Statistical Agency Considerations in Releasing DNA Test Results

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When Home is a Statistical Agency

- Advantages
  - Institutional commitment to data collection
  - Data Collection done as part of a statistical system
- Constraints
  - Confidentiality Protection
  - Appropriateness of Scope
    - Perception
    - Impact on 'core' mission

Challenges Related to DNA—Playing Devil's Advocate

- Is the collection of DNA pushing the scope boundary?
  - NHANES collects sensitive information
  - Is DNA too sensitive?
- Does reporting of results move NHANES over the line?
- Does the timing of the testing make a difference?
  - Immediate testing
  - Banking for future testing
- Should we address past collections or focus on the future or both?

NHANES DNA Collection History – a Somewhat Bumpy Road

- Modeled after surplus sera program
  - Testing of banked specimens
  - Testing limited to 'non-reportable' results – resolved logistical issues
- Major challenge of protecting confidentiality
- Now need to revisit reporting
  - Address past practices that are not consistent with current practices
  - Develop practices for future collections

Responsibility for Reporting of Results vs Statistical Agency Expertise

- Ongoing Determination of what to report
  - Similar to other test results but
    - Likely more volatile
    - Potentially less consensus
  - In-house expertise not sufficient
- Interpretation/Counseling
  - Much more costly and complex than for other test results
  - Lack of expertise

Unintended Consequences for NHANES

- Potential impact on participation in the survey or other components of the survey
  - Perception that government should not be collecting DNA
  - Need for complex informed consent especially if specimens are banked
- Additional funding needed or NCHS funds diverted from other components
  - For immediate testing
  - For recontact with subjects

Unintended Consequences on NHANES

- Potential negative impact on agency reputation
  - Complex ethical requirement
  - Changing ethical requirements especially if specimens are banked
  - Potential for errors in reporting

Are We at the End of the Road?

- DNA collection was added to NHANES to be better able to address public health issues
- NHANES remains a unique and potentially important resource for DNA linked to an array of health measures
  - Range of information collected
  - Random sample of the population with over sampling of subgroups of interest

Are We at the End of the Road?

- The road has been bumpy
- Maximizing use of the DNA results within the constraints of required confidentiality protection for NHANES continues to be a challenge
- Advancing technologies have made the existing (workable) approach to the release of results to respondents obsolete

Are We at the End of the Road?

- Is the road back too treacherous?
  - Recontacting respondents decades after their NHANES exam is logistically difficult with significant ethical challenges
  - Moving forward may be less difficult but still presents considerable reporting obstacles
- Do the challenges of DNA collection with the associated reporting requirements no longer fit within the constraints of a statistical data collection?

Genetic Exceptionalism

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Exceptionalism

- *Is genetic information sufficiently different from other types of biomedical information that special rules for management are justified?*
  - Treated differently when not justified
  - Treated the same when differences are justified

Soft Genetic Exceptionalism

- How is genetic information (somewhat) different from other biomedical information?
  - Information yields information relevant to the welfare of others
  - Can be highly predictive of future disease
  - Information can be stigmatizing
  - Information often complex to analyze and interpret

Green and Botkin. Ann Int Med 2003

Context

- Return of IF's within a larger debate about when to return any results in research
- Support for ROR is evolving among investigators and IRBs
- Discussion of incidental findings in research has been almost exclusively in the context of genetics and imaging
  - Limited discussion and debate in the pathology community beyond genetics

Genetic Exceptionalism

- The term assumes a set of rules for ROR for which exceptions might be applied for genetic results
- No generally accepted rules have been formulated for ROR in research
  - The notion of exceptions may not apply

NHANES

- Return of results for physical examinations and tests that are routinely conducted in clinical care
- No return of any research results generated later whether genetic or not
- No genetic exceptionalism with this current approach

What characteristics of information are relevant to ROR in research?

