Whole Genome Sequencing for Enteric Pathogen Surveillance and Outbreak Investigations

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Objectives

• To define what whole genome sequencing (WGS) is
• To describe the use of WGS in comparison to current laboratory methods used for bacterial enteric pathogen surveillance and outbreak support
• To describe WGS analytical methods, results and interpretation
• To describe the process of communicating WGS findings in Ontario
Outline

• Role of the laboratory and current typing methods
• Whole Genome Sequencing (WGS)
  • Process and data analysis
  • Interpretation
  • Implementation
• How are WGS findings being reported?
• Questions
**Context**

- Pulsed field gel electrophoresis (PFGE) is the current standard used for surveillance and outbreak investigation of enteric pathogens
- Laboratories are transitioning from PFGE to WGS through the PulseNet Canada laboratory program
- WGS is able to provide stronger laboratory evidence for surveillance and outbreak investigations
- This presentation will describe WGS so that front line staff understand this new laboratory typing method and its impact on public health units
Public Health Ontario Laboratory (PHOL)

Role:

• To provide laboratory evidence to support enteric foodborne illness surveillance and outbreak investigations

The laboratory strives to:

• Improve turn around time of laboratory results
• Provide higher resolution typing results
Laboratory Typing Methods - Considerations

• **Standardized** – are results comparable across laboratories and jurisdictions?

• **Reproducible** – if repeated, will the method give the same result every time?

• **Practical and useful** – can testing be done quickly enough to be relevant and is relatively affordable?

• **Supported by epidemiological evidence** - Is there sufficient evidence to support that epidemiologically related cases are linked by the typing scheme and unrelated cases are not linked?

• **“Discriminatory Power”** - is the typing method able to distinguish between unrelated strains and link related strains?

*Courtesy of Alex Marchand-Austin, PHOL*
Current Laboratory Typing Methods

- Phage Typing (PT)
- Pulsed-Field Gel Electrophoresis (PFGE)
- Multiple-Locus Variable number tandem repeat Analysis (MLVA)
- Multi-Locus Sequence Typing (MLST)

WGS is the most recent laboratory typing technique which has been added to support foodborne illness investigations
## Discriminatory Power - Book Analogy

<table>
<thead>
<tr>
<th>Typing Method</th>
<th>Book Analogy</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Phage typing (PT)</td>
<td>Compares the appearance of two books</td>
<td>Phenotypic test method which captures the susceptibility of an organism to a phage (virus)</td>
</tr>
<tr>
<td>Pulsed Field Gel Electrophoresis (PFGE)</td>
<td>Compares page numbers at each quarter of the book</td>
<td>DNA is cut into fragments of various sizes to create a molecular fingerprint based on fragment size</td>
</tr>
<tr>
<td>Whole Genome Sequencing (WGS)</td>
<td>Compares every single letter in the book</td>
<td>The complete DNA sequence or order of bases of an organism’s genome is determined</td>
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</tbody>
</table>

*Courtesy of Alex Marchand-Austin, PHOL*
What is Whole Genome Sequencing?

• The genome, or genetic material, of bacteria is made up of DNA.

• Each organism has a unique DNA sequence which is composed of four bases:
  • Adenine, Thymine, Cytosine and Guanine

• If you know the sequence of the bases in an organism, you have identified its unique DNA fingerprint, or pattern.

• Determining the order of bases is called sequencing.

Whole genome sequencing is a laboratory procedure that determines the order or sequence of bases in the genome of an organism.

https://www.cdc.gov/pulsenet/pathogens/wgs.html
The Whole Genome Sequencing (WGS) Process

WGS is a laboratory procedure that determines the order of bases in the genome of an organism in one process. WGS provides a very precise DNA fingerprint that can help link cases to one another allowing an outbreak to be detected and solved sooner.

1. DNA Extraction
   - Scientists take bacterial cells from an agar plate and treat them with chemicals that break them open, releasing the DNA. The DNA is then purified.

2. DNA Shearing
   - DNA is cut into short fragments of known length, either by using enzymes "molecular scissors" or mechanical disruption.

3. DNA Library Preparation
   - Scientists make many copies of each DNA fragment using a process called polymerase chain reaction (PCR). The pool of fragments generated in a PCR machine is called a "DNA library."

