An optimal design for hierarchical
generalized group testing

Yaakov Malinovsky *
Department of Mathematics and Statistics
University of Maryland, Baltimore County, Baltimore, MD 21250, USA

Gregory Haber and Paul S. Albert †
Biostatistics Branch, Division of Cancer Epidemiology and Genetics
National Cancer Institute, Rockville, MD 20850, USA

February 27, 2020

Abstract

Choosing an optimal strategy for hierarchical group testing is an important problem for practitioners who are interested in disease screening with limited resources. For example, when screening for infectious diseases in large populations, it is important to use algorithms that minimize the cost of potentially expensive assays. Black et al. (2015) described this as an intractable problem unless the number of individuals to screen is small. They proposed an approximation to an optimal strategy that is difficult to implement for large population sizes. In this article, we develop an optimal design with respect to the expected total number of tests that can be obtained using a novel dynamic programming algorithm. We show that this algorithm is substantially more efficient than the approach proposed by Black et al. (2015). In addition, we compare the two designs for imperfect tests. R code is provided for the practitioner.

Keywords: Dynamic programming; Disease screening

*Corresponding author
†The work was supported by the National Cancer Institute Intramural Program.
1 Introduction

Screening populations for infectious diseases is important for early detection; an example is screening for human papillomavirus (HPV) infection for the early detection of cervical cancer and its precursors (Nanda et al., 2000; Schiffman and Wentzensen, 2013). In under-resourced countries, individual testing may be expensive and therefore not feasible. The use of group testing where samples are combined in a single test can lead to cost savings. This paper proposes an optimal design for this type of screening.

Group testing for identification when the probability of disease varies across subjects, which has been called the generalized group testing problem (GGTP), is a challenging problem in applied statistics and was first introduced by Sobel (1960). Recently in this journal, Black et al. (2015) introduced an algorithm for the GGTP in a hierarchical class. A procedure is in the hierarchical class if two units are tested together in a group only if they have an identical test history, i.e., if each previous group test contains either both of them or none of them (Sobel and Groll, 1959; Hwang et al., 1981). Additional non-optimal hierarchical algorithms for the GGTP have been developed (Litvak et al., 1994; Bilder et al., 2010; Malinovsky, 2019a).

In this article, we develop an optimal hierarchical algorithm for GGTP that uses dynamic programming (DP) to find an optimal design with respect to the expected total number of tests. R code is available that computes the optimal design and the associated expected total number of tests for a given population size and individual-specific prevalences (https://github.com/habergw/genGT). We show that the proposed approach is substantially more efficient with respect to both the expected total number of tests and computational performance than the approach proposed by Black et al. (2015) (CRC procedure). Our focus is on an optimal hierarchical design for GGTP, where tests are error-free. A full discussion of the impact of using the algorithm with imperfect tests is presented in the Appendix.
2 An optimal Hierarchical Algorithm

We assume without loss of generality that $p_1 \leq p_2 \leq \cdots \leq p_N$ with the corresponding labels $1, \ldots, N$, where $N$ is the size of the population and $p_i$ is the known probability of an infection for each person in the population (as in Black et al. (2015)). We develop an optimal hierarchical algorithm with respect to the ordered values of $p_i$. This imposes the restriction that for any two subgroups, $p_i$ values in one subgroup are all greater than or equal to every $p_i$ value in the other subgroup. The ordering assumption is necessary in order to make the problem tractable since optimizing with respect to all possible permutations of $p_1, \ldots, p_N$ is impossible even for small $N$. Additional discussion regarding the issue of ordering can be found in Malinovsky (2019a) and references therein.

The DP algorithm begins by dividing the population $U = \{1, \ldots, N\}$ of $N$ units into $S$ subsets ($1 \leq S \leq N$) $I_1, \ldots, I_S$. The units in each subset are combined and tested together (stage 1). The $S$ tests in stage 1 are binary tests where $X_{I_i} = 1$, $i = 1, \ldots, S$ if at least one subject in $I_i$ is positive, and $X_{I_i} = 0$ otherwise. For $X_{I_i} = 0$, we conclude that all subjects in $I_i$ are negative; otherwise, $I_i$ proceeds to stage 2. In stage 2, we choose a proper subset $A_i$ from each $I_i$. If $X_{A_i} = 0$, we can infer that $X_{A_i^c} = 1$ without testing $A_i^c$, where $A_i^c = I_i - A_i$ (since $X_{I_i} = 1$). Then we proceed to stage 3 where we will test an appropriate subset of $A_i^c$. If $X_{A_i} = 1$, we proceed to stage 3 where we test appropriate subset of $A_i$ and $A_i^c$ as a whole. We proceed in a similar manner until the status of all units is known. Tests can be performed simultaneously at each stage.

The proposed hierarchical dynamic programming (HDP) algorithm differs from CRC in a number of ways. First, HDP explicitly computes the hierarchical design that minimizes the expected total number of tests. The CRC is not optimal in that sense. Second, CRC requires the implicit specification of the first stage configuration, which is difficult to choose in a principled way. The splitting of groups in subsequent stages for CRC is based on a heuristic search that is not necessarily optimal. In contrast, the HDP algorithm chooses the initial and subsequent groupings in an optimal way. Third, the CRC allows for the specification of the maximum number of stages, up to 4. In comparison, the HDP does not allow for the specification of the maximum number of stages apriori. Last, as we will show in Section 4, CRC is substantially more computationally expensive than HDP.
For the HDP algorithm, the optimal configuration is found through dynamic programming that uses backward induction (Bellman, 1957; Lindley, 1961). We use a heuristic argument to explain the algorithm to practitioners (the Appendix provides technical details). First, we explicitly find an optimal design for two subjects with corresponding probabilities \( p_{N-1} \leq p_N \). Then we find an optimal design for three subjects \( (p_{N-2} \leq p_{N-1} \leq p_N) \) using the optimal design previously found for two subjects. We proceed in this fashion through the entire population.

