Library of Medicine. When discussing WGS, "NCBI" is often used as slang for the WGS sequence databases that are maintained by NCBI (which all are available to the public). NCBI may be used in expressions such as *"Once it's in NCBI everyone can see it"* or *"I am worried any bacteria we get sequenced will be uploaded into NCBI"*. Essentially, the term "NCBI" is often used as to refer to the NCBI Pathogen Detection database (see separate entry).
Next Generation Sequencing (NGS)	Next Generation ("next gen") Sequencing (NGS) referd to very high throughput sequencing technologies (in contrast to classical "first gen" sequencing methods that sequence one small DNA fragment at a time, such as Sanger sequencing). Essentially, all WGS performed since about 2010 used NGS methods. NGS tools can be used for applications other than WGS, including metagenomics sequencing and large scale (highly parallel) amplicon sequencing, which is often used for microbiome studies.
Nucleotide	Nucleotide (often abbreviated as "nt") refers to one of the "letters" (i.e., A, C, T, or G) that make up DNA; the four nucleotide bases in DNA are adenine (A), Cytosine (C), Guanine (G) and thymine (T). "nt" is also a unit that is used to measure the length of DNA; base-pair and nucleotide can be used interchangeable (in expressions such as *"gene X is 600 nt long"* or *"gene X is 600 bp long"*).
Oxford Nanopore Technologies (ONT)	Oxford Nanopore Technologies (ONT) is a company that develops and sells nanopore sequencing products such as the MinION, which is a highly portable Third generation sequencing method (see separate entry) that provides for long read DNA sequencing. ONT and specifically the MinION are often used as example of NGS methods that can be applied and used in a highly distributed way, including in smaller labs and even in "the field" (e.g., in smaller labs located in processing plants). Other prominent companies that provide sequencing technologies include, but are not limited to, PacBio and Illumina (see separate entries for both).
PacBio	PacBio is a company that develops and sells Third Generation sequencing products that provide for long read DNA sequencing. Other prominent companies that provide sequencing technologies include, but are not limited to, Oxford Nanopore Technologies (ONT) and Illumina (see separate entries for both).
Pathogen Detection database (or "NCBI Database")	A WGS database maintained by NCBI (see entry for "NCBI" above). This database is publicly accessible at https://www.ncbi.nlm.nih.gov/pathogens/ and represents a repository of WGS data generated by different entities around the world. It contains WGS data for > 1 million foodborne pathogen isolates from humans, foods, and environmental sources.
Persistent pathogen	The term "persistent pathogen" is typically used to describe the presence of a specific strain of a pathogen (e.g., as determined by WGS) over time in a facility (the terms "persistent" and "resident" pathogen are often used interchangeably). There are, however, no standardized definitions as to how long an organism has to survive in a facility to be considered persistent; sometimes presence over multiple full sanitation cycles is considered a prerequisite for classifying an organism as persistent. In addition, differentiation of an organism that persists in an actual facility and an organism that is repeatedly introduced into a facility can be difficult or even impossible.

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TABLE 1. Key terms, definitions and abbreviations related to Whole Genome Sequencing (WGS) *(cont.)*

Abbreviation/Name	Definition and Explanation
Phylogenetic trees	A phylogenetic tree is a graphical representation of the evolutionary relationships between biological entities, usually sequences or species. Relationships between entities are captured by the topology (branching order) and amount of evolutionary change (branch lengths) between nodes. Phylogenetic trees can be easily misinterpreted by non-experts (e.g., by assuming vertical proximity reflects relatedness) and the food industry should consider seeking guidance from appropriately qualified experts when interpreting phylogenetic trees.
PulseNet	PulseNet is a laboratory network administered by the CDC that compares the DNA fingerprints of bacteria from patients to find clusters of disease that likely represent outbreaks. The name is based on the fact that this network was initially used to exchange pulsed field gel electrophoresis (PFGE) patterns. PulseNet USA is made up of > 80 federal, regional, state, and local laboratories with at least one PulseNet laboratory in every state. PulseNet International is in >80 countries and performs a similar role globally.
Sanger sequencing	A "first generation" low throughput sequencing method that is still used to sequence specific genes (for example, to sequence the 16S rRNA gene of a pure isolate).
Short read sequencing	Next generation sequencing (NGS) can be performed using a number of different methods, including (i) Short Read Sequencing and (ii) Long Read Sequencing. The length of the DNA sequenced in widely used Short Read Sequencing systems (e.g., different Illumina systems) is typically 75 to 300 nucleotides. To sequence a full genome enough reads need to be generated to cover the whole genome with a target set of redundancy (such as 20 X).
Single Nucleotide Polymorphism (SNP)	The term SNP (pronounced "snip") is used to refer to the genetic differences between two isolates based on WGS data (in expressions such as *"the food isolate obtained in 2023 differed by 3 SNPs from an environmental isolate collected in 2019"*). A 1 SNP difference means that isolates differ by 1 nucleotide in their genome (out of all nucleotides, such as 1 nucleotide out of the typical 3 million nucleotides that make up a *Listeria* genome). Depending on the data analysis approach, differences can also be expressed as the number of cgMLST or wgMLST allele differences (see those entries for details).
Third generation sequencing methods	Third generation sequencing techniques are able to sequence long (up to 30,000 bases) and ultra-long (up to several million bases) fragments of DNA, which makes it much easier and quicker to assemble full genomes. Examples include PacBio's Single-Molecule Sequencing in Real Time (SMRT) and Oxford Nanopore Technology (ONT), see separate entries for both.
Whole genome Multilocus Sequence Typing (wgMLST)	In wgMLST, all genes found in bacterial genomes are used for WGS data analysis. Hence it is possible that two isolates that show 0 allele differences with cgMLST do show allele differences when the analysis is performed with wgMLST; use of wgMLST may be valuable when analyzing closely related (i.e., very similar) isolates.
Whole Genome Sequencing (WGS)	Whole Genome Sequencing (WGS) refers to determining the sequence of the entirety of the DNA that makes up an organism (i.e., an organism's genome including extrachromosomal genetic materials such as plasmids). However, most methods do not truly determine the complete whole genome sequence, but only determine the sequence of the vast majority of the genome (typically >99%). To illustrate, while a whole bacterial genome typically is a single contiguous molecule, WGS typically provides a genome sequence in pieces (which are referred to as "contigs" (in expressions such as *"the sequence of isolate X represents 22 contigs"*). While sticklers for details sometime (correctly) proclaim that WGS does typically not really sequence the "whole genome," this is essentially irrelevant for outbreak investigations and source tracking; true complete genome sequences (referred to as "closed genomes") may however be useful for some basic research applications.

FAA Safe Harbor Side Bar:

The Aviation Safety Reporting System (ASRS) is an excellent example of collaborative and ongoing effort by government, individuals, and the aviation industry, namely the Federal Aviation Administration (FAA) and National Aeronautics and Space Administration (NASA), to share information to help maintain and improve aviation safety.

The ASRS collects voluntarily submitted aviation safety incident/situation reports from pilots, controllers, and others and acts on the information in these reports by identifying system deficiencies and issuing alerting messages to persons in a position to correct them. Its database is a public repository which serves the FAA and NASA's needs and those of other organizations world-wide which are engaged in research and the promotion of safe flight.

ASRS data are used to:

- Identify deficiencies and discrepancies in the National Aviation System (NAS) so that these can be remedied by appropriate authorities.
- Support policy formulation and planning for, and improvements to, the NAS.
- Strengthen the foundation of aviation human factors safety research. This is particularly important since it is generally conceded that over two-thirds of all aviation accidents and incidents have their roots in human performance errors.

Those who voluntarily share relevant safety data enjoy safe harbor protection. That is, the FAA will not use any reports submitted to NASA under the ASRS (or information derived therefrom) in any enforcement action, except information concerning criminal offenses or accidents that are covered in FAA policies regarding the ASRS covered by Advisory Circular 00-46F and Title 14 of the Code of Federal Regulations (14 CFR) part 91, §91.25. This safe harbor is not without some caveats; the waiver of penalties is subject to the following limitations: (i) the alleged violation must be inadvertent and not deliberate, (ii) it must not reveal an event subject to Section 609 of the Federal Aviation Act, (iii) the reporter must not have been found guilty of a violation of the FARs or the Federal Aviation Act during the preceding five years, and (iv) the ASRS report must be submitted within 10 days of the event *(14)*.

A similar model could be established for food safety reporting; one with reasonable (not unlimited) safe harbor protections, where data can be used to improve food safety globally, overseen and administered by neutral, experienced industry personnel.

Figure 1. FAA Safe Harbor Side Bar.

of proof that a certain food safety risk (e.g., outbreak, pathogen persistence, unhygienic conditions) can be linked to a given facility or product. Combined, these issues may lead to underutilization of WGS, despite the idea that in a perfect world, without legal and regulatory constraint, benefits of WGS would typically outweigh risks. Future efforts need to focus on (i) improved education on WGS to non-"hyper-technical" staff; (ii) identification of "win-win" WGS applications that build confidence and skills with WGS within acceptable risk tolerance (e.g., identification of lab cross contamination, source tracking), and (iii) generation of a transparent regulatory and legal environment as to how WGS data will be used in enforcement actions. These types of efforts will unlikely to be successful unless they include protections against legal liability such as a safe harbor (e.g., akin to what is currently in place for the US Aviation Safety Reporting System, which guarantees that information submitted will not be used against reporters in enforcement actions, subject to certain limits (see FAA Safe Harbor Side Bar *Figure 1*). Given the various current risks and future uncertainties involving WGS use and data sharing, firms who are considering adopting WGS should conduct a risk assessment with their key risk advisors (considering factors such as identifying how WGS results will be communicated, used, stored, and potentially shared) and weigh the impacts of these factors on the risk and benefits of WGS adoption for different purposes.

