Genome Sequencing and Its Prospects for Improving Food Safety

Agricultural Outlook Forum
Smart Agriculture in the 21st Century

Modernizing Food Safety: February 20, 2015

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Challenges for FDA

• Recent breakthroughs in science and technology have the potential to transform our ability to prevent, diagnose and treat disease.

• However, major investments in basic and translational research are not efficiently yielding new products needed to benefit consumers
  • Product development is increasingly costly, success rates remain low, and time is $
  • Development/evaluation tools and approaches have neither kept pace with nor incorporated emerging technologies

• FDA’s Advancing Regulatory Science Strategic Plan is designed to allow both to meet today’s public health needs and to be fully prepared for the challenges and opportunities of tomorrow
Advancing Regulatory Science at FDA

- Regulatory science is a relatively new term but an old concept

- The application of science to the development and utilization of new tools, standards, and approaches for the assessment of product efficacy, safety, and quality

- 8 Science priority areas
Advancing Regulatory Science at FDA

• Two key elements in plan
  • Evaluate innovative emerging technologies
  • Enhance multidisciplinary collaboration
  • Improved external partnerships
• Implement a new prevention-focused food safety system
  • Invest in emerging technologies to mitigate risk
  • Improve information sharing internally and externally

Economic Burden of 15 Major Pathogens

Whole genome sequencing is changing the science of food safety.

WGS has the potential to serve as the single assay for microbial surveillance/outbreak detection and supplant multiple methods:

1. Classical serotyping
2. PFGE and other strain typing methods
3. *In vivo* antimicrobial susceptibility testing
4. Piecemeal PCR gene detection and plasmid typing

And to provide:

1. Genome/nucleotide surveillance
2. Virulence profiles
3. Molecular phage typing
4. Markers for source attribution
5. Better understanding of emerging trends
6. Costs savings
DNA Sequencing

- Bases of DNA (ATGC) are sequentially identified from a DNA template strand.

- Next Generation Sequencing (NGS) extends this process across millions of reactions in a massive parallel fashion.

- NGS involves rapid sequencing of large DNA stretches spanning entire genomes:
  - Technology shift
  - 3-5 million data points for each isolate.

- Increasing availability and affordability of NGS is rapidly changing the face of microbiology.
How FDA is Using WGS

- To differentiate sources of contamination, even within the same outbreak
- To determine which ingredient in a multi-ingredient food harbored the pathogen associated with an outbreak
- To narrow the search for the source of a contaminated ingredient, even when the source may be halfway around the world
- As a clue to the possible source of illness – even before a food has been associated with illness using traditional epidemiological methods
- To determine unexpected vectors for food contamination
- To develop rapid methods to identify/characterize resistant bacteria
WGS of *Listeria monocytogenes* strains isolated from Roos Foods cheese products was performed by the FDA and Virginia’s Division of Consolidated Laboratory Services.

These strains were found to be highly related by WGS to the *Listeria* strains isolated from patients in this outbreak, adding further confidence that cheese products produced by Roos Foods were a likely source of the outbreak.

WGS provided genetic information that allowed investigators to rapidly identify differences among isolates.
SECRETARY PICK!

HHS INNOVATES CELEBRATES 7TH ROUND OF INNOVATIONS!

By Steven Randazzo On July 21, 2014

Today, the six finalist teams for Round 7 of HHS Innovates were celebrated by HHS Leadership and their peers for their innovative projects and their impact on the Department of Health and Human Services and services to the American people. The People’s Choice Award and Secretary’s Picks were announced today.

Whole Genome Sequencing: Future of Food Safety

Sometimes the food we eat can be hazardous and finding contaminated foods before consumers become ill is a major challenge. The process for identifying disease-causing organisms that can be found in food and can be a slow and cumbersome process using conventional detection testing methods. Whole genome sequencing is a new technology has the potential to speed up detection and enable faster interventions to stop an outbreak of disease in its tracks. The Centers for Disease Control and Prevention partnered with agencies across state and federal government, including the Food and Drug Administration and the National Institutes of Health National Center for Biotechnology Information to engage in a demonstration project to showcase the benefits of using Whole Genome Sequencing for food surveillance and detection purposes.

CFSAN, CDC, NIH, USDA Partnership

Potential biggest transformation of public health microbiology in decades

New technology has the capacity to revolutionize foodborne disease tracking by replacing current methods
An increased degree of certainty that comes with high resolution data allowed for detection of this Salmonella contamination event in nut butter across several states with low level contamination in a widely distributed product. In this case, WGS identified the link and preempted an outbreak even w/o availability of food - it informs the epidemiology and our inspectors actions.

