Optimal Risk-based Pooled Testing in Public Health Screening, with Equity and Robustness Considerations

Hrayer Aprahamian

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Ebru K. Bish, co-Chair
Douglas R. Bish, co-Chair
Diego Moran
Manish Bansal

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We study Dorfman and Array group testing designs under subject-specific risk characteristics, operational constraints, and imperfect tests, considering classification accuracy-, efficiency-, robustness-, and equity-based objectives, and characterize important structural properties of optimal testing designs. These properties provide us with key insights and allow us to model the testing design problems as network flow problems, develop efficient algorithms, and derive insights on equity and robustness versus accuracy trade-off. One of our models reduces to a constrained shortest path problem, for a special case of which we develop a polynomial-time algorithm. We also show that determining an optimal risk-based Dorfman testing scheme that minimizes the expected number of tests is tractable, resolving an open conjecture.

Our case studies, on chlamydia screening and screening of donated blood, demonstrate the value of optimal risk-based testing designs, which are shown to be less expensive, more accurate, more equitable, and more robust than current screening practices.

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Chapter 1

Introduction

1.1 Motivation

Screening a population of subjects so as to classify each subject as *positive* or *negative* for a binary characteristic (e.g., presence of a disease or genetic disorder, a product defect, error in a computer code) is essential in many settings. Individually testing each subject is often very costly, and hence, may not be a viable strategy for classification, especially when the prevalence of the binary characteristic in the population is low and the population size is large. Therefore, in 1943, Dorfman, an economist, [46] proposed the concept of *group testing,* which involves testing multiple subjects simultaneously using a single test, for the purpose of screening military inductees for syphilis in an economical manner.

An important consideration is that prevalence rates may vary, and sometimes substantially, with subject characteristics. For example, in the United States (US), subjects within the 15-24 age group are twelve times more likely to be infected with chlamydia, one of the most prevalent STDs in the US, than subjects from other age groups [55]; first-time blood donors

are seven times more likely to be infected with HIV than repeat donors [143]. The challenge, then, is to incorporate the heterogeneity of the population into the modeling framework and to design *risk-based testing schemes* (i.e., determining group sizes, and assigning subjects, with different risk, to the groups) so as to classify the set of subjects for the binary characteristic *accurately* (i.e., with minimum classification error), *equitably* (i.e., with a fair and even distribution of misclassification probability across subjects), and *efficiently* (i.e., with minimum resources). We identify important structural properties of optimal risk-based testing schemes with imperfect tests; use these properties to develop efficient algorithms; and derive key insights through realistic case studies that demonstrate the value of optimal risk-based testing designs, which are shown to be less expensive, more accurate, more equitable, and more robust than current screening practices.

1.2 Research Overview

We first consider models that attempt to accurately estimate the residual risk of transfusion-transmittable infections (TTIs), which include the human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV, HCV), among others. An accurate estimation of the residual risk of transfusion-transmittable infections (TTIs) is essential, as it provides the basis for blood screening assay selection. While the highly sensitive nucleic acid testing (NAT) technology has recently become available, it is highly costly. As a result, in most countries, including the United States, the current practice for HIV, HBV, HCV screening in donated blood is to use pooled NAT. Pooling substantially reduces the number of tests required, especially for TTIs with low prevalence rates. However, pooling also reduces the test's sensitivity, because the viral load of an infected sample might be diluted by the other samples in the pool to the point that it is not detectable by NAT, leading to potential

TTIs. Infection-free blood may also be falsely discarded, resulting in wasted blood. In this chapter, we derive expressions for the residual risk, expected number of tests, and expected amount of blood wasted for various two-stage pooled testing schemes, including Dorfman-type and array-based testing, considering infection progression, infectivity of the blood unit, and imperfect tests under the dilution effect and measurement errors. We then calibrate our model using published data and perform a case study. Our study offers key insights on how pooled NAT, used within different testing schemes, contributes to the safety and cost of blood.