This paper contains several recommendations, many focusing on governmental agencies and necessitating a collaborative approach between governmental organizations, industry, academia, and others (e.g., Food and Agriculture Organization of the United Nations [FAO], World Health Organization [WHO]). These types of collaborations will be critical to identify ways to use WGS and share WGS data in a manner acceptable to the industry, within reasonable levels of enterprise risk, to achieve the mutually shared goal of improving public health and enhancing food safety. It is recognized that these recommendations cannot be implemented overnight, nor without public-private collaboration and consensus. Importantly, there already is common ground upon which to start these conversations—both sectors believing that global public health will benefit from WGS use and data sharing, provided the risks, to the private sector as well as individual countries, can be appropriately and reasonably mitigated.

KEY TERMS, DEFINITIONS AND ABBREVIATIONS RELATING TO WGS USE AND SHARING

A key challenge in WGS and barrier to understanding WGS starts with its unique terminology. While a number of reviews and white papers provide highly technical explanation of terms, definitions and abbreviations related to WGS (e.g., reference *15*), we aim here to provide a lay dictionary of key terms and concepts to provide a common language, separated into Key Terms, Definitions and Abbreviations related to (i) Whole Genome Sequencing (WGS) *(Table 1)* and (ii) legal and business aspects of WGS *(Table 2)*.

OVERVIEW OF WGS ADOPTION BY THE FOOD INDUSTRY, REGULATORY AUTHORITIES, PUBLIC HEALTH AGENCIES AND ACADEMIA IN THE UNITED STATES AND SELECT COUNTRIES

This section will summarize historic and current uses of WGS by public health agencies, regulatory authorities, academia, and industry in various world regions.

Historical food safety related use of WGS by regulatory and public health agencies

WGS was first used by the US Centers for Disease Control and Prevention (CDC) to investigate foodborne disease outbreaks in 2013, even though researchers have used WGS for food safety applications before 2013 (see references *8* and *41* for a history of WGS implementation for food safety related applications in the US). Since then, according to US Food and Drug Administration (US FDA), US Department of Agriculture Food Safety Inspection Service (USDA-FSIS), and CDC authors *(9)*, WGS has helped to more quickly detect and solve foodborne outbreaks and has shaped food safety regulatory policies and industry practices. Since 2019, WGS has become the de facto standard method for characterizing foodborne pathogen isolates obtained from humans in the US. WGS has also been adopted by US food regulatory agencies, namely the US FDA and the USDA-FSIS and is now routinely used by these agencies to characterize food isolates as well as isolates obtained from food associated environments (e.g., from processing plant environments, produce fields, agricultural water). Routine use of WGS by public health and regulatory agencies has similarly been initiated by other countries after 2013. For example, since 2017, Canada, China, and several European countries (e.g., United Kingdom, Ireland, France, Denmark) have adopted the use of WGS to support routine surveillance and outbreak investigations for foodborne pathogens such as *L. monocytogenes*, *Salmonella*, and STEC *(12, 28, 38)*. However, incorporation of WGS in food safety regulatory and surveillance activities in low and middle income countries (LMIC) is typically limited; this may be related to technical gaps in WGS data acquisition and interpretation of bioinformatics data *(6)*. Thus, additional resources on how to integrate WGS-based approaches into developing nations' existing surveillance systems, such as the WHO's recently developed "Whole genome sequencing (WGS) as a tool to strengthen foodborne disease surveillance and response" guidance modules *(50-52)*, are needed.

In addition to WGS use by regulatory and public health agencies, research laboratories perform WGS on bacterial isolates, including isolates obtained from field studies (e.g. *40*), not only providing important insights on the biology of foodborne pathogens, but also providing data that can be used for development and improvement of rapid detection methods. Finally, as early as 2008, WGS studies also extended findings from previous subtyping studies and provided evidence for long term survival ("persistence") of foodborne pathogens (e.g., *L. monocytogenes*) in processing plants *(35)*.

Current uses of WGS in food safety

Since its early use, WGS processes, as well as bioinformatics tools used to analyze WGS data, have been consistently improved and developed. While concerns about reproducibility of WGS and standardization of WGS data analysis (such as determining the number of SNP differences between isolates) are at times still being raised, there is broad expert consensus that WGS and WGS data analysis approaches are at a point where the reproducibility of the actual WGS results is not a concern, unless analyses are performed by inexperienced laboratories or individuals. Reproducibility in this case could be defined as obtaining the same or essentially same results with regard to isolate relatedness (e.g., SNP distances) when multiple WGS analyses are performed on the same isolates.

However, interpretation of similarity metrics between isolates (e.g., X SNPs, Y cgMLST alleles; see *Table 1* for explanation of terms) remains an area of concern and confusion. Food industry professionals representing key supply chain nodes (from grower/farmer to manufacturer/processor and foodservice/restaurants) still sometimes believe that a standard global cut-off between "same" and "not same" should be instituted, which is unrealistic because accumulation of differences between isolates is driven by complex evolutionary and population genetic processes, which will differ by outbreak, facility, environmental conditions, product and organism. In addition, the number of generations per year of a pathogen is a key driver for the accumulation of SNPs per time (e.g., year). For example, if pathogens are present in an environment that supports limited replication (e.g., dry environments), two isolates that emerged from a single cell may show very limited number of genetic differences even after >10 years. On the other hand, in environments that allow for rapid replication and support large populations, two isolates that emerged from a single cell may show a large number of genetic differences even after

TABLE 2. Key terms, definitions and abbreviations related to legal and business aspects of Whole Genome Sequencing (WGS) Use

Abbreviation/Name	Definition and Explanation
Enterprise Risk Management	Enterprise Risk Management (ERM) is a methodology that looks at risk management strategically from the perspective of an entire organization. It is a top-down strategy that aims to identify and assess all risks in the organization, and mitigate potential losses, dangers, hazards, and other harm that may interfere with an organization's operations and objectives and/or lead to financial losses.
Freedom of Information Act (FOIA)	FOIA is a US law that provides the public the right to request access to records from any federal agency. Federal agencies are required to disclose any information requested under FOIA unless it falls under one of nine exemptions which protect interests such as personal privacy, national security, and law enforcement *(47)*. While FOIA does not apply directly to private organizations (e.g., a food company), certain data collected by federal regulatory agencies from private companies (e.g., WGS test results from regulatory inspections) may be subject to FOIA. WGS data can also be obtained through a subpoena, which is a legal document used by attorneys and government agencies in court proceedings requiring the recipient (including a food company) to produce requested documents, testify as a witness or take some other action relating to a legal proceeding.
Safe Harbor	A provision granting protection from liability or penalty if certain conditions are met. A safe harbor provision may be included in statutes or regulations to give peace of mind to good-faith actors who might otherwise violate the law beyond their reasonable control. Examples of safe harbors include (i) Force Majeure [acts of God] contract clauses, (ii) doctor-patient and attorney-client privilege, (iii) the "Online Copyright Infringement Liability Limitation Act" *(27)* providing four distinct safe harbors for online service providers, and (iv) the US Federal Aviation Reporting System, which guarantees that information will not be used against those reporting aviation safety concerns.
Statute of Limitations	A statute of limitations is a law applied by a statute assigning a certain time after which rights cannot be enforced by legal action or offenses cannot be punished *(33)*.

only a few years. Consequently, genetic differences between isolates need to be interpreted holistically taking into account overall context, including epidemiological and ecological data (emphasizing the importance of isolate associated metadata). For example, information on the environment where isolates were obtained and likely propagated is important as generation time will be an important driver for the number of genetic differences that accumulate in isolates over time. For a more technical discussion of some of the challenges (and possible solutions) to defining SNP cut-offs, readers may want to refer to a paper that discusses the challenges of defining SNP cut-offs when assessing the transmission of tuberculosis *(42)* or to a paper by US FDA, which can help provide details on US FDA's thoughts on this subject *(37)*.

Importantly, different approaches to communicate and discuss similarity metrics are needed to facilitate improved adoption and interpretation of similarity metrics for practical decision making. While several publications (e.g., *10, 37*) provide statements and illustrations on how SNP differences between isolates should be interpreted, there is limited practical guidance on how different data are used in "real world" decision making. For example, a frequently cited US FDA publication *(37)* details, in highly technical language, three different scenarios used to determine whether WGS data support a match between two or more genomes, including (i) data that support a match (i.e., SNP distance <21; Bootstrap support >0.89; monophyletic tree topology), (ii) data that are "neutral" (i.e., SNP distance 21–100; Bootstrap support 0.80 - 0.89; paraphyletic tree topology), and (iii) data that do not support a match ((i.e., SNP distance >100; Bootstrap support <0.80; polyphyletic tree topology). Practically, these definitions are typically of limited value to industry, not only due to their highly technical nature, but also due to the fact that many scenarios that do not fall into one of these three scenarios (10 SNP differences, bootstrap support of 0.85, for example, which neither fits into category (i) or (ii)). An additional challenge is the fact that there is no clear guidance on how other data (e.g., epidemiological data) should be used to inform interpretation of WGS data and SNP differences. Simplified communication of SNP (or allelic) differences could communicate the expected number of SNPs that occur per year (typically somewhere between 0.5 – 2 per year; see reference 42 and citations therein). This number may need to be adjusted based an ecological data; for example, more SNP differences may be expected for isolates obtained from environments that allow for rapid multiplication (such as wet environments with an appropriate temperature for growth of a given organism), while less SNP differences may be expected for environment that limits growth (e.g., dry environments). Even with its shortcomings and challenges, this "rule of thumb" can be valuable. For example, it can be used to determine that a pathogen that has been present over ten years in a facility allowing for typical levels of bacterial growth is expected to accumulate around 5 to 20 SNP differences (0.5 – 2 SNPs per year * 10 years).