A Growing Regulatory Role:

Outbreak/Pre-outbreak summer of 2014
WGS-surveillance approach to public health

- Earlier case recognition/reporting
- Faster, more targeted outbreak response

Potential cases prevented

Adapted from WHO
FDA WGS Application to Actual Food Contamination Events

S. Montevideo black and red pepper
S. Senftenberg black and red pepper
S. Enteritidis shell/liquid eggs
S. Heidelberg ground turkey
S. Heidelberg chicken broilers
S. Heidelberg chicken livers
S. Enteritidis custard
S. Bareilly tuna scrape
S. Tennessee peanut butter/peanut butter paste
S. Typhimurium peanut butter
S. Braenderup peanut butter/nut butter
S. Tennessee cilantro
S. Agona dry cereal
S. Agona papaya
S. Newport tomatoes
S. Newport environmental
S. Kentucky - Cerro dairy/dairy farms
S. Anatum spices/pepper flakes
S. Javiana cantaloupes
S. Saintpaul hot peppers
4,5,12: i –

L. mono cantaloupes
L. mono queso cheese
L. mono potato salad
L. mono artisanal cheeses
L. mono avocados
L. mono ricotta
L. mono celery/chix salad
L. mono smoked fish
L. mono other herbs
L. mono peaches

Cronobacter infant formula

V. para oysters

EcO157:H7 lettuce

STEC beef

…Numerous other taxa
Whole Genome Sequencing Program (WGS)

Genome Trakr

- State and Federal laboratory network collecting and sharing genomic data from foodborne pathogens
- Distributed sequencing based network
- Partner with NIH
- Open-access genomic reference database
- Can be used to find the contamination sources of current and future outbreaks
Basic Data Flow for Global WGS Public Access Databases

DATA ACQUISITION
Sequence and upload genomic and geographic data

DATA ASSEMBLY, ANALYSIS, AND STORAGE
International Nucleotide Sequence Database Collaboration (INSDC)
Shared Public Access Databases
- NCBI – National Center for Biotechnology Information
- EMBL – European Molecular Biology Laboratory
- DDBJ – DNA Databank of Japan

PUBLIC HEALTH APPLICATION AND INTERPRETATION OF DATA
- Find clinical links
- Identify clusters
- Conduct traceback
- Develop rapid methods
- Develop culture independent tests
- Develop new analytical software
24 labs, historical strains and real time surveillance isolates

External Labs
Alaska
Hawaii
New Mexico
Arizona
Texas
Minnesota
New York
NY agriculture
Maryland
Virginia
W Carolina U
USDA-FSIS
Florida
Argentina
Current status

- WGS clearly defines foodborne outbreaks – more than 15 different examples
- NGS network is reliable, efficient and can provide very good location specificity of outbreaks
- We have sequenced more than 5,500 Salmonella, more than 1,500 Listeria, and closed 100 genomes. Our current rate is about 500 draft sequences a month.
- The need for increased number of well characterized environmental (food, water, facility, etc.) sequences may outweigh need for extensive clinical isolates
- Highly successful partnership with CDC on real-time tracking of Listeria outbreaks
Antimicrobial Resistance

- President directed NSC and OSTP to assess the threat of AMR and develop a multi-sectoral plan to combat resistant bacteria
  - December, 2013

- 5 goals
  - Slow emergence
  - Strengthen One-health surveillance
  - Advance innovative diagnostics
  - Accelerate R&D
  - Improve international collaboration

- Judicious use of antimicrobials in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics
National Antimicrobial Resistance Monitoring System

- A national collaborative network between the FDA, CDC and USDA as well as public health laboratories in all 50 states and local health departments in three major cities

- NARMS was developed to monitor changes in susceptibility of select bacteria from animals, retail meats and humans to antimicrobial agents of human and veterinary importance
  - FDA/CVM (retail meat and poultry)
  - CDC (humans)
  - USDA (animal/slaughter)
NARMS Objectives

Dedicated to the protection of human and animal health
Through integrated monitoring of foodborne AMR

1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals

2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria

3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance

4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals
Structure of NARMS in 2015

Human Population → Physician Visit → Local Lab → State Lab → CDC

Retail Meats
Random stratified sampling in 14 States
ORA Imported Foods

Farm Pilots
Farm to Slaughter
Drug use data point

Animal Population
Random cecal sampling of national production at slaughter

USDA ARS
USDA FSIS

HACCP isolates

Data Integration

Campylobacter
Salmonella
Enterococcus
E. coli
Benefits of a WGS Strategy in NARMS

**Methods**

- Culture
  - Serotyping
  - Antibiotic Susceptibility
  - PFGE
  - Molecular study

- DNA → WGS

**Results**

- Serotype
- Resistance pattern
- Genetic relationship
- Resistance mechanisms

**Characteristics**

Traditional

- Historical continuity
- Low resolution typing
- Multiple assays and reagents
- Limited drug coverage
- Limited resistance mechanisms
- Specialized training
- Labor intensive
- Costly
- Slow and piecemeal

WGS

- Requires new standards
- Higher resolution typing
- Single assay/one instrument
- Extended drug coverage
- Detect all known mechanisms
- Details on genetic context
- Computation intensive
- Lower costs
- Rapid and comprehensive
MDR plasmid in Gen^R C. coli in U.S. Retail Meat
Future NARMS Objectives?