Although we delegate the technical details to an Appendix [A], we need to introduce notation in order for the practitioner to apply the algorithm. Let \( B_{n:N} = \{n, \ldots, N\} \) (Binomial set) denote the set of units with labels \( n, n+1, \ldots, N \) and corresponding probabilities \( p_n, \ldots, p_N \). By \( H(n : N) \), we denote the expected number of tests under an optimal HDP algorithm applied to the set \( B_{n:N} \). The backward induction process starts with \( H(N : N) = 1 \), and \( H(n : N) \) is determined recursively for \( n = N - 1, N - 2, \ldots, 1 \). In the process of testing, some groups will be identified as positive. Therefore, we introduce additional notation for the expected total number of tests under an optimal HDP algorithm conditional on the information that there is at least one infected individual in the group. Let \( D_{n:n_1} = \{n, \ldots, n_1\} \) (Defective set) denote the set of such units with labels \( n, \ldots, n_1 \). We denote by \( h(n : n_1) \) the expected total number of tests under an optimal HDP algorithm applied to the set \( D_{n:n_1} \), where \( h(n : n) = 0, \ n = 1, \ldots, N \). Let
\[ \Pi(a : b) = q_a q_{a+1} \cdots q_b, \quad q_i = 1 - p_i. \] The HDP algorithm is shown below.

**Algorithm:** An optimal HDP algorithm: design and the value of \( H(1 : N) \)

**Input**

\[ p_1 \leq p_2 \leq \cdots \leq p_N \]

**Initial Values:**

\[ H(N + 1 : N) = 0, \quad H(N : N) = 1, \quad h(n : n) = 0 \text{ for } n = 1, \ldots, N \]

1. for \( n := N-1 \) to 1 step 1 do
2.   for \( k := 1 \) to \( N-(n-1) \) step 1 do
3.     while \( k > 1 \) do
4.       for \( x = 1 \) to \( k-1 \) step 1 do
5.         \[ T(n, k, x) = 2 - \frac{\Pi(n:n+x+(k-1))}{1-\Pi(n:n+(k-1))} + \frac{1-\Pi(n:n+(x-1))}{1-\Pi(n:n+(k-1))} h(n : n + (x - 1)) \]
6.         \[ h(n : n + (k - 1)) = \min_{1 \leq x \leq k-1} T(n, k, x) \quad \text{// optimal expected value.} \]
7.       end
8.     end
9.   end
10. \[ k^*(n : n + (k - 1)) = \arg\min_{1 \leq x \leq k-1} T(n, k, x) \quad \text{// From the Defective set \{n, \ldots, n + (k - 1)\} is optimal to test first \( k^* \) items.} \]
11. \[ T_k(n : N) = 1 + \{H(n + k : N) + (1 - \Pi(n : n + (k - 1))) h(n : n + (k - 1))\} \]
12. \[ \quad \text{// the expected total number of test for the binomial set \( B_{n:N} \) if we first test \( k \) units.} \]
13. end
14. \[ H(n : N) = 1 + \min_{1 \leq k \leq N-(n-1)} \{T_k(n : N)\} \quad \text{// optimal expected value.} \]
15. See A.1 for developments.
16. \[ k^{**}(n : N) = \arg\min_{1 \leq k \leq N-(n-1)} \{T_k(n : N)\} \quad \text{// From the Binomial set \{n, \ldots, N\} is optimal to test first \( k^{**} \) items.} \]
3 Demonstration of the HDP Algorithm

We begin by demonstrating the HDP algorithm for two subjects \(a\) and \(b\), where \(q_a \geq q_b\) and \(q_i = 1 - p_i, \ i = a, b\). Denote by \(T\) the total number of tests. The left branch of the tree represents the negative test result, and the right branch represents the positive test result.

Algorithm \(A_{a,b}\)

![Algorithm Diagram]

Using algorithm \(A_{a,b}\), we show the implementation of the DP algorithm with probability vector \(p = (0.05, 0.07, 0.09, 0.11, 0.13, 0.15, 0.17, 0.19, 0.21, 0.23, 0.25)\) with corresponding labels set \(\{1, 2, \ldots, 11\}\). Through backward induction, the optimal configuration of the initial stage is \(I_1 = \{1, 2, 3, 4, 5, 6\}, I_2 = \{7, 8, 9\}, I_3 = \{10, 11\}\). Subsequent testing is done separately in each of the three groups based on the HDP algorithm. We present below three testing trees corresponding to the optimal initial configuration of three subgroups \(I_1, I_2, I_3\). Recall that the left branch of the tree represents the negative test result and the right branch represents the positive test result.

**Subgroup** \(I_1 = \{1, 2, 3, 4, 5, 6\}\):
test \{1, 2, 3, 4, 5, 6\}

\begin{itemize}
  \item Stop
  \item test \{1, 2, 3\}
\end{itemize}

\begin{itemize}
  \item test \{4\}
  \item test \{1\} and follow A
\end{itemize}

\begin{itemize}
  \item test \{5\}
  \item test \{5, 6\}: algorithm \(A_{5,6}\)
  \item test \{2\}
  \item test \{2, 3\}: algorithm \(A_{2,3}\)
\end{itemize}

\begin{itemize}
  \item Stop
  \item test \{6\}
\end{itemize}

\begin{itemize}
  \item Stop
  \item test \{3\}
\end{itemize}

\textbf{A:} test \{4, 5, 6\}

\begin{itemize}
  \item Stop
  \item test \{4\}
\end{itemize}

\begin{itemize}
  \item test \{5\}
  \item test \{5, 6\}: algorithm \(A_{5,6}\)
\end{itemize}

\begin{itemize}
  \item Stop
  \item test \{6\}
\end{itemize}

\textbf{subgroup} \(I_2 = \{7, 8, 9\}\):

\begin{itemize}
  \item test \{7, 8, 9\}
\end{itemize}

\begin{itemize}
  \item Stop
  \item test \{7\}
\end{itemize}

\begin{itemize}
  \item test \{8\}
  \item test \{8, 9\}: algorithm \(A_{8,9}\)
\end{itemize}

\begin{itemize}
  \item Stop
  \item test \{9\}
\end{itemize}
subgroup $I_3 = \{10, 11\}$:

test $\{10, 11\}$: algorithm $A_{10, 11}$.