Food safety related WGS use by public health agencies

As of 2024, WGS is routinely used in a number of countries (e.g., US, Canada, different countries in Europe) to characterize all human clinical isolates of key foodborne pathogens (e.g., *Salmonella*, *L. monocytogenes*, enterohemorrhagic *E. coli*, *Campylobacter*). In the US, WGS is coordinated by CDC, but most of the actual isolate sequencing is performed by state health departments. While use of WGS is being expanded to include human isolates of other pathogens, there are still a number of foodborne pathogens that are not routinely characterized by WGS (e.g., *B. cereus, Clostridium perfringens*). The scope of routine WGS of foodborne pathogens isolated from human clinical cases can however differ substantially, including (i) which pathogens are routinely characterized by WGS, (ii) how quickly WGS is performed, and (iii) how easily human isolates are available for WGS. In some countries it may not be mandatory to report isolation of specific foodborne pathogens from humans or it may not be mandatory to submit isolates to national public health agencies. Similar differences exist between US states where not all diseases are equally considered reportable or notifiable; these issues can substantially reduce the proportion of human isolates that are available for WGS. In addition, practices for sharing WGS data between regional jurisdictions may differ vastly between countries, including due to differences in privacy laws and how they may be interpreted (e.g., *24*).

Due to the number of factors affecting WGS use and implementation, coupled with frequent changes of practices relating to WGS use for characterization of human isolates around the world, it is extremely difficult to detail WGS use practices without this information quickly becoming outdated. However, the NCBI Pathogen Detection database (https://www.ncbi.nlm.nih.gov/pathogens/, see *Table 1* for details) can be used to extract the number of clinical isolates that have been added to this database from the different countries over the last 10 years (as a proxy for WGS coverage of human isolates), as shown in *Figure 2*. While this shows that the US and UK consistently add the largest number of foodborne pathogen isolates across 4 selected key pathogens, countries do seem to differ in their pathogen focus, as, for example, illustrated by the fact that Germany was the #3 reporter for *L. monocytogenes*, but was not in the top 10 for *Campylobacter*. Also, New Zealand is within the top 10 contributors for *L. monocytogenes* and *Campylobacter*, but not for *Salmonella* as well *E. coli* and *Shigella*, consistent with the fact that *Campylobacter* is a high priority reportable foodborne illness in New Zealand, which has been characterized as having a "long-running campylobacteriosis epidemic" *(7)*. It is important to emphasize however that *Figure 2* should be interpreted carefully, as, for example (i) human clinical isolates may be uploaded by sources other than public health laboratories (such as university labs, government research labs) (ii) disease frequency may differ between countries, and (iii) isolates labeled as clinical may include non-human isolates and human isolates may also not always be labelled as "clinical." Even with these caveats, *Figure 2* still provides valuable overall insights into human clinical WGS surveillance for foodborne pathogens across countries (which can easily be expanded to additional countries, different time frames and different organisms in future analyses).

Food safety related WGS use by food safety regulatory agencies

Like the situation in public health, WGS has also been adopted by food regulatory agencies in many countries (e.g., the US FDA and USDA-FSIS in the US) and is routinely used to characterize food isolates as well as isolates obtained from food-associated environments (e.g., from processing plant environments, produce fields, agricultural water). Implementation of WGS by regulatory agencies however may, in many countries, have lagged or still lags behind WGS use by public health agencies. Importantly, the specific agencies and jurisdictions that perform WGS-based characterization of food and food-associated isolates may differ. For example, in the US both national (federal) regulatory agencies (e.g., FDA, USDA), as well as state regulators (e.g., laboratories affiliated with Departments of Agriculture or similar), may perform WGS. It is important for industry and others to understand (i) who performs WGS of food and food-associated isolates, (ii) how quickly WGS is performed after isolation, and (iii) whether and how data is shared and exchanged with others, in particular public health agencies. Importantly, all of these factors, which impact use as well as risks and benefits of WGS, can change frequently.

Similar to human isolate contributions by country *(Fig. 2)*, it is also extremely difficult to detail WGS use practices for characterization of food and environmental isolates around the world. However, the NCBI Pathogen Detection database can be used to extract the number of isolates labelled as "environmental/other" that have been added to this database

L. monocytogenes	*Salmonella*	*E. coli* and *Shigella*	*Campylobacter*
USA (8,614)	USA (246,194)	USA (78,476)	USA (21,997)
UK (1,720)	UK (67,664)	UK (35,005)	UK (7,786)
Germany (1,377)	Australia (13,118)	China (7,582)	Denmark (1,674)
Netherlands (789)	Canada (11,667)	Australia (5,984)	Italy (1,100)
China (768)	South Africa (7,874)	France (5,778)	New Zealand (920)
Italy (525)	China (4,351)	Japan (5,436)	Australia (785)
Taiwan (488)	Ireland (1,462)	Canada (4,602)	Taiwan (560)
New Zealand (433)	Taiwan (1,183)	Netherlands (3,788)	Switzerland (449)
Denmark (413)	Denmark (962)	Germany (2,219)	Canada (431)
Portugal (407)	Germany (863)	Switzerland (1,882)	China (392)

Figure 2. Top 10 countries for number of clinical isolates added to pathogen detection over a 10-year time frame ("Create Date" between 11/26/2013-11/25/2023). Countries are color coded so that the same country listed in different columns is shown in the same color. Cells without color coding (i.e., shown in white) indicate countries that are only included among the top 10 for one pathogen.

from the different countries over the last 10 years (as a proxy for WGS coverage of food and environmental isolates), as shown in *Figure 3*. While this shows that the US and UK consistently add the largest number of foodborne pathogen isolates across 4 selected key pathogens, a comparison with the countries that add most human isolates (see *Fig. 2*) indicates that some countries that are not included in the top 10 contributors of human isolates (for any of the four pathogens analyzed) show up multiple times among the top 10 contributors of "environmental/other" isolates, including Chile, Mexico, Brazil, China, suggesting active WGS surveillance and data sharing activities in countries representing major food exporters. As a caveat, some countries may perform active WGS-based surveillance, but may not add data to the NCBI Pathogen Detection database. In addition, food and environmental isolates can be added to the NCBI Pathogen Detection database by a variety of groups and not just regulatory agencies. For example, isolates added for a given country may represent specific research projects or data collection efforts by international GenomeTrakr labs (supported by US FDA) and not regulatory data from the given country. However, regardless of the source of isolates, food and environmental isolates in the Pathogen Detection database may trigger and support regulatory actions (see below under "Food safety related WGS use in Academia and Research" for an example).

Food safety related WGS use in academia and research

In many countries, academia and research labs may be the groups that are responsible for the majority of WGS sequence data generated. Data may be generated by these labs for many reasons, including research projects on the biology, ecology, and evolution of foodborne pathogens as well as more applied studies on pathogen transmission. For example, one recent study *(29)* on basic aspects of the biology of *Listeria* has contributed almost 600 whole genome sequences for different *Listeria* species to the NCBI Pathogen Detection database. Data contributed to public databases by academic and research labs may still be used by regulatory and public health agencies to identify likely sources of outbreaks and contamination events. As a hypothetical, yet realistic example, if a human salmonellosis outbreak were to include 30 human cases which were all caused by a *Salmonella* strain that matched 5 isolates from fruit from country X (obtained and added by a research laboratory in country X) and epidemiological data (sometimes referred to as "epi") supported exposure to this type of fruit, then these data may be utilized to strengthening the link to fruit imported from this country, which may trigger a recall or import alert. The implication of this type of use of WGS data (for purposes that were not foreseen during sample collection) can be substantial and should be considered by regulatory agencies, public health agencies, researchers, and industry. For example, the authors believe that it may not be far reaching

L. monocytogenes	*Salmonella*	*E. coli* and *Shigella*	*Campylobacter*
USA (19,142)	USA (100,988)	USA (42,791)	USA (47,798)
UK (3,638)	UK (5,667)	Canada (2,829)	UK (2,603)
Canada (1,794)	Mexico (3,853))	UK(1,779)	Canada (817)
Norway (1,042)	Canada (3,278)	China (1,565)	Australia (702)
Chile (586)	Brazil (2,488)	Germany (1,128)	Taiwan (177)
Italy (522)	Chile (2,413)	Ecuador (956)	Switzerland (155)
China (448)	China (1,897)	Czech Republic (500)	Brazil (138)
Austria (401)	India (1,133)	Netherlands (470)	Germany (128)
Germany (311)	France (651)	Cambodia (464)	Sweden (108)
Mexico (282)	Nigeria (641)	Pakistan (432)	South Korea (101)

Figure 3. Top 10 countries for number of "environmental/other" isolates added to pathogen detection over a 10-year time frame ("Create Date" between 11/26/2013-11/25/2023). Countries are color coded so that the same country listed in different columns is shown in the same color. Cells without color coding (i.e., shown in white) indicate countries that are only included among the top 10 for one pathogen.

to expect that some countries (or even specific states in a country, e.g., the US) may try to, typically informally, limit research into the ecology of foodborne pathogens if this research may include deposition of WGS data into public databases; this could substantially impact foodborne disease prevention efforts and potentially result in long term negative impacts on food safety.