1. Monitor trends in antimicrobial resistance among foodborne bacteria from humans, retail meats, and animals
2. Disseminate timely information on antimicrobial resistance to promote interventions that reduce resistance among foodborne bacteria
3. Conduct research to better understand the emergence, persistence, and spread of antimicrobial resistance
4. Assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals

1. Monitor genomes in antimicrobial resistant foodborne bacteria from humans, retail meats, food animals, companion animals, feral animals, the environment etc.
2. Characterize the resistome in complex biological samples using culture-independent metagenomic analyses.
3. Disseminate timely information on precise changes in the resistome to promote interventions that reduce resistance among foodborne bacteria and to prevent rare resistances from becoming common
4. Conduct in vivo metagenomics research to better understand the emergence, persistence, and spread of antimicrobial resistance under different conditions.

Provide comprehensive genetic data, along with detailed antibiotic use information, to assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for animals.
**International Efforts**

- Global system of DNA genome databases for microbial and infectious disease identification, surveillance and diagnostics

- 5 Work groups
  - Political challenges, outreach and building a global network
  - Repository and storage of sequence and meta-data
  - Analytical approaches
  - Quality assurance
  - Pilot project

- 8th GMI meeting to take place in Beijing, China, May 11-13, 2015

Over 500 members

32 Countries represented

- Brazil 1
- Cameroun 1
- Chile 1
- India 1
- Iran 1
- Ireland 1
- Israel 1
- Japan 1
- Kenya 1
- Luxembourg 1
- Nigeria 1
- Thailand 1
- Tunisia 1
- Finland 1
- Greece 1
- Germany 2
- Malaysia 2
- Norway 2
- Poland 2
- Sweden 2
- Belgium 3
- France 3
- Australia 4
- Switzerland 4
- China 5
- Italy 5
- Canada 8
- Spain 8
- The Netherlands 8
- United Kingdom 14
- Denmark 18
- United States 48
Consortium for Sequencing the Food Supply Chain

- IBM and Mars, Inc will study the microbial ecology of foods and related processing environments

- Sequencing ALL microorganisms
  - Microbiome

Public-Private Partnerships

- America COMPETES Act and President Obama’s Strategy for American Innovation
  - Granted Agencies authority to offer prize competitions
  - Use Grand challenges as an innovation tool to engage the public
    - Ambitious goals – catalyze breakthroughs
    - Pay only for success
    - Leveraging outside novel approaches

- Open innovation challenge efforts
  - FDA/Federal Partners/Industry co-aligned interests lie in the realm of rapidly detecting foodborne pathogens
    - Largest benefit could be gained by making significant advances in pre-enrichment phase of microbiological testing
      - Rapidly recovering enough target organisms or genetic material for current detection/sensor technology platforms
  - Sept. 23rd, 2014 – Food Safety Challenge Announced
    - Incentive Prize Competition Assistance for Improvement and Validation of Methods for the Detection of Microbial Foodborne Pathogens
Advancing Breakthroughs in Foodborne Pathogen Detection

The FDA is calling on America’s innovators to submit concepts applying cutting-edge techniques to achieve revolutionary improvements in the speed of the FDA’s detection methods for *Salmonella* in produce.
Summing up ....

- WGS is revolutionizing the microbiology laboratory contribution to public health

- WGS can be used to mitigate tracebacks and delimit the scope of food contamination events unlike ever before

- Developing a mutual/shared understanding and vision how to advance real time surveillance for foodborne pathogens using WGS

- Looking to the future
  - Roles, responsibilities and coordination of partners
  - Resources, training, SOPs, QA
  - Metadata
  - Bioinformatics
  - Data presentation
With Additional Thanks….

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| **State Health Labs**        |                                                            |                               |
|                              |                                                            |                               |
| Bill Wolfgang (NY)           | Dave Boxrud (MN)                                          |                               |
| Elizabeth Driebe (AZ)        | Angela Fritzinger (VA)                                    |                               |
| Ailyn Perez-Osorio (WA)      |                                                            |                               |

| **CDC**                      |                                                            |                               |
|                              |                                                            |                               |
| Chris Braden                 | Duncan MacCannell                                         |                               |
| Cheryl Tarr                  | Eija Trees                                                |                               |
| Marguerite Pappaioanou       |                                                            |                               |

| **Illumina**                 |                                                            |                               |
|------------------------------|                                                            |                               |
| Susan Knowles                | Omayma Al-Awar                                            |                               |

And a Growing Cast of Colleagues....