The expected number of tests under this optimal HDP design is 6.820.

4 Numerical comparisons with Black et al. (2015) and common used algorithms

We compare the performance of the HDP algorithm with that of the CRC method proposed by Black et al. (2015). CRC requires the specification of the maximum number of stages therefore, we used either three or four stages, depending on $N$. We also compare the performance of HDP and CRC with those of two commonly used hierarchical algorithms: a Dorfman-type (Dorfman 1943) algorithm and a sequential algorithm proposed by Sterrett (1957). We abbreviate these algorithms as procedures $D'$ and $S$, respectively. In the GGTP setting, the optimum ordered configuration for both algorithms was characterized by Malinovsky (2019a). For the CRC, we obtained the expected total number of tests using R functions provided by Black et al. (2015). The comparisons are done in the following manner. We generate the vector $p_1, p_2, \ldots, p_N$ from a Beta distribution with parameters $\alpha = 1, \beta > 0$ such that $1 - p = \beta$, i.e., expectation equal to $p$ and repeat this process 1000 times for each value of $p$. In the following table, we present the mean and standard deviation of the mean (1000 simulated realizations of $p_1, \ldots, p_N$) of the expected total number of tests for $D'$, $S$, HDP, and CRC for population sizes of 20 and 100. In addition, we present the lower bound (Shannon entropy $H(p)$) of the optimal group testing algorithm among the general class (see discussion and references in Malinovsky (2019a)). For $N = 20$, we performed CRC with four stages since the performance of the algorithm was better than that with three stages in this case. For $N = 100$, we performed CRC with three stages since we were not able to execute the CRC with four stages even with single realization, while HDP requires less than 1 second (Lenovo X1 Carbon, Intel Core i5-7200U 7th Gen, 2.50HGz, 8GB Ram). The running time for the CRC algorithm with four stages is increasing exponentially with $N$. For a particular implementation, $p = 0.01$, the computational time was 0.85 and 3195 seconds for $N = 10$ and $N = 60$, respectively.
computational time increased by a factor of about 5 for each increase in \( N \) of 10.

Table 1 shows that particularly for large \( N \), HDP is substantially more efficient (expected number of tests) than CRC. Furthermore, the HDP algorithm is efficient relative to the unattainable lower bound \( H(p) \) for all but very small \( p \). Interestingly, both of the standard procedures \( D' \) and \( S \) outperform CRC when \( p \geq 0.05 \) and \( N = 100 \), and procedure \( S \) outperforms CRC when \( N = 20 \) for \( p \geq 0.05 \). Additionally, for \( p \geq 0.20 \) the expected total number of tests for CRC is greater than 100, showing that individual testing is more efficient than CRC in this case.

| \( p \) | \( D' \) | \( S \) | \( HDP \) | \( CRC \) | \( R \) | \( H(p) \) |
|-------|--------|--------|--------|--------|------|--------|
| 0.001 | 1.390 (0.003) | 1.178 (0.001) | 1.108 (0.001) | 1.146 (0.001) | 0.967 | 0.215 (0.001) |
| 0.010 | 3.624 (0.012) | 2.701 (0.012) | 2.052 (0.008) | 2.397 (0.010) | 0.856 | 1.488 (0.009) |
| 0.050 | 7.523 (0.024) | 6.357 (0.024) | 5.663 (0.026) | 6.871 (0.032) | 0.824 | 5.123 (0.025) |
| 0.100 | 10.147 (0.031) | 9.126 (0.033) | 8.656 (0.036) | 10.512 (0.042) | 0.823 | 8.088 (0.035) |
| 0.200 | 13.479 (0.035) | 12.784 (0.039) | 12.510 (0.041) | 14.715 (0.044) | 0.850 | 11.937 (0.041) |
| 0.300 | 15.580 (0.034) | 15.120 (0.037) | 14.932 (0.040) | 17.728 (0.069) | 0.842 | 14.082 (0.039) |

| \( p \) | \( D' \) | \( S \) | \( HDP \) | \( CRC \) | \( R \) | \( H(p) \) |
|-------|--------|--------|--------|--------|------|--------|
| 0.001 | 5.727 (0.009) | 3.737 (0.006) | 1.864 (0.003) | 2.740 (0.005) | 0.680 | 1.078 (0.003) |
| 0.010 | 17.297 (0.027) | 13.080 (0.023) | 8.788 (0.021) | 14.923 (0.034) | 0.589 | 7.437 (0.019) |
| 0.050 | 37.086 (0.055) | 31.793 (0.055) | 28.283 (0.059) | 39.021 (0.060) | 0.725 | 25.647 (0.057) |
| 0.100 | 50.733 (0.071) | 46.080 (0.075) | 43.714 (0.081) | 99.885 (0.235) | 0.438 | 40.835 (0.080) |
| 0.200 | 67.430 (0.080) | 64.209 (0.087) | 62.935 (0.092) | 101.000 (0.000) | 0.623 | 59.978 (0.092) |
| 0.300 | 77.665 (0.076) | 75.433 (0.083) | 74.662 (0.087) | 101.000 (0.000) | 0.739 | 70.383 (0.086) |

Table 1: The mean (standard deviation of the mean) (based on 1000 simulated realizations of \( p_1, \ldots, p_N \)) of the expected total number of tests for procedures \( D' \), \( S \), \( HDP \), and \( CRC \). The ratio \( R \) of the expectation of \( HDP \) to \( CRC \) and the lower bound \( H(p) \) is also presented.

The same numerical comparisons under a non-differential misclassification assumption
are presented in Appendix C with corresponding technical details in Appendix B.