Food safety related WGS use by industry

Industry use of WGS is difficult to assess as results are generally not published and are frequently treated as confidential. This said, based on the authors' experience with industry and third-party testing laboratories, in addition to interviews with key food industry players from throughout the supply chain, to date, WGS does not appear widely used within the broader food industry. This is especially true for small and midsize food businesses and for specific countries or regions of the world. If used, WGS is typically used in root cause analysis efforts and in exceptional situations (e.g., outbreaks, recalls). Routine use of WGS for pathogen subtyping is extremely rare but may occur (for example to confirm that pathogen positive tests results do not represent lab contamination events, to source track environmental or product isolates, or to determine whether environmental isolates match isolates that had previously been obtained by regulatory agencies). In addition, WGS may be used for pre-harvest surveillance, particular in the animal protein sector (e.g., to define circulating pathogen strains, which may provide information for development of autogenous vaccines).

The food industry's adoption apprehension as it relates to WGS use may be caused by a number of factors including, but not limited to (i) the cost of WGS; (ii) difficulty to obtain rapid turnaround time for WGS, particularly outside the US, Canada, and parts of Europe; (iii) perceived risk associated with high resolution identification of human pathogens in the environment, food contact surfaces or in product; (iv) a lack of WGS-related expertise (or access to the expertise) in most food companies; (v) a lack of exposure by technical experts (who typically spearhead WGS efforts) to the totality of enterprise risks as food safety leadership positions may not represent executive level position with access to the ERM strategy, constraining the ability to effectively understand the potential impact of WGS use or sharing on the entire risk portfolio; (vi) fear about data misinterpretation and the associated potential negative impact on business; and (vii) overall unclear regulatory and legal environment as to how WGS data may be used by regulatory agencies and in legal proceedings. Importantly, the relevance of these factors may differ by company size (as well as location) with small and medium size companies potentially having very limited, if any knowledge of WGS; these companies may heavily rely on 3rd party labs for any recommendation on use of technologies such as WGS.

KEY BENEFITS OF WGS USE IN FOOD SAFETY

WGS use and the sharing of WGS data provide numerous benefits to public health, regulatory agencies, and industry. Key applications and benefits of WGS are summarized in *Table 3*. In addition to possible public health and food safety benefits, increased WGS use and sharing may also foster other desired outcomes such as enhanced food security and strengthening of public/private trust. Increased speed and accuracy in identifying food safety issues with WGS may result in reduced food waste (e.g., due to incorrect identification of food products as contaminated, resulting in recall/destruction) *(15)*, particularly in locations with sophisticated lab and food testing infrastructure. Further, use of WGS may allow industry to demonstrate to its shareholders, employees, consumers, customers and regulators an increased commitment to food safety, resulting in enhanced industry technical and communication competencies around WGS use, implementation, and interpretation. It is recognized that realizing these outcomes will rely on substantial systematic changes, in particular, increased WGS adoption and the implementation of global, risk-based food safety systems.

ENTERPRISE RISKS OF WGS USE AND DATA SHARING AND POSSIBLE RISK MITIGATION CONSIDERATIONS

In general, enterprise risks associated with WGS use and sharing could be partitioned into (i) risks associated with misinterpretation of WGS data and (ii) risks that occur even when WGS is used correctly, and data are interpreted correctly. Risks associated with misinterpretation of WGS could include situations where a facility is incorrectly linked to an outbreak (e.g., a situation where there is a deemed WGS "match" between human isolates and an environmental sample in a facility without strong epidemiological evidence showing a cause-and effect relationship). This possibility is supported by research studies that found closely related *Listeria* in different packing houses *(44)* and different retail deli establishments *(40)*, which supports that isolates matching a human outbreak could be found in different locations, including some that may not be responsible for the outbreak. Risks associated with data interpretation can range from regulatory and/or business risks (e.g., unjustified recalls) to legal and reputational risks (e.g., due to lawsuits targeting the incorrectly implicated firm and their officers). On the other hand, risks associated with correct use of WGS may be more difficult to picture but may include situations where the magnitude of legal liability (or settlements) may be increased if a firm utilized WGS. In a hypothetical example, a company that is correctly identified as the source of a small outbreaks (e.g., 8 salmonellosis cases) may be less likely to incur severe legal consequences if no WGS data have been generated by the company, as compared to if the company had pre-outbreak WGS data that indicates the presence of persistent *Salmonella* contamination in their facility and failed to respond to eradicate the risk. Based on these scenarios, firm-level decisions on use of WGS (as well as on sharing WGS data) typically involve the assessment of many possible risks and benefits (with benefits detailed in the section above). Below, we will detail firm-level risks associated with "correct" use of WGS as well as with WGS "misinterpretation" to facilitate (i) improved firm-level decision making on WGS, and (ii) development of policies and regulations that will reduce firm-level risks associated with WGS use. Risks and risk management strategies covered will include (i) regulatory and (ii) legal risks, and other enterprise risks, specifically (iii) business risks (non-legal/regulatory) (e.g., loss of suppliers, loss of business trust), and (iv) reputational risks.

Regulatory risks

While different terms may be used, many international food safety regulations share similar definitions for food that is prohibited from the market for being deemed adulterated, contaminated, or unsafe. Some examples include:

- The US Federal Food Drug & Cosmetic Act includes many reasons a food may be "adulterated", including if the food (i) bears or contains any poisonous or deleterious substance which may render it injurious to health; (ii) consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food; or (iii) has been prepared, packed, or held under insanitary conditions whereby it may be rendered injurious to health) (21 CFR 342 (a)(1-7) *(26)*.
- The US Department of Agriculture materially mirrors the US FDA's definition for adulteration of meat products, found in 9 CFR 301.2 (e.g., if it contains poisonous substances, pesticides, or chemicals; or if it has been prepared under insanitary conditions).
- The EU General Food Law states that food shall not be placed in the market if it is "unsafe," unsafe defined as injurious to health or unfit for human consumption *(3)*.
- The FAO/WHO/Codex Alimentarius uses the term "contaminant," resulting in a substantively similar definition to the US and EU definitions (in summary, any substance not intentionally added to food or feed which is present as a result of the production, manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food or feed, or as a result of environmental contamination) *(16)*.

The above regulations all establish a risk of regulatory violation by firms if WGS identifies recurring environmental pathogen positives, particularly if the data indicates no or ineffective remediation. Environmental contamination deemed persistent by a regulator is sufficient to trigger the "unfit food" or prepared/held under "insanitary conditions"

TABLE 3. Key applications, benefits, and challenges of WGS

Key Application of WGS	Description	Benefit and Beneficiaries	Challenges
Foodborne disease outbreak detection	Public health use of WGS to detect foodborne disease outbreaks probably represents the most widespread use of WGS.	WGS typically allows for faster detection of outbreaks (i.e., after a few cases have occurred). WGS also allows for detection of smaller and temporally spaced outbreaks, which can identify new vehicles for foodborne pathogen transmission (such as a fruit commodity, as sources of, typically small, listeriosis outbreaks). Key beneficiaries: consumers; the public; the food industry, which can use this information to prevent outbreaks and reduce outbreak sizes.	While WGS can facilitate more effective detection of clusters of human cases (meaning multiple cases likely linked to the same source), identification of an outbreak source requires epidemiological data. Overreliance on WGS with limited epidemiological data can lead to implication of incorrect outbreak sources; this can be a particular risk if a given country/ jurisdiction prioritizes investment into WGS over building and maintaining capacity to conduct high quality epidemiological investigations.
Source tracking speed and accuracy	WGS characterization of isolates from different nodes of a supply chain (such as ingredients from different suppliers, processing plant environments, finished products) can help more quickly identify the source of a contamination event.	Determination that isolates from a finished product match environmental isolates or ingredient isolates can help more definitely determine contamination sources, which can allow for more rapid and reliable control of pathogen sources. Key beneficiaries: food industry.	WGS alone cannot identify sources of contamination and needs to be combined with investigational information. For example, identification, in an environmental sample, of a *L. monocytogenes* that matches a food product is not proof that the given environment is the source, as another source (e.g., ingredients, employees) could have contaminated both the environment and finished product.
Environmental monitoring and detection of persistence	WGS characterization of isolates obtained as part of environmental monitoring can help identify (i) pathogen persistence (presence of closely related pathogens over time) and (ii) provide insights into pathogen dispersal and transmission.	Better data on pathogen persistence and transmission in facilities can be used by firms to focus investments and preventive strategies (e.g., by prioritizing replacement of equipment that is found to allow for pathogen persistence). Key beneficiaries: food industry.	WGS alone cannot differentiate persistence from repeat introduction; foundational programs that include good sampling plans, root cause analysis procedures and investigational information are essential.

