Infectious disease detection using specimen pooling with multiplex assays when risk-factor information is present

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Background

Abstract

High-volume testing of clinical specimens for infectious diseases is performed by laboratories across the world. To make testing loads manageable, laboratories frequently employ the use of group testing (tests performed on pools of specimens) with multiplex assays (multiple-disease tests). In our presentation, we propose incorporating individual risk-factor information, such as exposure history and clinical observations, into this testing process. We show that significant gains in testing efficiency can be obtained in comparison to current testing procedures. Our application focus is on the Aptima Combo 2 Assay that is used by laboratories for chlamydia and gonorrhea testing.

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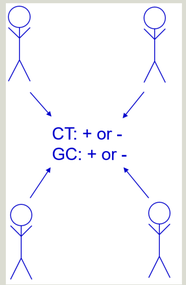
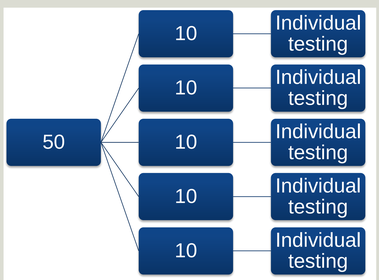
This research was supported by Grant R01 AI121351 from the National Institutes of Health.

What is group testing?

- Used to screen a large number of individuals for infectious diseases
- Example #1: Chlamydia (CT) and gonorrhea (GC) testing with a multiplex assay at the U. of Iowa's State Hygienic Laboratory (SHL)
  - Aptima Combo 2 Assay tests for both CT and GC simultaneously
  - An amalgamation of specimens from 4 individuals is a *group*
  - If a group tests negatively for both diseases, then all individuals within it are declared disease free
  - If a group tests positively for at least one disease:
    - Need to determine who is positive and who is negative for which diseases
    - SHL simply retests all group members individually with the same assay; thus, a 2-stage hierarchical process
  - Estimated savings over individual testing during a recent 5-year evaluation period $\approx$ \$3 million



- Example #2: HIV testing in San Francisco with a single-disease assay and a 3-stage hierarchical process
  - Initial group of 50 individuals
  - If group is positive, test 5 subgroups each of size 10
  - If a subgroup is positive, test its members individually
- Group testing works well in low disease prevalence settings because most groups will test negative for all diseases



Purpose

- Group testing with multiplex assay research
  - Tebbs et al. (*Biometrics*, 2013; 2-stage testing) and Hou et al. (*Biometrics*, 2017; $\geq$3-stage testing) are the only research in the area
  - Assume each individual has same probability of positivity for a particular disease
- Some individuals should be at a higher risk (probability) for being positive than others!
  - *Informative group testing* exploits risk differences to obtain more efficient testing algorithms
  - Past research has focused only on single-disease assays (e.g., Bilder et al. *JASA*, 2010; Lewis et al., *STDs*, 2012; Liu et al., *JAIDS*, 2017)
- Purpose: Develop informative group testing algorithms for multiplex assays

Optimal testing configuration

Notation

- G_{sjk}: Binary test result (1=positive, 0=negative) for kth disease in group j at stage s
- $G_{sjk}^{(t)}$: Ancestor group result for G_{sjk} at stage $t \leq s$, with $G_{sjk}^{(s)} \equiv G_{sjk}$
  - Denotes groups of prior stages that led to the testing of group j in stage s
- S: Number of stages
- c_s: Number of groups in stage s
- m_{sj}: Number of subgroups that group j at stage s is divided into if it tests positively for at least one disease
- $\tilde{Y}_{ik}$: True binary status (1=positive, 0=negative) for individual i and disease k
- $P(\tilde{Y}_{i1} = \tilde{y}_{i1}, \ldots, \tilde{Y}_{iK} = \tilde{y}_{iK}) = p_{i\tilde{y}_{i1}\ldots\tilde{y}_{iK}}$: Joint probability of disease positivity for K diseases
  - For $K = 2$ case, $p_{i00}, p_{i01}, p_{i10}$, and p_{i11}
  - Eventually, these probabilities will be estimated
- HIV testing example: $S = 3$; $c_1 = 1, c_2 = 5, c_3 = 50$; $m_{11} = 5, m_{2j} = 10, m_{3j} = 0$

