Biobanking for Public Health Research

Uses and Issues

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*McKing Consulting Corp
Outline

• Working definitions
• Public health research overview
• Case studies
  • E. coli infection and hemolytic-uremic syndrome
  • Chronic beryllium disease in exposed workers
  • Childhood leukemia cluster
  • Severe pediatric influenza
• Current status at CDC
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What is public health?

Public health is what we do collectively to fulfill society’s interest in assuring the conditions in which people can be healthy.

Institute of Medicine, *The Future of Public Health*, 1988
What is a biobank?

A repository of biological material (e.g. seeds) or information (e.g. DNA).

www.en.wiktionary.org
What is a public health biobank?

A repository of biological tissue stored for public health purposes. Such purposes could include:

• diagnosis (e.g. serology)
• surveillance (e.g. epidemiology)
• documentation (e.g. screening)
• quality assurance (e.g. laboratory tests)
• forensics (e.g. cause of death)
What is population-based research?

Population-based research is based on statistical sampling of a population that is defined by geopolitical boundaries. Advantages include:

• sound basis for inference (less bias)
• basis for monitoring (trends)
• relevant to public health (policy unit)
Population-based research?

Research studies that employ epidemiologic methods (e.g., case-control and cohort studies) are often self-described as “population-based” regardless of their methods for selecting participants. These include many genetic association studies.
Medicine

- Individual
- Diagnosis
- Treatment
- Private

Public Health*

- Population
- Risk assessment
- Prevention
- Public

* United States status quo
Individual vs. Population Research

Population
- establish distribution of risk factors
- study risk factor – disease associations
- assess interactions among risk factors
- develop and test interventions

Individual
- monitor effects of interventions
## Individual vs. Population Research

<table>
<thead>
<tr>
<th>Research Paradigm</th>
<th>Clinical Genetic Research</th>
<th>Population-Based Genetic Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Stage</td>
<td>Confirmatory</td>
<td>Exploratory</td>
</tr>
<tr>
<td>Nature of Participant Risks</td>
<td>Physical, Economic</td>
<td>Social, Psychological</td>
</tr>
<tr>
<td>Individual Relevance of Research Findings</td>
<td>Likely</td>
<td>Little immediately; possible in future</td>
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Adapted from M. Leinhos
Ethical Issues in Genetic Research

Clinical research
Population-based research
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Public Health Research at CDC

- **Goals**: disease detection, prevention, and control
- **Methods**: surveillance, epidemiology, laboratory studies, behavioral and social sciences
- **Settings**: outbreaks, populations in US and other countries
- **Framework**: requires invitation, protocols require review by Institutional Review Board(s)
- **Products**: outbreak control, notification, guidelines, “generalizable knowledge”
Public Health Investigations

- CDC collaborates with public health agencies worldwide
- Diseases
  - infectious disease outbreaks
  - cancer or birth defect clusters
- Exposures
  - environmental or occupational
  - bioterrorism
- Adverse response to interventions
  - vaccines
  - antibiotic prophylaxis
Public Health Investigations: Genomics

- Pathogen genomics
  - Trace epidemics
  - Monitor antimicrobial resistance
- Human genomics
  - Understand variation in disease outcomes
  - Characterize environmental exposures
  - Improve public health interventions
    - vaccines
    - chemoprophylaxis
    - exposure reduction
    - health promotion
Public Health Investigations: Human Genomics

- **Why:** understand variation in disease outcomes, characterize exposures, improve public health interventions
- **How:** technology has become cheaper and faster
- **What:** epidemiologic data, specimens, biomarkers, genotypes for $1-10^6$ variants
- **Ethical issues:** related to individual, community, and societal interests
Public Health Biobanking: Key Opportunities

- Diseases of unknown cause: identify agent, characterize human response (SARS, Spanish toxic oil syndrome)
- Mass exposures: assess risks, define vulnerable groups and safety thresholds (vaccines, workplace exposures)
- Clusters: identify exposures, accumulate sufficient sample size to study gene-environment interactions (birth defects, cancers)
- Pandemics: describe spectrum of disease, predict vulnerability, plan response (influenza)
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Hemolytic Uremic Syndrome (HUS)

- Potentially life-threatening: disseminated intravascular coagulation, acute renal failure
- No specific treatment available—supportive care
- Toxigenic *E. coli* O157:H7 infection is leading cause in children
  - incidence 5–10% in *E. coli* O157:H7 infection
  - case-fatality rate 3-5%
- Familial HUS
  - account for 5-10% of HUS cases
  - mutations in *CFH, CD46, F1*

