USING MOLECULAR EPIDEMIOLOGY TO INFORM PUBLIC HEALTH ACTION
Genotyping, cluster investigation and outbreak response in New York City

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Bureau of Tuberculosis Control
New York City Department of Health and Mental Hygiene

WHAT IS MOLECULAR EPIDEMIOLOGY?

- Application of molecular biology to the study of [infectious] disease epidemiology (Tompkins 1994)
  - Molecular epidemiology attempts to utilize a multidisciplinary approach to identify factors that determine disease causation, propagation/dissemination, and distribution in time and space (Mathema, 2006)
- Key components of molecular epidemiology:
  - Genetic information
  - Data analysis
  - Epidemiologic investigation

HOW IS MOLECULAR EPIDEMIOLOGY USED IN TB CONTROL?

- Identify false-positive cultures
- Identify and refute relapse/re-infection
- Identify and refute recent transmission
- Detect outbreaks
- Inform and enhance contact investigation and other TB control activities
- Identify high-priority groups for intervention
- Mechanism for better understanding TB transmission
- Help answer important research questions
Using Epidemiology for Data-Driven Decision-Making in Tuberculosis Programs
February 24, 2016

COMMONLY-USED TB GENOTYPING METHODS

- **Spoligotype analysis**
  - PCR-based
  - Detects presence or absence of 43 spacers

- **MIRU-VNTR analysis**
  - PCR-based
  - Determines the number of repeat units found at multiple loci

- **RFLP analysis**
  - Produces an image showing the pattern and number of copies of IS6110

- **Whole Genome Sequencing (WGS)**
  - Uniform genetic information from entire TB genome
  - Analyzes presence of single nucleotide polymorphisms (SNPs)

**Figure adapted from:**

TB GENOTYPING IN NYC

- Tuberculosis cases, rates, and genotyping methods, New York City, 1982-2014

**TB GENOTYPING IN THE US**

- The National TB Genotyping Service (NTGS) began in 2004 using spoligotyping and 12-loci MIRU
  - 24-loci MIRU-VNTR available in April 2009; WGS available in 2013; RFLP performed as needed
- **TB GIMS:** Secure web-based system launched in 2010 to improve access to and dissemination of genotyping information nationwide
  - Allows users to submit and track M. tuberculosis isolates to from contract genotyping labs
  - Stores and manages genotyping data for US TB cases
  - Links isolate data to patient-level surveillance data
  - Provides reports on genotype clusters (e.g. national distribution)
  - Generates alerts and provides tracking mechanisms for quickly-growing and other high-priority clusters

Using Molecular Epidemiology to Inform Public Health Action
OVERVIEW: GENOTYPING DATA REVIEW AND CLUSTERING PROCESS IN NYC

- Review
- Identify
- Prioritize
- Assign
- Investigate
- Intervene

DATA REVIEW AND CLUSTER IDENTIFICATION

- Genotype results are reviewed by epidemiologists as they are received from labs
- Considered alongside patient data and information from field and clinic staff
- Active surveillance for outbreak strains, unexpected results
- Identification of potential contamination and false positive isolates
- Cases with matching RFLP and spoligotype results are clustered
- Results and alerts from TB GIMS are reviewed and compared to existing genotype and patient data

EXAMPLE: DATA REVIEW AND CLUSTER IDENTIFICATION

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Octal Code</th>
<th>Spoligotype</th>
<th>RFLP</th>
<th>MIRU12</th>
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Patients C and D were referred by field staff to the Molecular Epi team due to a known epidemiologic link.

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Patients C and D were referred by field staff to the Molecular Epi team due to a known epidemiologic link.

- Different spoligotype results refute transmission.

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Patient D has a rare spoligotype, affiliated with a known outbreak.
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Patient D has a rare spoligotype, affiliated with a known outbreak

- Consider initiation/continuation of epidemiologic investigation

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Patients A, B and C have matching spoligotype results

- Consider possible contamination
- Review additional data (e.g. specimen collection and processing dates/facilities, patient characteristics, DST results)
- Contacts labs; notify staff as needed
Using Molecular Epidemiology to Inform Public Health Action

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<table>
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<th>Nature</th>
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Patients A, B and C have matching spoligotype results.