Testing configuration

- What hierarchical testing configuration will lead to the least number of tests?
  - Group sizes: Initial group size, subgroup sizes
  - Stages: Number of stages
  - Individuals: Which individuals are in what subgroups?
- Choose a configuration that minimizes the expected number of tests per individual
  - Minimize $E(T)/I$ where T is the number of tests for a group of size I
  - Examine all possible testing configurations with individuals ordered by their probabilities of being positive for at least one disease (for $K = 2$: $1 - p_{i00}$) and individuals sequentially assigned to groups of equal or smaller size
  - Resulting configuration is the *optimal testing configuration* (OTC)
- Expected number of tests for $S > 2$ stages:

$$E(T) = 1 + \sum_{s=1}^{S-1} \sum_{j=1}^{c_s} m_{sj} P(G_{sj+}^{(1)} > 0, G_{sj+}^{(2)} > 0 \ldots, G_{sj+}^{(s)} > 0)$$

  where $G_{sj+} = G_{sj1} + \cdots + G_{sjK}$
  - $P(G_{sj+}^{(1)} > 0, G_{sj+}^{(2)} > 0, \ldots, G_{sj+}^{(s)} > 0)$: Depends on joint probabilities of disease positivity, testing configuration, and assay sensitivity and specificity
- Expected number of tests for $S = 2$ stages: $E(T) = \sum_{j=1}^{c_1} m_{1j} P(G_{1j+} > 0)$ for a set of I individuals

Aptima Combo 2 Assay application

Implementation

- Emulate how testing would be performed by using retrospective data; 2-years worth of data from
  - Idaho, 2010 and 2011
  - Iowa, 2013 and 2014
  - Oregon, 2010 and 2011
- Example information available on each individual:
  - Final CT and GC diagnoses
  - Age
  - Personal behavior (e.g., risk history, reason for visit, patient reported symptoms)
  - Clinical observations by medical provider (e.g., urethritis, cervicitis)
- Use earlier year as training data
  - Estimate $p_{i\tilde{y}_{i1}\tilde{y}_{i2}}$ with a multinomial regression model
  - Approximate one OTC using these estimates
- Use later year as test data
  - Estimate $p_{i\tilde{y}_{i1}\tilde{y}_{i2}}$ using training data model
  - Apply approximate OTC obtained from training data
  - Include possibility of testing error using manufacturer reported sensitivity and specificity
  - Treat final CT and GC diagnoses as the "true" statuses
  - Simulate the group and individual responses that could occur while implementing group testing; repeat process 500 times
  - This process is necessary because the true disease statuses are not observable

Results

- Table of results; non-informative column denotes the use of methods from Tebbs et al. (2013) and Hou et al. (2017):

State	Gender	Number of Individuals	Stages	Mean (SD) number of tests: Non-informative	Informative	Reduction
Idaho	Female	4168	2	2211.0 (23.6)	2105.9 (24.9)	4.80%
			3	2029.9 (27.4)	1927.1 (25.4)	5.10%
	Male	2545	2	2014.7 (12.4)	1717.8 (12.5)	14.70%
			3	2103.9 (26.8)	1831.7 (24.8)	12.90%
Iowa	Female	4351	2	2460.7 (22.3)	2459.1 (22.2)	0.10%
			3	2305.2 (29.0)	2350.0 (27.6)	-1.90%
	Male	4358	2	3419.9 (15.2)	3201.6 (16.4)	6.40%
			3	3588.3 (26.6)	3214.6 (18.3)	10.40%
Oregon	Female	8381	2	4408.5 (30.5)	4250.2 (32.4)	3.60%
			3	4000.5 (37.9)	3948.8 (37.6)	1.30%
	Male	6865	2	5478.6 (19.9)	4936.4 (19.2)	9.90%
			3	5574.8 (40.6)	5059.9 (39.0)	9.20%

- Summary
  - Informative group testing leads to a reduced mean number of tests in all but one case
  - Reduction is much more pronounced for males than for females
    - Variability in probabilities of positivity (not shown) is larger for males
  - Accuracy (not shown) is very similar for informative and non-informative