Disseminated intravascular coagulation, kidney
http://cnserver0.nkf.med.ualberta.ca/cn/Schrier/Vol2/f3443-2.jpg
E. coli O157:H7 and HUS

- E. coli O157:H7 infection
- Hemolytic uremic syndrome
- Surveillance system (FoodNet)
  - >600 clinical laboratories in 10 states
- Study
  - Risk factors for HUS: antibiotics, other treatments, clinical and laboratory characteristics, microbial strains
  - Chart review, interview + DNA sample collection
  - Bank samples until sufficient number accumulated for analysis

www.fda.gov
Candidate genes not clinically relevant, but could be in the future:
- When and how should participants receive results?
  - Initial plan: participants would be notified if any results became clinically relevant

New candidates or methods could become available:
- how long should specimens be stored for future testing?
- should additional approval be sought from participants?
  - Storage of specimens and a link to the patient would be indefinite to allow recontacting for possible future testing
But:

- 10 state health departments with 10 different IRB guidelines → 10 different protocols
- Logistics and practicality of maintaining a link to patients: problems at the state health departments were insurmountable
- Revised draft stated that results will not be reported because they are not currently clinically relevant
  - Specimens will be stored for 5 years anonymously so that if additional genes involved in HUS are identified, the specimen may be tested
  - No link to the patient will be maintained

*E. coli* O157:H7 and HUS
Summary of issues:

- Surveillance infrastructure does not support routine sample collection
- Research protocols must be approved at each state IRB
- Outbreaks require rapid response and surge capacity in communications, enrollment, data collection
- Control has first priority—research is secondary
- High visibility, public concern, potential for litigation
- Difficult to justify long-term research investment without immediate impact

E. coli O157:H7 and HUS
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Chronic Beryllium Disease (CBD)

- Beryllium (Be) is a light metal with many industrial uses (e.g., aerospace, nuclear, machining)
- Exposure causes progressive, granulomatous lung disease in workers
- Marked individual variation in disease onset and progression
- U.S. Dept of Energy required to monitor exposure and maintain disease registries
  - Cumulative data (2009) for 13,583 active employees: 1.7% sensitized to Be, plus 0.8% with CBD

CBD of lungs on CT scan
http://www.hss.energy.gov/healthsafety/berylliumaffectedworkers/
Chronic Beryllium Disease (CBD)

- Immune factors suspected for 50 years
- Association with HLA-DPB1 recognized in 1990’s
- HLA-DPB1 Lys69Glu polymorphism associated with both sensitization (in vitro activation of T-lymphocytes) and CBD
- HLA-DPB1 polymorphism has poor predictive value for CBD

Chronic Beryllium Disease (CBD)

Summary of issues:

• Understanding gene-environment interactions could lead to improved prevention and control strategies

• Measurement challenges:
  – exposures: component(s), route, dose, time course
  – human response: choice of biomarkers, normal ranges, subgroups
  – both: standardizing technologies for comparison, communication

• Cohort studies of exposed workers conducted with cooperation of industry/employers

• Genetic information (including family history) is kept in workers’ personnel and workplace health records

• Premature use of unvalidated “tests” can lead to employment discrimination
Report newly published by the National Institute of Occupational Safety and Health (NIOSH)

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Childhood Leukemia, Fallon, Nevada

- 2001: statistically significant increase in acute lymphocytic and myelocytic leukemias (ALL and AML): 15 cases
- Nevada expert panel recommended cross-sectional exposure assessment
- CDC opened clinic in Fallon, where case and comparison families were enrolled and interviewed and biologic samples were collected.

Childrenhood Leukemia, Fallon, Nevada

- Community-wide elevated levels in drinking water:
  - Tungsten
  - Arsenic
  - DDE, organochlorine

- Sulfite oxidase \( SUOX \) -628G>A

OR = 6.81  
(95% CI = 1.28 – 257)  
p = 0.007
Childhood Leukemia, Fallon, Nevada

Communicating results

- Consent form  “You will receive a general report of the research findings that does not include any personal identifying information. However, should the genetic research done on your DNA identify something that could significantly affect your health or reproductive choices, we will notify you personally.”