- Consider possible contamination
- Review additional data (e.g. specimen collection and processing dates/facilities, patient characteristics, DST results)
- Contacts labs; notify staff as needed
- Conduct quick review of patient data
- Review additional genotype results as they are received

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Different RFLP results:

- Contamination ruled out
- Transmission ruled out

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Different RFLP results:
- Contamination ruled out
- Transmission ruled out

Matching RFLP and spoligotype results:
- Assign to NYC cluster
- Review for cluster investigation eligibility and prioritization
- Notify relevant staff

**Additional genotype data are reviewed as they are received**
- MIRU-VNTR results help prioritize and differentiate clusters
- TB GIMS/CDC alerts for high-priority clusters are reviewed alongside NYC data

**Similar review occurs at the national level and in jurisdictions using spoligotype and MIRU-VNTR results to cluster**
### CLUSTER REVIEW AND PRIORITIZATION

- Clustered cases are reviewed and prioritized for investigation based on an algorithm:
  - Focus is on possible recent transmission, potential for intervention
  - **High-priority**: Children, HIV-infection or other immuno-suppression, multidrug-resistant strain, healthcare worker, history of homelessness, incarceration, substance abuse
  - **Time component**: Diagnosis within 24 months of a previous case
  - **Other factors**: Country of birth, patient demographic and clinical characteristics, strains new to NYC, size of cluster, rapid cluster growth

### EXAMPLE: CLUSTER REVIEW AND PRIORITIZATION

#### EXAMPLE 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Spoligotype</th>
<th>RFLP (bands)</th>
<th>Cluster</th>
<th>Homeless history</th>
<th>Substance Abuse</th>
<th>Disease Site</th>
<th>Eligible</th>
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<td>B</td>
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- Patient C has recently been assigned to Cluster 22

- Patient C was counted <24 months after Patient B
### Example: Cluster Review and Prioritization

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<table>
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<tr>
<th>Case</th>
<th>Count Date</th>
<th>Spoligotype</th>
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<td>W748 (20)</td>
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<td>22</td>
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- Patient C was counted <24 months after Patient B
- Patient C has a history of homelessness and substance abuse

For these reasons, Patient C is eligible for investigation.

**Example 2**

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- Should Patient C be assigned for investigation?
EXAMPLE: CLUSTER REVIEW AND PRIORITIZATION

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<th>Case</th>
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<th>Spoligotype</th>
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<th>Country of birth</th>
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- Should Patient C be assigned for investigation? No.
  - The only other cases in this cluster were non-infectious and had extra-pulmonary TB.
  - There is no reason to investigate further.
  - Patient C is given a low priority.

EXAMPLE 2

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<td>S02430</td>
<td>AI329 (13)</td>
<td>999</td>
<td>Haiti</td>
<td>Brooklyn</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>B</td>
<td>Dec 2014</td>
<td>S02430</td>
<td>AI329 (13)</td>
<td>999</td>
<td>Haiti</td>
<td>Brooklyn</td>
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<tr>
<td>C</td>
<td>June 2015</td>
<td>S02430</td>
<td>AI329 (13)</td>
<td>999</td>
<td>United States</td>
<td>Brooklyn</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
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</tbody>
</table>

- Patient C was newly assigned to cluster 999.
- Eligible for investigation? Yes. Patient C was diagnosed <24 months after Patient B.
### Example: Cluster Review and Prioritization

**Example 2**

<table>
<thead>
<tr>
<th>Case</th>
<th>Count</th>
<th>Date</th>
<th>Spoligotype</th>
<th>RFLP (bands)</th>
<th>Cluster</th>
<th>Country of birth</th>
<th>Borough of residence</th>
<th>Age</th>
<th>Eligible</th>
<th>Assigned</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>August 2014</td>
<td>S02430</td>
<td>AI329 (13)</td>
<td>Haiti</td>
<td>Brooklyn</td>
<td>50</td>
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<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Dec 2014</td>
<td>S02430</td>
<td>AI329 (13)</td>
<td>Haiti</td>
<td>Brooklyn</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>June 2015</td>
<td>S02430</td>
<td>AI329 (13)</td>
<td>United States</td>
<td>Brooklyn</td>
<td>30</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Should we assign Patient C for investigation?
  - Yes!
  - Patient C is U.S.-born in a majority Haiti-born cluster
  - This is a new strain in NYC with rapid cluster growth concentrated in one borough