5 Screening analysis for oral HPV

We evaluate different designs for oral HPV screening using the NHANES cohort from 2011-2012. The publicly available NHANES data contain screening information on 37 HPV subtypes for men and women ages 18-69 (the full list is available at https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/ORHPV_G.htm, where HPV is defined as being positive on any subtype. Table 2 shows individual characteristics for participant in this cohort, including 8.1% overall HPV prevalence.

We develop a prediction model using individual-specific characteristics that are known to affect HPV prevalence in order to choose the design configuration \( p_i \)’s. A logistic regression model was fit to an earlier NHANES cohort (2009-2011) with covariates chosen based on the findings of Gillison et al. (2012) and included gender, age, ethnicity, smoking status, and the lifetime number of sexual partners.

Figure 1 shows the initial group size distribution as determined by the HDP algorithm. The group sizes range from 1 to 89, with a total of 442 groups among 3883 individuals. We use this initial group configuration for the CRC algorithm, since this method requires that initial group sizes be specified, and no guidance for large \( N \) is provided (Black et al., 2015).
| Variable          | Count (Percentage) |
|-------------------|--------------------|
| N                 | 3883               |
| Gender            |                    |
| Female            | 1886 (48.6%)       |
| Male              | 1997 (51.4%)       |
| Age (mean (se))   | 42.10 (15.25)      |
| Ethnicity         |                    |
| African American  | 1101 (28.4%)       |
| Caucasian         | 1333 (34.3%)       |
| Mexican American  | 413 (10.6%)        |
| Other             | 635 (16.4%)        |
| Other Hispanic    | 401 (10.3%)        |
| Smoker            |                    |
| Current (< 10/day)| 574 (14.8%)        |
| Current (> 10/day, ≤ 20/day) | 238 (6.1%) |
| Current (> 20/day)| 74 (1.9%)          |
| Never/Former      | 2997 (77.2%)       |
| Lifetime Partners |                    |
| 1                 | 519 (13.4%)        |
| 11-20             | 555 (14.3%)        |
| 2-5               | 1204 (31.0%)       |
| 6-10              | 793 (20.4%)        |
| > 20              | 545 (14.0%)        |
| None              | 267 (6.9%)         |
| HPV Positive      | 315 (8.1%)         |

Table 2: Basic summary of the prediction model variables for the 2011-2012 NHANES cohort, which is used for illustration.
Figure 1: Initial group sizes as determined by the HDP algorithm.

We compare the total number of tests required to screen the population using the HDP and CRC algorithms in Table 3. We used a 3-stage CRC algorithm since a 4-stage algorithm is not computationally feasible with this population size and first-stage configuration (Figure 1). The HDP algorithm shows a 16% (1-1588/1894) efficiency gain relative to the CRC procedure. In addition, we executed the CRC procedure with three stages (CRC*(3S)) and four stages (CRC*(4S)) by grouping all subjects into groups of size 20 as done by Black et al. (2015). This latter first-stage configuration for the CRC procedure is less efficient than using the HDP initial configuration (i.e., CRC has a smaller number of tests than CRC*(3S) and CRC*(4S)).
| Number of Tests |
|-----------------|
| HDP            | 1588 |
| CRC            | 1894 |
| CRC*(3S)       | 2011 |
| CRC*(4S)       | 1907 |

Table 3: Comparison of HDP with CRC. CRC uses the same initial configuration as HDP with a maximum of three stages. The initial configuration for three stages (CRC*(3S)) and four stages (CRC*(4S)) was found by grouping all subjects into groups of size 20.

An analysis that compares the HDP and CRC designs for oral HPV under non-differential misclassification is presented in Appendix C.

6 Discussion

This article presents an optimal design strategy (HDP) for hierarchical generalized group testing. We compared the performance of the HDP and CRC approaches, and showed a marked improvement in the efficiency of HDP. As compared with CRC, the HDP is substantially more efficient in terms of both the expected total number of tests and computational feasibility. In fact, in our experience, the CRC could not be executed in population sizes larger than 100 with prevalences that are not extremely small ($p_i$'s $\geq 0.01$).

The maximum number of stages in the HDP algorithm can be determined based on a function of the individual prevalences. Therefore, the maximum number of stages can be determined before beginning the screening protocol since the individual prevalences will be specified. However, if we want to limit the maximum number of stages (without respect to population size and individual prevalences), deriving the optimal design subject to an arbitrary maximum number of stages is a very difficult optimization problem. If the practitioner needs to restrict the maximum number of stages to a value $k$ that is less than the one corresponding to an optimal design, she/he can use the design specified by the first $k - 1$ stages of an optimal design followed by individual testing in the last stage.

There are practical considerations that need to be addressed in designing screening
studies using group testing. Large scale screening programs may be implemented across large geographical areas. In these situations, there may be a choice between implementing the algorithm across the entire population or within smaller geographic areas. The former design would be more efficient. However, practical considerations (e.g., combining samples from different geographic regions may be logistically difficult) may make implementing the algorithm within regions more advantageous.

We examined the performance of all of the discussed algorithms for the case of imperfect tests under the non-differential misclassification assumption in Appendices B and C. However, we recognize that the optimality criterion of minimizing the expected number of tests is problematic since the classification ability needs to be considered. To be specific, group testing for screening under misclassification should consider an objective function that factors in the overall sensitivity and specificity in addition to the expected total number of tests (Graff and Roeloffs, 1972; Hwang, 1976; Malinovsky et al., 2016). Future research should focus on the optimal design of hierarchical generalized group testing with erroneous tests that incorporates misclassification into the design criterion.

Acknowledgments

The authors thank the editors, the associate editor and the referees for their thoughtful and constructive comments and suggestions.

Appendices

Appendix A Development of an optimal HDP algorithm for GGTP

Appendix B Hierarchical Algorithm to minimize Expected number of Tests in the presence of non-differential misclassification

Appendix C Design considerations with imperfect tests
Appendix

A Development of an optimal HDP algorithm for GGTP

We show here the development of an optimal HDP for GGTP. As we already discussed in Section 2, we impose an order restriction $p_1 \leq p_2 \leq \cdots \leq p_N$. In the homogeneous case, i.e., $p_1 = p_2 = \ldots = p_N = p$ an optimal hierarchical DP algorithm was obtained by Sobel and Groll (1959) and recently rediscovered and computationally improved by Zimmerman (2017) (see also Malinovsky (2019b) for the discussion).