4. DNA Library Sequencing
   - The DNA library is loaded onto a sequencer. The combination of nucleotides (A, T, C, and G) making up each individual fragment of DNA is determined, and each result is called a "DNA read."

5. DNA Sequence Analysis
   - The sequencer produces millions of DNA reads and specialized computer programs are used to put them together in the correct order like pieces of a jigsaw puzzle. When completed, the genome sequence containing millions of nucleotides (in one or a few large pieces) is ready for further analysis.
Whole Genome Sequencing - Data Analysis

• When WGS is completed the genetic sequences need to be analyzed

• Two methods have been used in Canada
  • Single Nucleotide Variant (SNV) analysis – SNVPhyl* pipeline
  • Whole Genome Multi Locus Sequence Typing (wgMLST/allele) analysis – BioNumerics

• Both methods compare the genetic sequences of the bases from different perspectives

* Single Nucleotide Variant PHYLogenomics
Whole Genome Sequencing – Data Analysis

Definitions

• Base/nucleotide – DNA is composed of nucleotides which are composed of one of four bases - Adenine, Thymine, Cytosine and Guanine

• Whole Genome Sequencing - is a laboratory procedure that determines the order or sequence of bases in the genome/DNA of an organism

• Single Nucleotide Variant - is a variation of a single nucleotide that occurs at a specific position in the genome

• Gene/locus – is a sequence of DNA that encodes a function of the organism

• Allele - is a variant of a gene; one gene may have a single or multiple genetic differences but still be considered one allele
Whole Genome Sequencing - Data Analysis

Single Nucleotide Variant (SNV) analysis

• Individual bases are reviewed to identify single nucleotide differences or variants
• Changes not included in a SNV analysis
  • If more than one base in a row / two consecutive bases are different
  • Insertions or deletions – additional or missing fragment of DNA

Whole Genome Multi Locus Sequence Typing (wgMLST) analysis

• Multiple loci (genes) are reviewed to identify ANY differences between two isolates whether it is one SNV, or two or more consecutive bases, insertions or deletions
• In wgMLST, an allele is a variant of a gene – one gene may have multiple base changes and still be considered one allele
## Whole Genome Sequencing – SNV Analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>TCCTCATCAGCCGTAT</th>
<th>SNV</th>
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<tbody>
<tr>
<td>Isolate 1</td>
<td>TCCTCGTCAGCCGTAT</td>
<td>1 SNV</td>
</tr>
<tr>
<td>Isolate 2</td>
<td>TCCTCGTCCCGGTAT</td>
<td>1 SNV</td>
</tr>
<tr>
<td>Isolate 3</td>
<td>ATCTCGGCTCCGTGT</td>
<td>2 SNV</td>
</tr>
</tbody>
</table>

- **Isolate 1** - one base change from the reference sequence
- **Isolate 2** - same as isolate 1 plus a deletion. *The SNV analysis does not consider insertions or deletions*
- **Isolate 3** – same as isolate 2, plus one single nucleotide difference, plus two consecutive base changes. *The consecutive nucleotide differences are not considered in a SNV analysis*
Whole Genome Sequencing – wgMLST Analysis

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Gene/Locus Sequence</th>
<th>wgMLST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolate 1</td>
<td>TCCTCGTCAGCCGTAT</td>
<td>Allele 1</td>
</tr>
<tr>
<td>Isolate 2</td>
<td>TCCTCGTC----CCGTAT</td>
<td>Allele 2</td>
</tr>
<tr>
<td>Isolate 3</td>
<td>ACCTCTG----CCGTTG</td>
<td>Allele 3</td>
</tr>
<tr>
<td>Isolate 4</td>
<td>TCCTCGTCAGCCGTAT</td>
<td>Allele 1</td>
</tr>
</tbody>
</table>

- In wgMLST independent gene or locus sequences are compared to a pool of all known genes specific to a species or serotype
- Isolate 1 – considered allele 1
- Isolate 2 – considered allele 2 – different version of same locus
- Isolate 3 – considered allele 3 – different version of same locus
- Isolate 4 – considered allele 1 – same as isolate 1
## Whole Genome Sequencing – SNV vs. wgMLST