### Cluster Assignment and Investigation

- Eligible cases/clusters are assigned to an epidemiologist and investigated systematically.
CLUSTER ASSIGNMENT AND INVESTIGATION

- Eligible cases/clusters are assigned to an epidemiologist and investigated systematically

Routine cluster investigation steps, NYC:

- Prioritize
- Assign
- Investigate
- Intervene

CLUSTER ASSIGNMENT AND INVESTIGATION

- Eligible cases/clusters are assigned to an epidemiologist and investigated systematically
- Extent of investigation varies depending on patient and cluster characteristics
  - Epi Review: Brief review of patient information to look for obvious links or something to prompt further action or review
  - Mini Investigation: Further review; may involve contacting case managers, gathering data not in Maven, or patient interview
  - Full Investigation: Collect data, contact case managers, interview cases with cluster-specific questionnaires, create maps or other relevant data collection/visualization tools, communicate results

DOCUMENTING FINDINGS AND COMMUNICATING RESULTS

Findings are communicated to internal and external stakeholders through multiple mechanisms
- Maven/TB Registry
- Informal communication
- Cluster summaries
- Epidemiologic curve, diagrams, tables, maps, timelines
- Quantify and describe epidemiologic links
- Reports, meetings, presentations, posters, manuscripts, media
DETERMINING WHEN TO INITIATE PUBLIC HEALTH ACTION

- Is there reason to suspect false-positive lab results?
- Are there newly-identified contacts or exposure sites?
- Is there evidence of recent transmission?
  - Does the cluster include children under age 5?
  - Do cases in the cluster have evidence of recent infection (e.g., TB test conversions)?
  - Were strong epidemiologic links identified between recently-identified cases?
  - Is it a newly identified genotype in NYC?

DETERMINING WHEN TO INITIATE PUBLIC HEALTH ACTION

- Was an opportunity or need to improve routine TB control activities identified?
- Is there potential for rapid cluster growth?
  - Exposure in congregate setting(s) or healthcare facilities
  - Patient clinical characteristics suggestive of infectiousness
  - Patient social characteristics suggestive of high-risk settings/contacts
  - Contact characteristics suggestive of high risk for infection or progression
  - Incomplete/difficult contact investigations

OUTBREAK INVESTIGATION AND RESPONSE
Using Molecular Epidemiology to Inform Public Health Action

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

- Quickly identify outbreak-associated cases
- Ensure treatment completion among cases
- Ensure thorough and complete contact investigations
- Identify and interrupt transmission
- Ensure prompt TB evaluation and diagnosis
  - Healthcare providers
  - High-risk individuals and affected communities
- Identify mechanisms to prevent future outbreaks

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

- Quickly identify outbreak-associated cases
  - Create an outbreak case definition
    - Genotype(s)
    - Patient characteristics
    - Geography
    - Exposure site(s)
    - Time frame
  - Enhance surveillance for outbreak strain(s), patient characteristics
    - Generate reports and/or watch lists (Maven, TBGIMS)
    - Engage clinic, field staff and community healthcare providers
    - National genotype surveillance and interjurisdictional collaboration
    - Consider/implement active case-finding

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

- Quickly identify outbreak-associated cases
- Ensure treatment completion
- Identify and address barriers to treatment adherence
- Implement DOT (video DOT)
- Identify/engage potential partners to facilitate treatment, locate lost patients (e.g. shelters, schools, community orgs.)
- Consider Incentives
- Last resort: legal interventions
Using Epidemiology for Data-Driven Decision-Making in Tuberculosis Programs

February 24, 2016

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

• Quickly identify outbreak-associated cases
• Ensure treatment completion
• Ensure thorough and complete contact investigations
  • Create data management system for contacts
  • Utilize public records and other databases (e.g. vital statistics, incarceration history, homeless history, social service utilization) and social media (e.g. Facebook, LinkedIn)
  • Re-interview cases and contacts
  • Facilitate evaluation of contacts
  • Field testing, extended clinic hours, local healthcare providers
  • Consider DOT, 3HP for LTBI treatment
  • Consider incentives

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

• Quickly identify outbreak-associated cases
• Ensure treatment completion
• Ensure thorough and complete contact investigations
• Identify and disrupt transmission
  • Conduct field visits
  • Re-interview patients (cases and contacts)
  • Consider photo/name recognition with patient permission
  • Conduct/expand contact investigations at exposure sites
  • Conduct targeted testing as needed
  • Assess/improve infection control practices
  • Consider environmental assessment/environmental controls

OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

• Quickly identify outbreak-associated cases
• Ensure treatment completion
• Ensure thorough and complete contact investigations
• Identify and disrupt transmission
• Ensure prompt TB evaluation and diagnosis
  • Identify and engage local healthcare providers
  • Develop and disseminate educational resources (e.g. provider alerts)
  • Increase awareness of TB and enhance healthcare access among affected community members and the public
  • Identify barriers and enablers
  • Utilize local media outlets, digital/social media, print materials, community organizations, elected officials, word-of-mouth

Using Molecular Epidemiology to Inform Public Health Action
OUTBREAK INVESTIGATION AND RESPONSE OBJECTIVES

• Quickly identify outbreak-associated cases
• Ensure treatment completion
• Ensure thorough and complete contact investigations
• Identify and interrupt transmission
• Ensure prompt TB evaluation and diagnosis
• Identify mechanisms to prevent future outbreaks
  • Policy and procedure changes
  • Training/education needs
  • Relationships with newly identified stakeholders
  • Opportunity/need to improve healthcare access
  • Ongoing collaboration with internal and external partners

CASE STUDY: SUNSET PARK OUTBREAK, NEW YORK CITY

NYC TUBERCULOSIS CLUSTER 795 (G12645) JUNE 2010-AUGUST 2012

In NYC, a TB cluster is defined as two or more cases having matching restriction length polymorphism (RFLP) and spacer oligonucleotide typing (spoligotyping) results.

Data reported to NYC Department of Health.

Number of cases
Using Epidemiology for Data-Driven Decision-Making in Tuberculosis Programs
February 24, 2016

NYC TUBERCULOSIS CLUSTER 795 (G12645) JUNE 2010-AUGUST 2013

NYC TUBERCULOSIS CLUSTERS 795 (G12645) AND 782 (G22736), JUNE 2010-AUGUST 2013

NYC TUBERCULOSIS CLUSTERS 795 (G12645) AND 782 (G22736), JUNE 2010-AUGUST 2013

Using Molecular Epidemiology to Inform Public Health Action
NYC TUBERCULOSIS CLUSTERS 795 (G12645) AND 782 (G22736), JUNE 2010-AUGUST 2015

PATIENT CHARACTERISTICS, NYC TB CLUSTERS 782 AND 795 (N=32)

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>94%</td>
</tr>
<tr>
<td>Born in China (%)</td>
<td>100%</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>25 (19-40)</td>
</tr>
<tr>
<td>Median time in the United States at time of diagnosis (range)</td>
<td>7.5 (0-23)</td>
</tr>
<tr>
<td>History of illegal drug use (%)</td>
<td>15%</td>
</tr>
<tr>
<td>Pulmonary disease site (%)</td>
<td>94%</td>
</tr>
<tr>
<td>Cavitory chest x-ray (%)</td>
<td>41%</td>
</tr>
<tr>
<td>Positive smear for acid-fast bacilli (%)</td>
<td>50%</td>
</tr>
<tr>
<td>Linked to same Brooklyn neighborhood (%)</td>
<td>100%</td>
</tr>
<tr>
<td>History of work in restaurants (%)</td>
<td>74%</td>
</tr>
<tr>
<td>History of internet café use (%)</td>
<td>62%</td>
</tr>
</tbody>
</table>

HEALTHCARE-SEEKING AMONG PATIENTS

- Median time from TB symptom onset to TB treatment initiation: 28 days (Range 11-281 days)
- 18% first sought care from a community provider
- 75% patients first sought care at a local hospital ED
- 7% first sought care at a NYC Health Department clinic
- 38% patients had a regular primary care provider at time of TB diagnosis
- During re-interview, patients indicated that they had identified a healthcare source through word-of-mouth and local Chinese language newspapers
EXPOSURE SITES AND EPIDEMIOLOGIC LINKS, CLUSTER 782

POSSIBLE SITES OF TRANSMISSION

• Internet cafes and karaoke bars (73%)
  • Small crowded spaces with little ventilation
  • Patients reported many hours per visit, several visits per week
  • Confusion over site names, locations (rapid turnover)
  • Possibility of illegal activity
  • 8 sites identified; 4 linked to four or more outbreak patients