A.1 Evaluation of $H(n : N)$

Recall that we are dealing with the binomial set $B_{n;N}$. We begin with the case $n = N$. In this case $H(N : N) = 1$. For subsequent evaluation, when $n \leq N - 1$, we have to find the size of $k$ of the subset $B_{n:n+k-1}$ from $B_{n;N}$ to test. If the test outcome of $B_{n:n+k-1}$ is negative, then we test the remaining units $n + k, \ldots, N$ that form a binomial set $B_{n+k;N}$. Otherwise, if the test outcome of $B_{n:n+k-1}$ is positive, then its units form the defective set of size $k$, which we abbreviate as $D_{n:n+k-1}$, and remaining units from $B_{n;N}$ form the binomial set $B_{n+k;N}$. We summarize these situations in the following binary testing tree. Recall that, the left branch of the tree represents a negative test result, and the right branch represents a positive test result.

\[
\text{test } B_{n:n+k-1} (\subseteq B_{n;N})
\]

\[
B_{n+k;N} \text{ with prob. } q_n \cdots q_{n+k-1} \quad D_{n:n+k-1} \cup B_{n+k;N} \text{ with prob. } 1 - q_n \cdots q_{n+k-1}
\]

Denote by $T_k(n : N)$ the expected total number of tests. Then,

\[
T_k(n : N) = 1 + \{q_n \cdots q_{n+k-1} H(n + k : N) + (1 - q_n \cdots q_{n+k-1}) [h(n : n + (k - 1)) + H(n + k : N)]\}
\]

\[
= 1 + \{H(n + k : N) + (1 - \Pi (n : n + k - 1)) h(n : n + (k - 1))\}, \quad (1)
\]
where \( \Pi (n : n + k - 1) = q_n \cdots q_{n+k-1} \).

Since the optimal value \( H(n : N) \) is obtained by choosing the best \( k \) among \( k = 1, \ldots, N - (n - 1) \), we have

\[
H(n : N) = \min_{1 \leq k \leq N - (n - 1)} T_k(n : N), \ n = N - 1, \ldots, 1. \tag{2}
\]

Then \( H(n : N) \) is calculated in a recursive manner for \( n = N - 1, \ldots, 1 \). This calculation required the conditional expectation \( h() \), which is developed as follow.

### A.2 Evaluation of \( h(n : n + (l - 1)) \)

Recall that we are dealing with the defective set \( D_{n:n+(l-1)} \). If \( l = 1 \), then \( h(n : n+(l-1)) = h(n : n) = 0 \). If \( l \geq 2 \), we have to find a proper subset \( \{n : n + x - 1\} \) of size \( x \) from \( D_{n:n+(l-1)} \) to test. If the binary test outcome of \( \{n : n + x - 1\} \) is negative, then we conclude that the remaining units \( n + x, \ldots, n + (l - 1) \) form a defective set \( D_{n+x:n+(l-1)} \), which does not need to be tested as a whole set. If the test outcome of \( \{n : n + x - 1\} \) is positive, then the conditional posterior distribution of units \( n + x, \ldots, n + (l - 1) \) is the same as it was before any testing and they form a binomial set \( B_{n+x:n+(l-1)} \) (similar arguments as in Sobel and Groll (1959)). Therefore, we divide the defective set \( D_{n:n+(l-1)} \) into two subsets \( \{n, n + 1, \ldots, n + (x - 1)\} \) and \( \{n + x, \ldots, n + (l - 1)\} \) and test them separately from left to right. We have three possible states of these subsets, i.e., \(-+, +-+, ++\), where, for example, \(++\) represent the situation where both subsets are positive. Denote by \( T_{ab} \) the expected total number of tests corresponding to the situation \( ab \), \( ab \in \{-+, +++, ++\} \). The following diagram represents all these possible outcomes with corresponding conditional (on the event that there is at least one defective element) probabilities.
Figure 2: Possible outcomes with corresponding conditional (on the event that there is at least one defective element) probabilities.

Denote by \( T(n,l,x) \) the expected total number of tests in this case. Then,

\[
T(n,l,x) = \left[ 1 + h(n + x : n + (l - 1)) \right] \frac{\Pi(n : n + (x - 1)) (1 - \Pi(n + x : n + (l - 1)))}{1 - \Pi(n : n + (l - 1))} \\
+ \left[ 2 + h(n : n + (x - 1)) + h(n + x : n + (l - 1)) \right] \frac{(1 - \Pi(n : n + (x - 1))) (1 - \Pi(n + x : n + (l - 1)))}{1 - \Pi(n : n + (l - 1))} \\
+ \left[ 2 + h(n : n + (x - 1)) + h(n + x : n + (l - 1)) \right] \frac{(1 - \Pi(n : n + (x - 1))) (1 - \Pi(n + x : n + (l - 1)))}{1 - \Pi(n : n + (l - 1))} \\
= \frac{1 - \Pi(n : n + (x - 1)) (1 - \Pi(n + x : n + (l - 1)))}{1 - \Pi(n : n + (l - 1))} + \frac{1 - \Pi(n : n + (x - 1))}{1 - \Pi(n : n + (l - 1))} h(n : n + (x - 1)) \\
+ \frac{1 - \Pi(n + x : n + (l - 1))}{1 - \Pi(n : n + (l - 1))} h(n + x : n + (l - 1)).
\]

Since an optimal value \( h(n : n + (l - 1)) \) is obtained by choosing the best \( x \), among \( x = 1, \ldots, l - 1 \) we have,

\[
h(n : n + (l - 1)) = \min_{1 \leq x \leq l - 1} T(n,l,x).
\]