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TABLE 3. Key applications, benefits, and challenges of WGS *(cont.)*

Key Application of WGS	Description	Benefit and Beneficiaries	Challenges
Detection of cross-contamination in testing labs	WGS characterization of all isolates from all samples that test positive for pathogens (particularly finished product samples) can identify instances when a pathogen positive test is a false positive due to cross-contamination in the lab.	False positive test results due to cross-contamination in the lab can have major negative business impacts that can be identified and prevented; cross-contamination can occur from strains other than lab control strains (which are often genetically marked and thus can be easily identified). Key beneficiaries: food industry.	Detection of cross-contamination from different sources and through different strains requires a comprehensive genomic sequence database of lab control strains and other strains that may be frequently handled in labs (e.g., surrogates, strain used in proficiency trials). Better information will be needed on how to interpret SNP differences between control strains and isolates representing putative cross contamination. WGS data for certain control strains may be considered confidential, which may complicate the required data sharing.
Isolate characterization	WGS can allow for faster characterization of isolates as compared to phenotypic methods (e.g., serotyping, antimicrobial resistance, detection of toxin genes).	Rapid isolate characterization can provide actionable data that can be used to drive quick actions (e.g., recalls). Isolate characterization data can also determine whether strains differ in virulence, allowing regulators and industry to not consider all strains as equally likely to cause disease, this could facilitate more risk-based approaches that focus on those strains likely to cause human disease. Key beneficiaries: food industry, public health.	Further research and data are needed to reliably predict many phenotypes of interest (e.g., enhanced resistance to processing treatments). While virulence prediction for certain organisms (e.g., *L. monocytogenes*, clostridia that can cause botulism) may be relatively reliable, it may not yet be possible for other organisms (e.g., diarrheal *B. cereus*).
Confirmation of pathogen detection results	WGS of isolates obtained from samples that tested pathogen positive can be used to quickly confirm test results and resolve ambiguous results.	Pathogen positive test results can sometime be caused by closely related organisms that are not pathogens (e.g., hemolytic *Listeria innocua, Clostridium* species that are different from *C. botulinum*); WGS can replace classical confirmation methods that often are time consuming. Key beneficiaries: food industry, regulators, testing labs.	For some pathogens (e.g., diarrheal *B. cereus*) there is insufficient data to use any DNA sequence or phenotypic data to differentiate pathogenic and non-pathogenic strains. There often is an unclear regulatory framework on how to address detection of organisms that are assigned to a species considered a pathogen but lack key virulence genes and hence are unable to cause the typical disease associated with a given pathogen.

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TABLE 3. Key applications, benefits, and challenges of WGS *(cont.)*

Key Application of WGS	Description	Benefit and Beneficiaries	Challenges
Root cause analysis	WGS can provide information that expedites root cause investigations to accurately identify the source and root cause of microbial contamination and to inform an effective corrective action preventive action (CAPA) plan.	WGS data (e.g., for environmental, ingredient, and food samples) can help to focus factory teams when conducting investigations (e.g., to rule in or out hypotheses that may otherwise take a lot of time and/or cost to rule in or out). WGS can also help identify likely contamination sources by comparing WGS data for incident related isolates to databases that may indicate that a specific strain is associated with a specific country, region, or animal reservoir. Key beneficiaries: food industry.	Access to improved databases that are easily accessible without confidentiality and privacy concerns. Limited metadata available for isolates can be an impediment to effectively using WGS data for root cause analyses. Reliance on WGS data without appropriate investigational information and data can lead to incorrect conclusions.
Source attribution	Source attribution is a process where one tries to attribute overall foodborne illness cases (e.g., all *Salmonella* cases in the US) to specific food sources (e.g., what % of all foodborne salmonellosis infections are caused by raw chicken, pork, produce, etc.).	Source attribution is often used to identify focus areas for new policies or enhanced enforcement. Traditionally, source attribution has heavily relied on outbreak data and therefore may not have correctly captured the most frequent sources of sporadic cases. Better source attribution data for specific pathogen strains (as defined by WGS) can also provide information on likely pathogen sources. Source attribution is distinct from root cause analyses and source tracking (which typically focus on specific contamination instances). Key beneficiaries: regulatory agencies food industry.	In many cases, the source identified (e.g., chickens) may contribute to human illness through very distinct transmission routes (e.g., consumption of undercooked poultry, exposure to live pet chickens, etc.), which may not be easily or at all differentiated by WGS-based source attribution. Source attribution data should thus be interpreted with caution and context.

definitions even without a pathogen positive product or a link to human illness cases (a specific challenge in these cases is that the term "persistent" is undefined and subject to the same ambiguity and potential subjectivity as the interpretation of SNP differences). For example, if a regulatory agency identifies pathogen isolates that are identified as closely related by WGS multiple times (over months or years) in a facility and/or in food produced by that facility, this facility may at some point be considered as operating under "insanitary conditions", which can consequently classify all food produced in this facility as adulterated, hence leading to a large recall. While subtype-based evidence for "insanitary conditions" is typically based on subtype data for both food and environmental isolates, there have been instances where subtype data for only environmental isolates appear to have been used by regulatory agencies to identify "insanitary conditions" (for example, see reference *17*). While, based on the authors experience, regulatory agencies may sometimes imply that WGS alone cannot be used to identify insanitary conditions and that other findings (e.g., observations during inspections) need to support insanitary conditions, we are not aware of any documentation or guidance documents that outline more detailed examples how different information may or may not be combined with WGS data to identify insanitary conditions. In addition, it is unclear whether and when WGS data generated by companies could be used as evidence to identify insanitary conditions, opening firms to increased liability without protection, such as that granted to the airline industry under the Federal Aviation Administration (FAA) Aviation Safety Reporting System (ASRS) safe harbor *(14)* (*Fig. 1*; FAA Safe Harbor Side Bar).

Thus, there appears to be enough subjectivity on the part of regulatory agencies and individual inspectors' perception of insanitary conditions (particularly as it relates to WGS data) to cause the industry to tread cautiously. This issue only represents part of a firm's total regulatory risk exposure when having produced food deemed "adulterated," "contaminated," or "unsafe/unfit" in violation of applicable food safety regulations—a risk more likely to occur with WGS-level discrimination. While multiple detections of a given pathogen (e.g., *Salmonella*) in a facility represent a regulatory risk per se, use of WGS-based subtype data is likely to increase the risk of recalls if two or more temporally separated pathogen detections are found to be caused by the same subtype.

Additional regulatory enterprise risks may include, but are not limited to, the following:

- Non-compliance reports
- Warning letters
- Re-inspection fees
- Product recalls
- Suspension/revocation of facility registration
- Product seizure
- Fines
- Increased inspections, likely unannounced
- A more scrutinizing, less trusting relationship with regulators

Any of these risks could start a domino effect of legal, business, and reputational risks, summarized in subsequent sections. Consider a scenario as simple as this:

- Company A produces nut butter where WGS correctly links three human isolates to two environmental positives of *Salmonella* taken 6 months apart. No product positive exists, but epidemiological data support the link (even though epidemiological data alone would not have been able to conclusively link this small cluster to the outbreak).
- This leads Company A to recall affected products.
- The recall is communicated to affected customers, which may lead to a number of consumers stopping to buy Company A's product.
- The recall is publicized, catching the attention of consumers who ate the product, who seek out a lawyer and file individual personal injury lawsuits.
- Plaintiffs' class action attorneys see the recall announcement and start hunting for affected consumers to file a class action lawsuit.
- Sales staff report losing prospective customer opportunities; the recall being the stated reason.

The plausibility of substantial business impacts with evidence that does not include a finished product positive is supported by (i) a 2020 *Salmonella* outbreak linked to onions, which resulted in a large recall with no product testing positive for the outbreak strain *(31)* as well as (ii) a 2021 greenhouse grown leafy greens recall/outbreak due to *Salmonella* Typhimurium resulting in a large recall with no products testing positive for the outbreak strain *(30)*.

The scenario detailed above supports how regulatory risks are unlikely to stand alone and may cause additional legal, business, and reputational consequences. However, the reality is complicated by how one interprets the risks and benefits of WGS use in similar circumstances. For example, one could convincingly reason that the hypothetical example above illustrates a case where the benefits of WGS outweighed the risk and costs - arguing that this small outbreak was detected earlier than would have been without WGS, limiting the impact for the consumers and the company, which could have been much larger if the outbreak would have not been detected until hundreds of cases were caused by the product.

Legal risks

Various legal definitions for terms that all result in violative/prohibited food (e.g., "adulterated," "contaminated," "unsafe," and/or "unfit" food), coupled with the legal doctrines of product liability, strict liability, and Responsible Corporate Officer (RCO) liability (see below for further details on these), are currently perceived by many firms as creating a high level of legal risk that outweighs the rewards of using WGS or sharing WGS data. Further and specific industry concerns include (i) a publicly accessible database where WGS data remains in perpetuity, (ii) unclear and disparate regulatory use of WGS, and (iii) plaintiff-friendly legal systems in several countries (especially in the US and the EU due to reforms in the pro-plaintiff direction [*20*]). Consequently, many food companies may be hesitant to proactively use or share WGS data, unless additional legal and regulatory protections are put in place.