- Analytic validity
- Clinical validity
- Clinical utility
  - Urgency of response
- Personal utility
- Context specificity
- Informed consent
- Whether results are plainly evident from research procedures or must be sought through additional analysis

Types of Testing

- Physiologic: Tests of current biological function (blood counts, blood gases, electrolyes, renal function tests, LFTs, EKG, etc)
- Imaging or other physical or anatomic testing
- Genetic/Genomic testing

	Clinical Validity	Clinical Utility	Urgency	Plainly Evident	Context Specific
Physiologic	Y	Y	Y	Y	N
Imaging	Variable	Y	Y	Y	N
Genomic	Variable	Variable	N	N	Y

	Clinical Validity	Clinical Utility	Urgency	Plainly Evident	Context Specific
Physiologic	Y	Y	Y	Y	N
Imaging	Variable	Y	Y	Y	N
Genomic	Variable	Variable	N	N	Y

Exceptionalism

- These differences in test characteristics tend to favor ROR for physiologic and imaging tests
  - Urgent
  - Plainly evident
  - Not context specific

ROR

- How do laboratorians manage return of results in clinical medicine?
- Return of results should not be more stringent than this standard

AMA Council on Medical Services

1999 Statement

- "[I]t is largely understood that "discrete analyzers" have replaced most automated laboratory equipment, which routinely performed all of the tests on a panel, regardless of the test or tests ordered."
- "The widespread use of discrete analyzers makes it unlikely that a laboratory would conduct a test or tests other than those that are specifically requested."
- "CLIA requires laboratories to 'perform tests only at the written or electronic request of an authorized person,' thereby further decreasing the likelihood that a laboratory would conduct a test without receiving a specific order from an authorized person to do so."

AMA Statement 1999

- "According to CAP, a laboratory would most likely respond to an abnormal result generated by a test that was not ordered -- an unlikely scenario as noted above -- by notifying the physician verbally of the result and, consistent with CLIA, releasing the result once the physician had ordered the test."
- "However, billing for tests that were not ordered could subject a laboratory to accusations of fraud and abuse."

AMA Statement 1999

- "Similarly, the Council believes that the AMA should support modifying CLIA to require laboratories to provide a written report of all critical results to the physician, regardless of the test or tests that the physician requested…"
- "…[I]t is the policy of the AMA that, in the best interest of patient safety, laboratories should provide a written report of all critical results to the physician, regardless of the test or tests that the physician requested, and that a physician order should not be required for written release of this information."

Laboratorian Interviews

- Small, unscientific convenience sample (N=8) in two different health systems
- Results
  - Little discussion at the professional level of ROR
  - Lab-by-lab SOP's
  - Machines are made or set to report and record results only for ordered tests
    - Multiplex analyses are uncommon
    - Comfort with "gating" machines to produce only ordered results
  - When non-ordered tests were reported for critical values, physicians would sometimes "game the system" by ordering a specific test and assume that other results were normal if they were not informed otherwise

Laboratorian Interviews

- Comments regarding concerns that non-ordered tests are a breach of privacy
- Concerns about fraud for charging for non-ordered tests
- Definitions: *"A 'critical value' is a laboratory result that suggests a patient is in imminent danger unless appropriate therapy or further evaluation is initiated promptly."*
  - Abnormal values are not returned unless "critical"

Conclusions

- Clinical laboratories strive to avoid multiplex platforms for analyses
- Professional standard is to report critical values for non-ordered tests
  - Critical is defined as results indicating imminent danger
- Ethical obligation to respond to critical results

Conclusions

- Genetic/genomic tests
  - No exceptionalism with respect to ethical obligation to respond to critical values
  - Lack of urgency in most genetic results is *not* analogous to other testing domains
  - Potential exceptionalism with respect to the need to conduct further analyses of primary sequence data to identify potentially critical values

Conclusions

- Ethical analyses suggest that investigators do not have an obligation to search for IF's
- Ethical standard is to report critical values that are plainly evident
  - Acceptable to "gate" machines to minimize undesired results
- A new standard suggesting that *additional* genomic analyses should be done to identify actionable results would constitute genetic exceptionalism

Conclusions

- NHANES context
  - Genetic/genomic analyses can be gated or focused to avoid known pathologic variants when not relevant to the research
  - Variants that become plainly evident in the conduct of research that have high clinical validity and utility should be considered for disclosure

Thought Experiment

- A university has collected biospecimens on 50,000 individuals over a 10 year period. The specimens are annotated with clinical information and banked in a coded fashion.
- The informed consent process includes information that unspecified genetic studies will be done with the samples but that no results will be returned.
- An investigator proposes to the IRB a study that will look for new genetic associations with lung cancer but will also assess known variants for breast, ovarian and colon cancer.
- She proposes to return all genetic results to participants