• Out-of-state restaurant work (74%)
  • Little locating information provided by patients
  • Long work hours; sleeping/shelter on-site or nearby via management
  • Transportation via bus/van over many hours
  • Unknown/unnamed contacts
  • Locations named by patients: NJ, IL, PA, NYS, FL, MA, CT, Washington DC, OH, VA, MS, GA, VT

OUTBREAK RESPONSE

• Enhance surveillance to identify outbreak-associated cases
  • Internal reports based on patient characteristics and geography
  • Engage field and clinic staff, local hospitals, community providers
  • National genotype surveillance (TB GIMS)

• Encourage prompt TB diagnosis, reporting and referral
  • Phone calls, education sessions presentations, meetings
  • Develop and disseminate healthcare provider resources
  • Guidelines, resources
  • Provider Alerts
  • Epi Data Brief: March 2015
OUTBREAK RESPONSE

- Identify and interrupt transmission
  - Conduct and expand contact investigations
    - Household, family and social contacts
  - Challenges:
    - Difficult to identify exposed individuals
    - Fear/distrust of Health Department (among patients, contacts, business owners, community members)
    - Barriers to accessing Health Department clinic services (e.g., work hours, geographic proximity, fear/distrust, perception of cost)
    - Language/cultural barriers

OUTBREAK RESPONSE

- Identify and interrupt transmission
  - Conduct and expand contact investigations
    - Household, family and social contacts
  - Targeted TB testing among individuals at high risk
    - At known exposure sites
      - Internet cafes; karaoke bar; restaurants
    - At community health events
      - With hepatitis testing, influenza vaccination, dental exams
    - Via mobile van in affected neighborhood
      - Co-sponsored by local politicians, community organizations
      - Chinese-speaking Health Department staff and community volunteers
      - Surveys conducted to assess utilization by target population

Using Molecular Epidemiology to Inform Public Health Action
OUTBREAK RESPONSE

• Increase healthcare-seeking and awareness of TB/TB-related services among community members
  • Through local media outlets
    • Print (Chinese language newspapers)
    • Radio, TV
    • Internet-based
  • Through digital media
    • Geo-targeted web ads
    • Social media platforms
    • Website
  • Through print materials
    • Posters, flyers

NEXT STEPS

• Develop a mechanism for using incentives to enhance contact elicitation/evaluation/treatment
• Formalize a task force for outbreak response/community outreach in the Chinese community in NYC
• Conduct formal evaluation of outbreak response/outreach activities
• Utilize mobile van for on-site testing at known exposure sites, community events

CONCLUSIONS
CONCLUSIONS

- Molecular epidemiology can inform public health action
  - To improve routine TB control practices
  - To identify and interrupt recent transmission
  - To identify high-risk groups
- Cluster prioritization, investigation and response should be systematic, data-driven and account for new information
- Heterogeneity of groups affected by TB requires tailored public health interventions—Know your local epil!
- Outbreak response requires time and resources, but epidemiology can help focus investigations
  - Data management and stakeholder engagement are crucial
  - Core outbreak investigation and control activities are scalable
  - Ultimate goal...outbreak PREVENTION

WITH MANY THANKS TO

- NYC Bureau of TB Control and NYC Health Department colleagues
- Lab partners:
  - NYC Public Health Laboratory
  - NY State Department of Health Wadsworth Center
  - Public Health Research Institute at Rutgers University
  - Michigan Community Health Department Bureau of Labs
  - Centers for Disease Control and Prevention (CDC)
  - The Union (NAR) and National TB Controller’s Association
  - Regional Training and Medical Consultation Consortium (RTMCCs)
  - Community and healthcare-provider partners and our patients

Charles B Wang Community Health Center, Chinese American Planning Council, NY Presbyterian Lower Manhattan, Chinese American Community Health, Responding to Health, Alliance for Medical Services, Chinese American Independent Providers Association, Lower East Side Tenants Union, Chinese American Heritage Center, Sunset Park 5th Avenue Business Improvement District, Mayor’s Office of Immigrant Affairs, Manhattan Hospital, Metropolitan Hospital, Long Island Jewish Medical Center, Hospital for Joint Diseases, Lutheran Family Health, Family Health Centers, Lutheran Family Medical Center, Lutheran Family Medical Group, Lutheran Family Physicians, Lutheran Family Community Health, Public Health Research Institute, Wadsworth Center, CDC, NYC Department of Consumer Affairs...