Product liability is a legal doctrine that gives plaintiffs a cause of action if a defective consumer item caused them harm. This doctrine is generally associated with the standard of strict liability, meaning that defendants can be held liable regardless of their intent, knowledge or negligence *(25)*. Product liability and strict liability are not just US legal concepts. The EU has regulations, notably The Products Liability Directive (signed in 1985), that are materially similar to US product liability laws, including the concept of strict liability *(19)*. Additional countries have since aligned but with various nuances that impute longer risk exposure to firms (e.g., Australia's product liability law, providing a 20-year statute of limitation to bring a lawsuit after alleged harm has occurred). Comparatively, the EU's Product Liability Directive provides a 10-year statute of limitation, and individual states within the US range from one to twelve years *(34)*. This results in firms, especially those who distribute globally, being subject to legal risk for up to 20 years after distributing their products.

A legal doctrine known as the "Responsible Corporate Officer" (RCO) doctrine adds to this legal risk recipe. This doctrine was initially adopted by the US Supreme Court in 1943 in United States vs. Dotterweich *(48)* and upheld in 1975 in United States v. Park *(49)* (commonly known as "The Park Doctrine"). The Park doctrine declared corporate officers in industries that can adversely affect public health (e.g., pharmaceutical, food) legally responsible for a misdemeanor violation of the US Federal Food, Drug, and Cosmetic Act, if, due to one's corporate position, one could have prevented or corrected the actions of the firm that sent adulterated or mislabeled product into interstate commerce.

Legal risks may be higher yet in countries with a precautionary principle—a legal framework allowing enforcement action before confirmation of a source. The precautionary principle is integrated in the US and EU domestic laws and in many international conventions, justifying precautionary actions if an activity in question poses a threat to human health or the environment, even if the cause is not yet scientifically substantiated *(21)*. An example of risks associated with this could be if regulators see a WGS match between an environmental isolate and a small number of human clinical isolates, regulators may cite the precautionary principle to force a recall in the absence of epidemiological data supporting a link. Ultimately, however, one may convincingly argue that, on average, WGS use reduces uncertainty in outbreak investigations and therefore will possibly reduce the number of unjustified recalls.

While many individuals in the food industry may see all of the above as an argument not to use WGS (to reduce the risk of being identified, correctly or incorrectly, as the source of an outbreak), one could also use the above points as an argument for industry use of WGS, particularly in jurisdictions where WGS is less likely or unlikely to incorrectly incriminate a company (e.g., due to lack of trained professionals). More specifically, industry use of WGS may potentially be an advantage in locations with a precautionary principle legal framework. For example, if a corporate president required and funded WGS to be used in root cause investigations, one could argue they were leveraging the most current and advanced available science to do everything the company could to understand the extent of potential contamination in its facility and to most effectively eliminate contamination and prevent recurrence, thereby doing everything in its power to "prevent or correct" (the duty set forth in the Park Doctrine). WGS use may thus help demonstrate that the company is not the source of health threat before regulators may leverage the precautionary principle to take action that may be more fully scientifically supported. In short, the beneficial defense of using WGS may ultimately outweigh the legal risks, and decisions to use WGS will be highly dependent on individual firms' corporate risk tolerance. Corporate decision making on this will also be influenced by early adopters of WGS and the benefits and negative consequences they may experience.

Legal risks associated with incorrect use/misinterpretation of WGS

It can be very difficult for companies to "prove" regulatory test results or subsequent enforcement actions taken based on agency test results were "incorrect." Said differently, it is hard to "undo" the damage of an incorrect regulatory determination. One example, pre-dating WGS, is from 2008 when FDA issued a public *Salmonella*-related non-consumption warning for raw tomatoes even though FDA ultimately conceded the source of the outbreak were certain hot peppers. This incorrect non-consumption warning cost the tomato industry millions of dollars, prices falling by 50% industry-wide. One uncontaminated farm alone alleged $15 million in lost sales in an unsuccessful lawsuit against FDA, where the court sided with FDA citing, in essence, federal immunity from the alleged claims *(4, 23)*.

In short, if a regulatory agency incorrectly attributes an outbreak to a company, then it is very conceivable that consumers of the product who believe they became ill from that product will sue the food company and possibly also its officers under the RCO/Park Doctrine, particularly if regulatory agencies such as FDA do not or are unable to withdraw incorrect assignment of an outbreak to a given firm. Additionally, customers who purchased the implicated product may sue the falsely accused company for credit and any resulting damages they may have suffered, etc. and the wrongfully accused food company may spend significant resources defending these actions, which could be due to an error by a regulatory agency, sparking additional legal, business and reputational risk. While it is possible that incorrect attribution to the company may eventually become public knowledge, the damage from public warnings, customer costs, relationship damage and adverse reputational impact is already done (just like the tomato industry experienced). However, the risks detailed here should not be over-emphasized as WGS in general should facilitate correct identification of outbreak sources (at least as long as WGS implementation does not lead to an erosion of epidemiology capacity).

In conclusion, firms are unlikely to adopt WGS unless there are clear procedures provided by regulatory agencies that transparently set forth the ground rules for use, interpretation and enforcement authority. This needs to include clear procedures that firms can use to contest WGS and epidemiological findings, including procedures that will allow firms access to all relevant data (such as WGS data and data analysis outputs [e.g., phylogenetic trees], metadata, including epidemiological data), which is currently often not provided by regulators. Firms need the ability to meaningfully analyze, evaluate and interpret the data in order to understand and defend their position. As mentioned, there is a dearth of bioinformatic/data analytics professionals in the food industry with this capability, placing most firms at a significant disadvantage in representing themselves (the section entitled "Future Vision and Recommendations" for additional discussion and associated recommendations on this topic).

Legal risks associated with correct use/interpretation of WGS data

Risks associated with correct use of WGS may include situations where the magnitude of legal liability (or settlements) may be increased if a firm utilized WGS. For example, a hypothetical company that is correctly identified as the source of a small outbreak may be less likely to incur significant legal or regulatory consequences if no WGS data had been generated by the company, as compared to if the company had WGS data that (i) indicated persistent *Salmonella* contamination in their facility and (ii) linked this contamination to existing clinical isolates. This type of evidence may be viewed by regulators or plaintiffs' attorneys as supporting failure to implement effective preventive controls to prevent or correct the contamination, potentially triggering the RCO/Park doctrines. As another hypothetical example, an apple grower and packing house operation may have historically received 2-3 *L. monocytogenes* environmental positives every fall over the last 10 years. It took industry standard steps towards cleaning, sanitizing, and vectoring to verify effectiveness. Two years ago, they worked with their testing lab to start using WGS for isolate characterization (of note, this would be highly unusual to occur at the time this paper was written), which revealed the same *L. monocytogenes* subtype recurring in the same zones over the last two seasons (with unrelated subtypes found elsewhere in the facility). Potential benefits include that the facility can perform more informed root cause analyses and target corrective actions, such as purchasing new equipment, or making infrastructure improvements towards sites that have been identified as likely facilitating pathogen persistence. There are, however, several possible risks. For example, a regulatory agency may gain access to industry WGS data (e.g., during inspections) that shows repeat isolation of the same pathogen subtype in the same areas, indicating what could be considered ineffective sanitation. As a result, the regulatory agency may deem products produced since the first positive result as adulterated for being produced under insanitary conditions, triggering a recall and subsequent financial damages. This scenario illustrates a substantial risk to the operator who may have to recall its entire season, possibly pushing it into bankruptcy. This example also illustrates that it is important for industry to understand whether laboratories in a given country may be required to share WGS data with regulatory agencies (or may elect to do so voluntarily). In addition, it also is important to understand whether laboratories that may perform WGS on industry isolates are likely to publish results in a way that includes information that could identify a company.

There is no question that when correctly used and interpreted, WGS can be a powerful tool that can aid in faster detection of outbreaks, benefiting public health as well as the food industry. Early detection of outbreaks limits the number of consumers exposed, benefiting firms by limiting legal, regulatory, business, and reputational risks and associated financial losses. Despite this recognition, industry may often view legal risks as outweighing these benefits. For example, in an interview, one multinational food company voiced that if the legal risks could be "shelved" or "set aside," then "the entire industry would use WGS routinely." Perceptions that legal risks outweigh the benefits of using WGS may also be inextricably linked to risks that may be associated with sharing of WGS data, as further discussed below.

Additional legal and regulatory enterprise risks associated with sharing WGS data

Lack of global alignment

Food production and distribution are increasingly global. Yet, WGS data collection, use, and sharing practices and requirements vary globally. Many countries (e.g., some LMICs) either do not use WGS at all or use it for limited reasons other than for foodborne disease surveillance, with no central database to aggregate data. Some countries may have closed databases that only provide limited access to known subscribers and/or on a need to know basis. On the other hand, some countries (e.g., the US) deposit WGS data in an open access database that anyone can use without a subscription. Finally, countries may have a "mixture" of different approaches in sharing WGS data; for example, some data may be available in a public database, while other WGS data (e.g., those that may relate to an outbreak in legal proceedings) may be, at least temporarily, only be deposited in a closed database. With many countries having disparate laws and regulations governing data privacy and sharing, and intellectual property rights, these must be addressed and harmonized for purposes of industry's willingness to share WGS data given the global nature of food production and distribution.