- Town hall meetings
- Meetings with families to present results
- Peer-reviewed articles in *Environmental Health Perspectives*
- CDC website
Childhood Leukemia, Fallon, Nevada

Outcomes:

• Exposure to health hazards documented
• Recommendations made for avoiding hazard
• New water treatment facility built
• NTP agreed to study toxicity and carcinogenicity of tungsten
• Results of genetic testing generated a hypothesis about gene environment interaction
Childhood Leukemia, Fallon, Nevada

Summary of issues:

• Affected and unaffected children were enrolled as research subjects.
• Results were not clinically useful for treatment or prevention.
• Initial plan not to share individual results changed during study.
• Community concerns focused on controversial environmental issues involving litigation.
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<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>2003-04</td>
<td>Unexpected increase in severe flu among children</td>
</tr>
<tr>
<td>2005-06</td>
<td>Familial clustering of severe H5N1 flu</td>
</tr>
<tr>
<td>2006</td>
<td>CDC-sponsored workshop on human genetics / flu</td>
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<td></td>
<td></td>
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<tr>
<td>2008-10</td>
<td>Extramural study of genetic, immunologic, and clinical factors in children</td>
</tr>
<tr>
<td></td>
<td>with severe flu</td>
</tr>
<tr>
<td>2010</td>
<td>H1N1 vaccine effectiveness studies in development</td>
</tr>
</tbody>
</table>
Severe Influenza in Children

NVSN Influenza Laboratory-Confirmed Cumulative Hospitalization Rates for Children 0 - 4 Years, 2004-05 and Previous 4 Seasons

International Workshop

State of the science

Priorities
- severe influenza in children
- vaccine adverse effects

Potential opportunities
- outbreak investigations
- biobanks in clinical settings

Issues
- “off-the-shelf” protocols
- privacy, confidentiality
- collaborations
Severe Influenza in Children

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09

Second wave, H1N1

typical flu epidemic
Severe Influenza in Children

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09

- A (2009 H1N1)
- A (Unable to Subtype)
- A (H3)
- A (H1)
- A (Subtyping not Performed)
- B
- Percent Positive

Number of Positive Specimens vs. Week

- First site
- Last site
Severe Influenza in Children

Summary of issues:

- Rapidly evolving epidemic(s)
- Viral genetic variation a dominant factor
- Surveillance infrastructure not readily adaptable for research
- Existing clinical network (29 ICUs) with multiple IRBs led to 10-month start-up
- Fortuitous capture of H1N1 pandemic
- Clinical network now harnessed for other studies
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Trends in Public Health Research Involving Genomics, CDC

- Pathogen genomics a mainstay of public health research and practice
- Human genomics increasingly integrated into research
- Ethical considerations related to genetics mostly similar to population-based research in other settings
- Special considerations related to:
  - public health goals, priorities, and capacity
  - role of the state in research
Medicine
- Individual
- Diagnosis
- Treatment
- Private

Public Health
- Population
- Risk assessment
- Prevention
- Public
Ethical Issues in Biobanking

Public health research
- “crisis” setting, staff expertise
- government information
- public records
- public services
- adverse publicity
- outside clinical setting
- public investment, public benefit?
- government authority

Human genome research
- informed consent
- privacy
- confidentiality
- discrimination
- stigmatization
- access to results
- return on investment
- accountability
Public Health Research at CDC

- Mechanisms for researchers to interact on protocol development issues are not well-developed
- Multiple IRBs review research protocols
- Default has been not to report individual genetic research results
- Individual research results can be obtained by participants via the Privacy Act
- Guidance that is accessible and can be consistently applied across CDC studies is needed
Review of CDC IRB-approved Protocols Involving Human Genomics, 2009

Study plan

- Identify and collect protocols
- Extract information on study objectives and methods, including consent language and procedures
- Review relevant literature in research ethics
- Develop guidelines
- Analyze options and procedures for returning results to participants
Other topics: organic dust disease, lower back pain, Gulf War illness, disinfection by-products, biomarkers of sexual activity, thrombosis, norovirus, MI, pesticides, lymphedema, HUS, puberty

S. Giordano, CDC
Public Health Research Involving Human Genomics: Current Status

- Reporting individual genetic results to research participants has generated debate and lack of consensus.
- Guidance for researchers and IRBs is generally not clear.
- Public health and clinical research perspectives should be better integrated to assure that interests of individuals, groups, and society are recognized and balanced.
Acknowledgements

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Case Studies

E. coli and hemolytic-uremic syndrome: Linda Demma, Tim Jones
Chronic beryllium disease: Erin McCanlies, Ainsley Weston
Childhood leukemia: Carol Rubin, Karen Steinberg
Severe influenza in children: Jill Ferdinands, Nicole Dowling