<table>
<thead>
<tr>
<th>Variant</th>
<th>SNV</th>
<th>wgMLST</th>
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</thead>
<tbody>
<tr>
<td>All isolates compared to a reference genome</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>All isolates compared to a database of all the known genes of the specific species or serotype</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Each individual variant is counted as the number of SNVs different</td>
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</tr>
<tr>
<td>Any change to a gene is considered to be a new variant or allele – a gene may have multiple genetic changes but still be considered one allele</td>
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</tbody>
</table>
Whole Genome Sequencing – SNV vs. wgMLST

wgMLST analysis

• is currently routinely used by the PulseNet Canada program through the National Microbiology Laboratory in Winnipeg for surveillance and outbreak support
• utilizes a commercial program (BioNumerics) to perform standardized data analysis between all provincial and federal laboratories
• analysis includes a larger set of genes and therefore provides greater discrimination between isolates

SNV analysis

• may be used if further laboratory evidence is required to support an investigation by providing additional genetic resolution
Whole Genome Sequencing – Interpretation Guidelines

• The following PHAC/PulseNet Canada guidelines are being used to interpret the relatedness of isolates

<table>
<thead>
<tr>
<th>Organism</th>
<th>SNV differences</th>
<th>wgMLST / allele differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Salmonella spp.</em></td>
<td>0 - 10</td>
<td>0 - 10</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>0 - 10</td>
<td>0 - 10</td>
</tr>
</tbody>
</table>

• It is also recommended to assess isolates within the 11 – 25 difference range
  • to compare how they relate to the 0 – 10 group
  • review for consistent epidemiological information

• Surveillance period for matches; *Salmonella spp.* = 60 days and *Listeria monocytogenes* = 120 days
Whole Genome Sequencing - Considerations

- Mutation rates vary between organisms
- Multiple strains of bacteria may be present in clinical cases or food products
- Sequences which appear to be related because they are less than 10 allele differences may or may not represent a common source outbreak/cluster

Laboratory and epidemiological data are essential to be reviewed together to determine potential clusters or outbreaks
Whole Genome Sequencing – Implementation

*Listeria monocytogenes*
- WGS has been performed on all isolates at the NML since January 2017
  - PFGE continues to be concurrently performed

*Salmonella spp.*
- WGS has been performed on all isolates at the NML since May 2017
  - PFGE continues to be performed as required
  - Phage typing for *Salmonella* spp. will be discontinued on January 1, 2018

*E. coli STEC*
- WGS is proposed to be initiated sometime in 2018
Whole Genome Sequencing – Phylogenetic Trees

- **SNV or wgMLST phylogenetic tree** will be very similar in presentation and include scale, branches, nodes

- **Scale** – provides a measure of the relatedness of the isolates included in the analysis

- **Branches** – horizontal lines show the degree of genetic change between isolates – the longer the branch the larger the amount of change

- **Nodes** – a number is associated with a node which provides the number of SNVs or alleles difference between the two branches
Whole Genome Sequencing – Phylogenetic Trees

- A and B are 40.7 alleles different from each other; not considered related
- C and D are 5.1 alleles different from each other; related; C, D and E are grouped together with a difference of 9.7 alleles; also related
- F and G are 0 alleles different; identical
- H and I are 1 allele different; related

Reporting notes:
wgMLST - Comparison generated using BioNumerics v 7.6.2 based on 4553 alleles

SNV - Reference: PNUSA473; Method: NML Bioinformatics SNVPPhyl Pipeline: Maximum-likelihood phylogenetic tree based on 52 high-quality core genome single nucleotide polymorphism (SNV) positions identified among 14 isolates over 99% of the reference genome
How are WGS findings provided to PHO?

• The National Microbiology Laboratory in Winnipeg performs WGS twice weekly.

• The WGS findings are provided to the provincial laboratories once or twice weekly.

• The Public Health Ontario Laboratory provides the WGS trees to the Enteric, Zoonotic and Vectorborne Diseases Unit.
wgMLST Phylogenetic Tree

1710SENWGS-8MP Analysis 2
## Ontario wgMLST Analysis 2017-05-01 to 2017-11-14

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</table>
Determination of Which Cases are Investigated Further

Federal

• Public Health Agency of Canada staff make determinations for multi-provincial (MP) investigations.