Combining [2] and [3], we obtain an optimal ordered HDP algorithm:
\[ H(N + 1 : N) = 0, \quad H(N : N) = 1, \quad h(n : n) = 0, \quad n = 1, \ldots, N \quad (4) \]

\[ H(n : N) = 1 + \min_{1 \leq k \leq N - (n-1)} \{ H(n + k : N) + (1 - \Pi (n : n + (k - 1))) h(n : n + (k - 1)) \}, \]

\[ h(n : n + (l - 1)) = 2 + \min_{1 \leq x \leq l-1} \left\{ \frac{-\Pi (n : n + (x - 1)) (1 - \Pi (n + x : n + (l - 1)))}{1 - \Pi (n : n + (l - 1))} \right\} \cdot \frac{1 - \Pi (n : n + (x - 1)) h(n : n + (x - 1))}{1 - \Pi (n : n + (l - 1))}, \]

\[ n = N - 1, N - 2, \ldots, 1; \]

\[ l = 2, \ldots, N - n + 1, \]

where \( \Pi (a : b) = q_a q_{a+1} \cdots q_b \).

### B Hierarchical algorithm to minimize expected number of tests in the presence of non-differential misclassification

In this section we extend the algorithm presented in Appendix A to the case where tests are subject to the non-differential misclassification. It can be done in a straightforward manner by re-calculating \( H(n : N) \) and \( h(n : n + (l - 1)) \) from Appendix A.

#### B.1 Evaluation of \( H_M(n : N) \)

\[ T_{k,M}(n : N) = 1 + \{ H_M(n + k : N) + (1 - \Pi_M (n : n + k - 1)) h_M(n : n + (k - 1)) \}, \quad (5) \]

where \( \Pi_M (n : n + k - 1) = S_p \Pi (n : n + k - 1) + (1 - S_v) (1 - \Pi (n : n + k - 1)), \)

\[ \Pi (n : n + k - 1) = q_n \cdots q_{n+k-1}. \]

\[ H_M(n : N) = \min_{1 \leq k \leq N - (n-1)} T_{k,M}(n : N), \quad n = N - 1, \ldots, 1. \quad (6) \]

#### B.2 Evaluation of \( h_M(n : n + (l - 1)) \)

Given that the test outcome of the items \( n : n + l - 1 \) is positive, we have to calculate the below probabilities, which correspond to all possible situations.
\[ P_- = P(\text{test outcome of } n + x - 1 \text{ is negative} \mid \text{test outcome of } n + l - 1 \text{ is positive}) \]
\[ = \frac{S_e(1 - S_e) + \Pi_a (S_p S_e - S_e(1 - S_e)) + \Pi_{ab} (S_p - S_e^2 - S_p S_e)}{1 - \Pi_M (n : n + l - 1)} \]

\[ P_{+-} = P(\text{test outcome of } n + x - 1 \text{ is +} \cap n + x : n + l - 1 \text{ is -} \mid \text{test outcome of } n + l - 1 \text{ is +}) \]
\[ = \frac{S_e^2(1 - S_e) + \Pi_a (S_e(1 - S_e)(1 - S_p - S_e)) + \Pi_b (S_e^2 S_p + S_e - 1))}{1 - \Pi_M (n : n + l - 1)} \]
\[ + \frac{\Pi_{ab} (S_e(1 - S_e)(S_e + S_p - 1) + S_p(1 - S_p)^2 - S_e^2 S_p)}{1 - \Pi_M (n : n + l - 1)} \]

\[ P_{++} = P(\text{test outcome of } n + x - 1 \text{ is +} \cap n + x : n + l - 1 \text{ is +} \mid \text{test outcome of } n + l - 1 \text{ is +}) \]
\[ = \frac{S_e^3 + \Pi_a (S_e^2(1 - S_p - S_e)) + \Pi_b (S_e^2(1 - S_p - S_e))}{1 - \Pi_M (n : n + l - 1)} \]
\[ + \frac{\Pi_{ab} ((1 - S_p)^3 - 2S_e^2(1 - S_p) + S_e^3)}{1 - \Pi_M (n : n + l - 1)} \]

We summarize the above probabilities with the corresponding total number of the tests in Figure 3 below.

Figure 3: Possible outcomes with corresponding conditional (on the event that test outcome of the items \( \{n, \ldots, n + l - 1\} \) is positive) probabilities.

\[ P_- + P_{+-} + P_{++} = 1 \]

where \( \Pi_a = \Pi (n : n + x - 1), \Pi_b = \Pi (n + x : n + l - 1), \Pi_{ab} = \Pi (n : n + l - 1) \). We have \( P_- + P_{+-} + P_{++} = 1 \) and

\[ T_M(n, l, x) = T_- \times P_- + T_{+-} \times P_{+-} + T_{++} \times P_{++} \]
Remark 1 \((h_M)\). Probabilities \(P_-, P_+, P_{++}\) were calculated by conditioning on the true status of subsets \(n : n + x - 1\) and \(n + x : n + l - 1\), i.e., on 4 possibilities. Given that the test outcome of the set \(n : n + l - 1\) of size \(l\) is positive we proceed in the following way:

- if the test outcome of its proper subset \(n : n + x - 1\) of size \(x\) is negative, then we do not test the remainder subset \(n + x : n + l - 1\) and conclude that it is positive. Therefore, the left branch of the tree has \(T_- = 1 + h_M(n + x : n + (l - 1))\) number of tests.

- otherwise, if the test outcome of its proper subset \(n : n + x - 1\) of size \(x\) is positive, then we test the remainder subset \(n + x : n + l - 1\) of size \(l - x\) and
  
  - if its test outcome is negative, then we have \(T_{+-} = 2 + h_M(n : n + (x - 1))\) tests to perform.
  