Lack of regulatory transparency

As detailed above, interpretation of WGS requires integration of different data streams (e.g., epidemiological data, market share and distribution data, root cause analysis data) to define the scope of an outbreak and to determine outbreak sources or to determine whether WGS data support pathogen persistence. Transparency on how different data streams are acquired and used will be important to allow industry to better assess and potentially minimize regulatory and legal risks associated with sharing WGS data. This issue could be addressed by publishing guidance on how WGS data are used and shared for regulatory enforcement purposes within and across countries. This type of guidance could be published by individual regulatory agencies (e.g., US FDA), but could also be facilitated by internationally recognized and adopted standards agencies and groups (e.g., International Organization for Standardization [ISO], International Commission on Microbiological Specifications for Foods [ICMSF], WHO, FAO, including Codex Alimentarius).

Loss of data ownership/control

Increasing use of WGS by regulators around the world, and the fact that some, including the US, use an open-access database to indefinitely store WGS data available to anyone, raises a number of concerns for industry. Key concerns include:

- *Data ownership:* Who owns the physical isolate, the sequence results and associated metadata appears unclear especially when a regulatory agency is the entity who collected samples and performed WGS *(15)*. This raises concerns about data privacy laws (e.g., where sequence results or associated metadata may reveal personally identifiable / protected information) and other unintended ways the data could be used (e.g., lawsuits). It is unlikely industry will broadly test and share until these types of ownership concerns are clarified.
- *Data control:* Anyone can access and further share the information in the NCBI Pathogen Detection database, including regulators with enforcement authority, customers, consumer advocacy groups, government and plaintiffs' lawyers, the media, etc. Many of these groups may not have the education or experience to interpret WGS data in the larger context of microbial evolution and other factors. This increases legal, regulatory, reputational, and business risk to a food company with isolates in this database.
- *Indefinite retention period:* As previously explained, there is no maximum time period that this data is retained, creating long-term risk exposure for companies to manage. While indefinite retention may be valuable for scientific research and public health, there should at least be some clarity on limitations for use of shared WGS data for legal liability or regulatory enforcement purposes.
- *International data sharing:* International sharing through different platforms, such as GenomeTrakr *(41)* is increasing (e.g., FDA is working with WHO and FAO to support WGS adoption in developing countries and sharing to GenomeTrakr); other databases are being stood up in other countries, such as the EU European Food Safety Agency [EFSA] One Health WGS System *(39)*. International data sharing may, however, have negative impacts on food trade potentially resulting in unwarranted trade barriers if pathogen subtypes identified in one country are found to cause illness cases in another country, and import alerts are placed or importation ceases due to incorrect source identification.

With the data-related risks detailed above, many firms are unlikely to generate and/or share WGS data unless there is a clear framework in place to reduce the risks associated with these concerns.

Business risks

While legal and regulatory risks may often represent primary industry concerns when deciding to use WGS or share the data, firms also realize that non-legal risks can pose substantial risks to their operations.

Examples of key business risks that industry may be concerned about include (this list is not exhaustive, and companies may have additional concerns):

- *Supply chain disruption:* Different WGS-related actions, such as (i) an overly broad recall scope caused by overly cautious or misinterpretation of WGS results, or (ii) holding of lots until WGS and/or interpretation of WGS data is completed may lead to unfulfilled or partially fulfilled customer orders (especially for short shelf-life products) as well as delivery delays. Consequences of this could include a loss of customers, resulting in financial loss, in addition to legal risks (e.g., a customer may potentially sue for breach of contract). Further, firms may not be able to source key ingredients from a supplier who is subject to WGS-related actions.
- *Cost:* While the cost of WGS has been diminishing over the years, WGS is often still expensive compared

with other subtyping tools *(1)*. WGS may be worth the additional investment given the benefits WGS data provide over other methods. However, some firms view the higher cost as an "opportunity cost," defined by The New Oxford American Dictionary as "the loss of potential gain from other alternatives when one alternative is chosen." In this case, the opportunity cost may be that the money used for WGS could be used in a different way that may generate an even larger food safety impact. Opportunity costs are often considered in companies' ERM strategy, which may ultimately impact testing budget allocations.

- *Timing:* Turnaround time for WGS may often exceed 1 week and may be substantially longer in some countries and regions *(1)*, which may negatively impact business continuity, particularly if unanticipated delays occur. In addition, potentially lengthy turnaround times may increase risk of product release before results are obtained, increasing the risk of recall (if the test results are unfavorable).
- *Customer use:* Key customers may monitor the NCBI Pathogen Detection database and make assumptions (correct or incorrect) that a cluster involves one of its suppliers or comanufacturing partners, resulting in cessation of purchasing, supplier disqualification, etc.
- *Competitor use:* Competitors may use WGS against one another to gain competitive advantage or redirect outbreak investigations (e.g., if competitor A sees a cluster in the NCBI Pathogen Detection database that appears to be associated with competitor B, and raises this in sales discussions with a key customer account of competitor B, implying evidence of environmental contamination at competitor B).

For these and other reasons, while recognizing several business-related benefits to using WGS, companies may have the perception that the business risks associated with WGS use (and data sharing) outweigh the benefits.

Reputational risks

As the famous quote goes, *"It takes many good deeds to build a good reputation and only one bad one to lose it"* (Benjamin Franklin, former US politician and inventor of the lightning rod) *(5)*. Despite a firm's best intention to use WGS to better understand and manage its food safety risk exposure, such use could result in adverse consequences (as detailed in the previous hypothetical example of a company that is correctly identified as the source of a small outbreak, but may be more likely to incur severe adverse reputation impact if the company had pre-outbreak WGS data that indicates the presence of persistent *Salmonella* contamination in their facility).

Reputational risks, at least to some degree, result from and are inseparably linked to, the legal, regulatory, and business risks discussed in this paper. Many firms may believe that, in the current state of WGS use and sharing, reputational risks can pose one of the biggest risks associated with WGS use, with potential threats to a brand or firm's survival.

If WGS is correctly applied, some would argue that adverse publicity is a just consequence, but as explained, the risk of incorrect use or misinterpretation may be higher than the corresponding risk for classical methods and incorrect use or misinterpretation could cause potentially devasting risk to a brand or company's reputation. Examples of key reputational risks that industry may be concerned about include (this list is not exhaustive and companies may have additional business risk they are concerned about):

- *Loss of trust by regulators:* If a firm is associated with an outbreak, it may lose the "benefit of the doubt"– at least near-term–in regulatory actions and inspections.
- *Loss of trust by customers:* Loss of customer trust risks can impact short term cashflow as well as long-term financial viability (e.g., losing key customer accounts could severely impact or even destroy a brand or worse a company). This risk is especially high if WGS data were incorrectly applied and mistakenly link a firm with an outbreak that it did not cause.
- *Loss of trust by consumers:* Admittedly dated, but still relevant, a Harris Interactive poll revealed that 55% of people said they would switch brands temporarily in the case of a safety and health recall on a product they usually purchase, and 15 % of respondents would never again purchase a recalled brand *(46)*. Additionally, 21% of those polled said that they would avoid using any brand made by the manufacturer of the recalled product *(45)*. This risk does not vanish if a recall represented a mistake due to incorrect interpretation of WGS data.
- *Loss of trust by shareholders:* If publicly traded, a product recall may cause the subject company's stock price to fall, hurting its performance in the market and harming its reputation, particularly in recalls involving serious food safety hazards, thus diminish the value of investors' holdings *(45)*.

Notwithstanding these reputational risks, there are also reputational benefits in using WGS and sharing the data. Companies who perform WGS testing and voluntarily share the results in WGS databases, may be seen as industry leaders with a strong food safety and corporate culture committed to public health and safety. This often affords these firms the "benefit of the doubt" and trust in the eyes of regulatory authorities as well as with their key customers. Further, as previously mentioned, having the WGS data may provide the ability to support that a given outbreak or contamination event is not or is unlikely to be associated with a given firm, thereby reducing the legal, regulatory, business and reputational risks due to incorrect outbreak assignment or pathogen detection (as supported by a recalls that were rescinded due to WGS-based detection of laboratory errors [*18*]). As such, it is important for firms to consider both the risks and the benefits of using WGS and WGS data sharing, rather than assuming that the risks outweigh the benefits.

FUTURE CONSIDERATIONS AND RECOMMENDATIONS

As detailed above, WGS has become a reliable and mature technology that can deliver substantial value for food safety and public health. While WGS is currently used very effectively in a select number of countries for public health applications and specifically improved detection of foodborne disease outbreaks, broad adoption is limited to a few, typically high income, countries. Where implemented, WGS-based surveillance typically targets a select few bacterial pathogens. However, additional pathogens and pathogen groups (e.g., viruses) are being added to these surveillance systems. Hurdles often cited as preventing more widespread adoption in a public health setting, as well as in the food regulatory space, include (i) WGS costs and complexity, (ii) time to results, and (iii) the need for specialized workforce (e.g., appropriately trained bioinformaticians). These challenges will likely be overcome, in the medium term, by technology advancements and improved training and education. However, a bigger challenge for more wide-spread and efficient public health use of WGS will likely be the lack of a public health infrastructure and foodborne disease surveillance infrastructure in many countries, which may be difficult to overcome as it requires substantial public investments including prioritization of foodborne disease surveillance. This may be challenging in some countries (including some LMICs) where other public health and infectious disease challenges (e.g., malaria, HIV, tuberculosis) may be or may be seen as bigger priorities. Furthermore, indiscriminate implementation of WGS-based characterization of foodborne pathogens may actually be detrimental and distract from the needed investments into foundational foodborne disease surveillance capabilities, such as trained epidemiologists and basic laboratory infrastructure. Importantly, even in countries with strong WGS-based food safety related public health and regulatory efforts, the availability of appropriate foundational surveillance capabilities (including epidemiologists) can be a concern, particularly as improved detection of outbreaks increases the strain on epidemiology capacities (as more outbreaks need to be investigated).