Provincial

• The Enteric, Zoonotic and Vectorborne Diseases Unit staff make decisions for related cases within Ontario.
Criteria to Determine When Cases Should be Investigated as a Cluster/Outbreak

*Salmonella*: Prioritization based on the following considerations

- **Serotype frequency**
  - Is it a rare serotype?
    - Current NML definition of rare is anything other than S. Enteritidis, S. Typhimurium, or S. Heidelberg

- **Number of cases in the cluster**
  - More cases receive greater priority
Criteria to Determine When Cases Should be Investigated as a Cluster/Outbreak

*Salmonella*: Prioritization based on the following considerations

- **Allele range and branching**
  - Less allele range receives greater priority
  - E.g., cases with 0 allele differences versus cases that all differ from each other by several allele differences

- **Demographic profiles**
  - Is there something interesting in the patient demographics?
  - E.g., age, sex, geographic location, or certain ethnicity
Criteria to Determine When Cases Should be Investigated as a Cluster/Outbreak

*Salmonella*: Prioritization based on the following considerations

- **Isolation dates**
  - The greater the number of new isolates added to the most recent analysis increases the priority

- **Presence of a non-clinical isolate in the cluster**
  - A matching food sample would increase the priority of the cluster
How Will WGS Findings be Provided to Public Health Units?

Previous laboratory typing reporting methods included:

- *Salmonella* Enteritidis **PT 13**
- *E. coli* PFGE - **ECXAI.1182 / ECBNI.0297**

**WGS**

- Nomenclature to describe results for each isolate (or case) has not been developed yet
- A numerical identification system is being considered
- Until a nomenclature is developed, isolates belonging to a cluster or outbreak investigation will be linked by an assigned cluster code
### Ontario wgMLST Analysis 2017-05-01 to 2017-11-14

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How Will WGS Findings be Provided to Public Health Units?

WGS trees currently pose a constraint for reporting findings

- Trees include Lab ID# but not iPHIS Case ID.
- Trees contain information that may be identifiable.

The development of nomenclature for individual cases should make communication easier.
How Will WGS Findings be Provided to Public Health Units?

Currently, WGS findings are being provided to PHUs only for cases involved in outbreaks.

- PHO will communicate to PHUs by email or phone.
- Cases with iPHIS Case ID, by PHU, will be provided on Ontario Outbreak Central

What is “Ontario Outbreak Central”? 

- A tool or platform for sharing outbreak related information
- e.g., Epi Summaries, Outbreak Investigation Coordinating Committee (OICC) minutes
How Will WGS Findings be Provided to Public Health Units?

Ontario Outbreak Central

• On the Canadian Network for Public Health Intelligence (CNPHI) website

• Instructions for accessing this tool are available through the *Weekly Enhanced Surveillance Directives and Monitored Situations* document
  • User Name and Password are required
WGS Impact on Enteric Disease Investigations

In general, it is expected that:

• For some pathogens, the number of clusters/outbreaks identified will increase.

• The average number of cases included in the cluster/outbreak will be smaller.

• WGS will be able to better predict which cases are included in a cluster/outbreak (and which cases are not included).

The source of more clusters will be identified.
WGS Impact on Enteric Disease Investigations

The following trends have been observed in the first seven months of implementation of WGS for *Salmonella* (but remain to be seen if they will continue)

- More multi-provincial (MP) clusters being identified
- More frequently, iPHIS case data are provided to PHAC for centralized analysis
- The previous hypothesis that many *Salmonella* cases were caused by chicken has been strengthened
Conclusion

Participants should have:

• An understanding of the WGS test procedure, interpretation, reporting and communication process of results

• An awareness that laboratory testing is transitioning to WGS over the next few months/years – ongoing process

• Knowledge that WGS will provide stronger laboratory evidence than previous typing methods to support enteric foodborne illness surveillance and outbreak investigations

The success of the enteric program requires a supportive network among all food safety partners to ensure the safety of public health
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- Ashley Kerr (PHAC) for presenting the section on WGS and frozen processed chicken products
- PHU staff for providing information regarding case histories as well as food samples, both of which complement WGS findings, for the purposes of enteric illness investigations
Questions

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