  - otherwise, if its test outcome is positive, then we have \(T_{++} = 2 + h_M(n : n + (x - 1)) + h_M(n + x : n + (l - 1))\) tests to perform.

\[
h_M(n : n + (l - 1)) = \min_{1 \leq x \leq l-1} T_M(n, l, x). \tag{8}
\]

B.3 An optimal HDP algorithm with respect to the expected total number of tests

In the Algorithm (Section 2), change \(T(n, k, x)\) into \(T_M(n, k, x)\) from (7). This will allow calculation of \(h_M(n : n + (l - 1))\) in (8), which will replace \(h(n : n + (l - 1))\) in the Algorithm (Section 2). Then in the Algorithm (Section 2), change \(T_k(n : N)\) into \(T_{k,M}(n : N)\) (equation (5)). This will allow calculation of \(H_M(n : N)\) in (6), which will replace \(H(n : N)\) in the Algorithm (Section 2).

C Design considerations with imperfect tests

Black et al. (2015) incorporated non-differential misclassification (not dependent on prevalence or group sizes) for the CRC design and used the expected total number of tests as a
design criterion. In a similar setting, we found the HDP design that minimizes the expected total number of tests (Appendix B).

We compare HDP and CRC in the setting where tests are subject to misclassification. We follow Black et al. (2015) and assume that test sensitivity (Se) and specificity (Sp) are known. The comparison was done by executing the design (Appendix B), formulating the groups, and then misclassifying either the group or individual tests with sensitivity Se and specificity Sp. Table 4 shows the comparison of CRC and HDP with respect to the expected total number of tests and overall sensitivity (SE) and specificity (SP) for the two population sizes considered in Table 1 (N=20 and 100). The HDP algorithm was more efficient than CRC among all choices of \( p \) and for both population sizes. The increased efficiency was particularly notable for N=100 for all but \( p = 0.05 \), where HDP has an expected number of tests that is less than half of those with CRC. That said, the sensitivity for HDP is substantially lower than that for CRC in the case of the larger population size. The reason is that in order to minimize the expected total number of tests under misclassification, the HDP algorithm tends to form groups that are as large as possible, thus creating very low overall sensitivity. This illustrates the danger in using the expected number of tests as an optimality criterion when tests are imperfect (Graff and Roeloffs, 1972; Malinovsky et al., 2016).

To avoid the large group sizes for the HDP algorithm that accounts for misclassification, we used the design computed with DP assuming no misclassification. We subsequently evaluated this design under misclassification (HDP*). Generally, this approach showed a smaller expected total number of tests with similar overall sensitivity and specificity as compared with CRC.

In Section 5, we evaluated designs for oral HPV under the assumption that tests are error-free. We now consider screening designs assuming non-differential misclassification with both sensitivity and specificity equal to 0.95 (Hyun et al., 2018). This was done by executing the design, formulating the groups, and then misclassifying either the group or individual tests with sensitivity and specificity of 0.95. Table 5 shows the total number of tests as well as overall sensitivity and specificity for the CRC and HDP algorithms. The HDP algorithm is much more efficient than CRC with respect to the expected total
### Table 4

The mean (standard deviation of the mean) (based on 1000 simulated realizations of $p_1, \ldots, p_N$) of the expected total number of tests $E(T)$, overall sensitivity (SE), and overall specificity (SP), for the CRC and HDP algorithms. Test sensitivity (Se) and specificity (Sp) are set at 0.95 each.

| $p$  | Method | $N = 20$ |   | $N = 100$ |   |
|------|--------|---------|----|---------|----|
|      | E(T)   | SE      | SP | E(T)    | SE | SP |
| 0.001| CRC    | 1.2570  | 0.8169 (0.0001) | 0.9999 (0.0000) | 3.6008 (0.0062) | 0.8574 (0.0000) | 0.9992 (0.0000) |
|      | HDP    | 1.1124  | 0.7616 (0.0012) | 0.9971 (0.0000) | 1.5524 (0.0019) | 0.4797 (0.0018) | 0.9986 (0.0000) |
|      | HDP*   | 1.2913  | 0.8738 (0.0008) | 0.9973 (0.0000) | 2.1916 (0.0030) | 0.8298 (0.0004) | 0.9992 (0.0000) |
| 0.010| CRC    | 2.4794  | 0.8227 (0.0003) | 0.9989 (0.0000) | 16.8756 (0.0358) | 0.8574 (0.0000) | 0.9956 (0.0000) |
|      | HDP    | 1.9053  | 0.7969 (0.0007) | 0.9947 (0.0000) | 7.6063 (0.0207) | 0.7372 (0.0003) | 0.9958 (0.0000) |
|      | HDP*   | 2.2004  | 0.8709 (0.0003) | 0.9956 (0.0000) | 9.0722 (0.0248) | 0.8258 (0.0004) | 0.9966 (0.0000) |
| 0.050| CRC    | 6.7019  | 0.8370 (0.0003) | 0.9952 (0.0000) | 39.7957 (0.0549) | 0.8579 (0.0000) | 0.9901 (0.0000) |
|      | HDP    | 5.3465  | 0.8406 (0.0003) | 0.9890 (0.0000) | 26.2597 (0.0487) | 0.6779 (0.0012) | 0.9900 (0.0000) |
|      | HDP*   | 5.6745  | 0.8726 (0.0004) | 0.9893 (0.0001) | 28.5490 (0.0601) | 0.8736 (0.0001) | 0.9893 (0.0000) |
| 0.100| CRC    | 10.2127 | 0.8499 (0.0003) | 0.9908 (0.0001) | 86.9833 (0.4329) | 0.8594 (0.0000) | 0.9590 (0.0003) |
|      | HDP    | 8.4694  | 0.8757 (0.0004) | 0.9836 (0.0001) | 33.6802 (0.0222) | 0.4458 (0.0009) | 0.9869 (0.0000) |
|      | HDP*   | 8.7259  | 0.8949 (0.0003) | 0.9835 (0.0001) | 43.8472 (0.0766) | 0.8953 (0.0001) | 0.9835 (0.0000) |
| 0.200| CRC    | 14.1723 | 0.8684 (0.0003) | 0.9833 (0.0001) | 92.2475 (0.0000) | 0.8590 (0.0000) | 0.9549 (0.0000) |
|      | HDP    | 12.3358 | 0.9113 (0.0003) | 0.9762 (0.0001) | 36.3820 (0.0082) | 0.3685 (0.0005) | 0.9873 (0.0000) |
|      | HDP*   | 12.5043 | 0.9194 (0.0002) | 0.9758 (0.0001) | 62.8737 (0.0923) | 0.9198 (0.0001) | 0.9758 (0.0000) |
| 0.300| CRC    | 16.5500 | 0.8585 (0.0003) | 0.9772 (0.0001) | 92.2475 (0.0000) | 0.8587 (0.0000) | 0.9549 (0.0000) |
|      | HDP    | 14.7381 | 0.9276 (0.0002) | 0.9710 (0.0001) | 37.0501 (0.0046) | 0.3401 (0.0004) | 0.9892 (0.0000) |
|      | HDP*   | 14.8583 | 0.9324 (0.0002) | 0.9706 (0.0001) | 74.4149 (0.0874) | 0.9329 (0.0001) | 0.9708 (0.0000) |
number of tests but has very low overall sensitivity. As explained above, this is due to the tendency to form large groups in order to minimize the total number of tests. This very small number of tests and low sensitivity demonstrate the danger of simply using the total number of tests as a design criterion under misclassification. As recommended earlier, we used the HDP algorithm without misclassification for design purposes (HDP*). The HDP* algorithm results in a larger total number of tests than HDP, but with reasonable overall sensitivity. In fact, this design resulted in a smaller number of tests than using CRC (14% reduction), but with similar overall sensitivity and specificity. In addition, we follow Black et al. (2015) (Section 5, data example) and execute the CRC algorithm with a maximum of three stages (CRC* (3S)) and four stages (CRC* (4S)) by grouping all subjects into groups of size 20 in the first stage. In this case, CRC* (3S) has a similar overall sensitivity and specificity but is inefficient relative to HDP*. The CRC* (4S) procedure is more efficient than CRC* (3S) and has lower overall sensitivity than HDP*.