Importantly, application of WGS has raised some larger issues in food safety frameworks that are used around the world, including concerns whether historical food safety systems really provide an appropriate framework for use of WGS in foodborne disease surveillance and for continued food safety improvements in general. More specifically, while "risk-based" food safety systems have been promoted for years, most food safety regulations and enforcement actions still take a very "hazard-based" approach to food safety, which may have been appropriate when traditional food safety surveillance systems detected primarily large outbreaks that typically could have been prevented. WGS on the other hand can detect very small and temporally distributed outbreaks (e.g., 2 – 3 cases annually during harvest season of a seasonal produce or fruit), which may represent a minimal residual risk *(47)* that may be largely unavoidable, particularly for foods that do not undergo a "kill step" (e.g., fresh produce). A reformation of food safety systems into truly risk-based systems (including risk-based enforcement) may thus be needed as an insistence on zero risk food systems may lead to negative consequences and inappropriate resource allocations as well as large recalls (using precautionary principle approaches) that will not benefit overall food safety.

Expanded industry use of WGS, particularly as technologies improve and availability of an appropriate bioinformatics workforce increases, can have substantial benefits and potentially improve food safety management. While on-going and future development of easier and user-friendly tools to analyze and interpret WGS data, including for specific pathogens of interest (e.g., *Salmonella*) will play an important role in expanding industry applications of WGS, there also will be a need for industry to be able to easily access WGS subject matter experts with industry expertise to help interpret data analysis outputs. Additional developments that may facilitate enhanced industry use of WGS include the development of easy-to-use tools that allow for comparisons of industry genome sequences with data in the NCBI databases without requiring an upload of the genome data into NCBI. Moving to a future state of increased WGS use by industry will however also require changes in regulatory approaches and the use of public health information in food safety to allow industry to appropriately use these tools. Potential changes that may facilitate adoption of WGS include the development of safe harbors as well as changes in regulatory approaches that emphasize and include government-industry collaboration and a focus on risk-based prevention rather than a predominantly hazard-based approach that uses an overly risk averse precautionary principle-based approach and emphasizes "punishment" of firms that may be involved in foodborne disease outbreaks or food contamination events. A specific important change in application of WGS data in food safety incidents and outbreaks would be for regulatory agencies (e.g., the US FDA) to work with implicated industries to not just use data to determine whether a larger recall is needed (e.g., a recall covering a large number of production lots), but to also facilitate application of these data to define the smallest recall needed to protect public health to a reasonable degree (which could help avoid unnecessarily large recalls). For example, detailed analyses of epidemiological and WGS data (including WGS data that may have been generated by industry), along with industry data on sanitation practices, may allow for definition of specific time periods or product lines that should be covered by a recall. This approach could and should be supported by regulatory agencies providing firms with agency-recommended subject matter experts that will facilitate discussion between firms and regulatory agencies when WGS-based evidence is presented to a given firm (somewhat equivalent to a "court appointed lawyer").

In addition, there is an urgent need for more transparency in the use of WGS data by regulatory and public health agencies, particularly since it is well established that it is not possible to define a single "cut-off" such as number of SNPs or allelic differences, to define two isolates as the same or "closely related." As interpretation of WGS data hence depends on context, transparency as to how context is used by public health and regulatory agencies would be extremely valuable and important to foster greater industry adoption. Practical approaches that would facilitate this would be for regulatory and public health agencies to provide case studies that detail how WGS data were used and interpreted in different investigations.

Considerations and criteria to weigh when considering WGS adoption

Given the various current risks and future uncertainties involving WGS use, as well as data sharing concerns, it may be prudent for firms who are considering adopting WGS to conduct a risk assessment on WGS use, involving external and internal experts and stakeholders. Some tips and considerations for this risk assessment include:

- Know what to do with the WGS results before WGS use is initiated and ask "why" WGS is the best subtyping method to use, while considering whether other methods (for example MLST, serotyping, PFGE) may provide the needed information. Understanding that WGS is just one tool in a much larger toolkit is important.
- Understand the regulatory and legal implications and consider the associated risks in light of the public health and other benefits.
- Determine (i) who will be perform WGS (e.g., internal or external labs) and (ii) if there are any mandatory reporting requirements. For example, in some countries (e.g., China), laboratories may need to report positive pathogen findings to government agencies *(2, 36)*.
- Identify where and how results are stored, interpreted, and shared. It may be helpful to partner with (i) external experts to guide development of a risk management strategy around these elements and (ii) legal counsel to direct WGS under attorney-client privilege (this approach is already used by some firms of minimize the legal risk associated with of collecting WGS data).
- Develop a written standard operating procedure (SOP) that outlines when and when not to use WGS. This should include conducting training and verifying understanding before testing commences and periodically thereafter.
- Consider the risks of NOT using WGS. The benefits of industry use of WGS outlined in this paper can serve as a starting point for this.

SUMMARY OF SPECIFIC RECOMMENDATIONS AND CALL TO ACTION

In an effort to summarize a call to action, the key recommendations from this paper are outlined below. While most of these may be seen as predominantly targeting government agencies, a number of these recommendations may be best approached collaboratively, including by governmental organizations, industry, academia, and others (e.g., Non-governmental organizations , FAO, WHO).

- Build, maintain, or expand foundational public health infrastructure (in particular, epidemiology capacity) to facilitate appropriate use and interpretation of WGS data.
- Reform food safety systems globally to be truly risk-based and move away from continued use of hazard-based food safety approaches and the concept of "zero risk" food systems *(53)*; this is important as WGS may yield increased identification of hazards that represent minimal risks (see reference 8 for a discussion of hazard and risk-based food safety approaches).
- Develop a safe harbor for WGS data, which protects companies from legal proceedings that use WGS data a firm created or shared.
- Change regulatory approaches so that they emphasize government-industry collaboration rather than a "policing" or "punishing" approach. This should include enhanced data sharing with industry, by public health and regulatory agencies, during outbreak investigations, including sharing of WGS data and raw data as well as appropriate epidemiological and metadata; this already occurs, to some degree, in some countries and jurisdictions.
- Develop and empower "Foodborne pathogen WGS advisory groups" that include industry and non-industry subject matters experts (e.g., from academia), as well as representatives of regulatory and public health agencies that utilize WGS, to provide WGS use and data sharing guidance.
- Provide transparency in how public health and regulatory agencies use and interpret WGS data. This could, at least initially, be in the form of case studies that detail how WGS data were interpreted along with other data to reach different conclusions (e.g., if a company was or was not considered the likely source of an outbreak).
- Provide industry with appropriate independent resources (e.g., bioinformaticians, epidemiologists, lawyers) needed to effectively understand WGS results to protect its interests as well as public health and encourage firms to use these types of experts, including in calls with government officials.
- Assess the nature and use of the NCBI Pathogen Detection database and other open-access databases, for example, by putting restrictions on the use of these databases for civil and other legal actions.

Specific industry recommendations include:

- Develop in-house or contract expertise in WGS data analytics and run appropriate simulations to assure that this expertise can be accessed quickly and appropriately.
- Continue to work with trade associations and other groups (e.g., universities) to promote understanding of WGS and the potential benefits of its use by industry.
- Improve collection of (standardized) metadata for bacterial isolates obtained in facilities, from ingredients, or anywhere throughout the supply chain to facilitate proper interpretation of genetic differences between isolates. For example, data that can be used to assess the ability of the source environments to support rapid microbial growth may suggest that genetic differences between isolates are accumulated more rapidly.
- Drawing on appropriate expertise, decide whether use of WGS or other subtyping methods is appropriate for a given company and facility and define the scope of WGS use (e.g., all pathogen isolates, only for root cause analyses triggered by >X pathogen positive test results within a given time frame). Develop a timeline for re-assessing this decision.
- Decide whether to design and execute a WGS pilot study; such a pilot study could involve WGS-based characterization of isolates from a past incident to assess whether WGS data would have provided insights that could have improved incident management and root cause analysis.

It is recognized that these recommendations cannot be implemented overnight, nor without public-private collaboration and consensus. There however appears to be a common ground upon which to start these conversations, including what appears to be a broadly shared believe that global public health will benefit from WGS use and data sharing, particularly if different private sector risks associated with WGS use can be appropriately and reasonably mitigated. It is imperative that these discussions accelerate in earnest—starting with the "why" and identifying lower risk data (e.g., spoilage data) to start with to build trust, as supported by some promising existing initiatives; for example, The University of Maryland and the Institute for the Advancement of Food and Nutrition Sciences (IAFNS) have been collaborating with USDA-FSIS through a Cooperative Agreement *(43)*. These types of collaborations are critical to move the needle forward to identify ways to use WGS and share WGS data in a manner acceptable to the industry within a reasonable level of enterprise risk to achieve the mutually shared goal of improving public health and enhancing food safety.

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