|                | Number of Tests | SE  | SP  |
|----------------|-----------------|-----|-----|
| HDP            | 10              | 0.010 | 1.000 |
| HDP*           | 1606            | 0.895 | 0.985 |
| CRC            | 1877            | 0.870 | 0.994 |
| CRC* (3S)      | 2031            | 0.889 | 0.987 |
| CRC* (4S)      | 1778            | 0.797 | 0.992 |

Table 5: Results from screening algorithms with both sensitivity and specificity equal 0.95

Our analysis using both the HPD and CPC shows the advantages of the HPD in this setting. However, it also shows the problem with using the expected number of tests as an optimality criterion under testing error.

References

Bellman, R. (1957). Dynamic Programming. Princeton University Press.

Bilder, C. R., Tebbs, J. M., Chen, P. (2010). Informative retesting. J. Am. Stat. Assoc. 105, 942–955.
Black, M. S., Bilder, C. R., Tebbs, J. M. (2015). Optimal retesting configurations for hierarchical group testing. Appl. Statist. 64, 693–710.

Dorfman, R. (1943). The detection of defective members of large populations. The Annals of Mathematical Statistics 14, 436–440.

Gillison, M. L., Broutian, T., Pickard, R.K., Tong, Z.Y., Xiao, W., Kahle, L., Graubard, B. I., Chaturvedi, A. K. (2012). Prevalence of Oral HPV Infection in the United States, 2009-2010. JAMA 307, 693–703.

Graff, L. E., and Roeloffs, R. (1972). Group testing in the presence of test error: an extension of the Dorfman procedure. Technometrics 14, 113–122.

Hwang, F. K. (1975). A generalized binomial group testing problem. J. Amer. Statist. Assoc. 70, 923–926.

Hwang, F. K. (1976). Group testing with a dilution effect. Biometrika 63, 671–673.

Hwang, F. K., Pfeifer, C. J., and Enis, P. (1981). An Optimal Hierarchical Procedure for a Modified Binomial Group-Testing Problem. J. Amer. Statist. Assoc. 76, 947–949.

Hyun, N., Gastwirth, J. L., Graubard, B. I. (2018). Grouping methods for estimating prevalences of rare traits for complex survey data that preserve confidentiality of respondents. Statistics in Medicine 37, 2174–2186.

Lindley, D. V. (1961). Dynamic Programming and Decision Theory. Appl. Statist. 10, 39–51.

Litvak, E., Tu, X. M., and Pagano, M. (1994). Screening for the Presence of a Disease by Pooling Sera Samples. J. Amer. Statist. Assoc. 89, 424–434.

Malinovsky, Y., Albert, P. S., and Roy, A. (2016). Reader Reaction: A Note on the Evaluation of Group Testing Algorithms in the Presence of Misclassification. Biometrics 72, 299–304.

Malinovsky, Y. (2019a). Sterrett procedure for the generalized group testing problem. Methodology and Computing in Applied Probability. 21, 829–840.
Malinovsky, Y. (2019b). End Notes. Math. Mag. 92, 398.

Nanda, K., McCrory, D. C., Myers, E. R., Bastian, L. A., Hasselblad, V., Hickey, J. D., Matchar, D. B. (2000). Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. Ann.Intern.Med. 132, 810–819.

Schiffman, M., Wentzensen, N. (2013). Human papillomavirus infection and the multistage carcinogenesis of cervical cancer. Cancer Epidemiol Biomarkers Prev. 22, 553–560.

Sobel, M., Groll, P. A. (1959). Group testing to eliminate efficiently all defectives in a binomial sample. Bell System Tech. J. 38, 1179–1252.

Sobel, M. (1960). Group testing to classify efficiently all defectives in a binomial sample. Information and Decision Processes (R. E. Machol, ed.; McGraw-Hill, New York), pp. 127-161.

Sterrett, A. (1957). On the detection of defective members of large populations. The Annals of Mathematical Statistics 28, 1033–1036.

Zimmerman, S. (2017). Detecting deficiencies: an optimal group testing algorithm. Math. Mag. 90, 167–178.