In Chapter 3, we propose and study an *adaptive risk-based pooling* scheme, which considers important test and population level characteristics often over-looked in the literature (e.g., dilution of pooling and heterogeneous subjects). We characterize important structural properties of optimal subject assignment policies (i.e., assignment of subjects, with different risk, to pools), and provide key insights. Our case study, on chlamydia screening, demonstrates the effectiveness of the proposed pooling scheme, with the expected number of false classifications reduced substantially over policies proposed in the literature.

In Chapter 4, we study optimal group testing designs under subject-specific risk characteristics and imperfect tests, considering classification accuracy-, efficiency- and equity-based objectives, and characterize important structural properties of optimal testing designs. These properties allow us to model the testing design problems as partitioning problems, develop efficient algorithms, and derive insights on equity versus accuracy trade-off. One of our models reduces to a constrained shortest path problem, for a special case of which we develop a polynomial-time algorithm. We also show that determining an optimal risk-based Dorfman testing scheme that minimizes the expected number of tests is tractable, resolving an open conjecture. We demonstrate the value of optimal risk-based testing schemes with a case study of public health screening.

Finally, in Chapter 5 we study optimal group testing designs that take into account important operational constraints, subject-specific risk characteristics, imperfect tests, and uncertainty in risk estimates, while considering classification accuracy- and robustness-based objectives. We characterize important structural properties of optimal testing designs, which allow us to model them using network flow formulations, develop efficient algorithms, and derive insights on the robustness versus classification accuracy trade-off. We demonstrate the impact of this research through a case study on the screening of donated blood for the human immunodeficiency virus. Our numerical results highlight the value of optimal risk-based testing designs, which are shown to be less expensive, more accurate, and more robust than current screening practices.

Chapter 2

Residual Risk and Waste in Donated Blood with Pooled Nucleic Acid Testing

2.1 Introduction

Maintaining a constant supply of infection-free blood is of utmost importance for the society, as the consequences of transmitting an infection through blood transfusion can be potentially severe and even life-threatening for the recipient. Recognized transfusion-transmittable infections (TTIs) include the human immunodeficiency virus (HIV), hepatitis viruses, with the major ones being hepatitis B and C viruses (HBV and HCV), West Nile virus (WNV), human T-cell lymphotropic virus (HTLV), syphilis, and babesiosis, among others. Throughout the last decade, blood screening has seen substantial advances, especially with the introduction of the more accurate *virologic* testing technology (i.e., *Nucleic acid testing* (*NAT*)) that measures viral RNA and DNA in blood. In the United States (US), NAT technology for

blood screening is recently licensed by the Food and Drug Administration (FDA) for the HIV, HBV, HCV, and WNV (respectively in 2005, 2001, 1999, and 2005 [53]). Virologic testing has higher *sensitivity* (the probability of correctly identifying an infected sample) than traditional *serologic* testing, especially for recently infected donors.

The *residual risk* (the probability of releasing a potentially infectious donation into the blood supply [34]) is predominantly caused by recently infected donors, i.e., donors within the *window period,* which refers to the time it takes for the donor's bio-marker load (e.g., viral load) to reach a level detectable by screening. An infected individual goes through various phases of viral load growth rates: pre ramp-up phase, ramp-up phase with accelerating growth rates, and post ramp-up phase during which the growth rate slows down, eventually reaching a plateau [25, 33, 52, 61, 138, 139]. NAT has reduced window periods compared to serologic testing, but NAT is considerably more expensive (costs vary, but as an example, the cost of HIV NAT is reported to be at least 3 to 4-fold higher than that of serologic testing [42, 45, 68, 78, 86]). Because of the high testing cost, NAT is often used on *pools* of blood samples collected from multiple donors. Pooled testing can substantially reduce the number of tests required, hence the testing cost, especially in blood screening where TTI prevalence rates are typically low. This is highly desirable, especially because blood is a high-volume product and is becoming increasingly expensive (the unit cost of a red blood cell has tripled in the US over the last decade [108,112]), and testing cost constitutes a large portion of the cost of blood [108].

Of course, pooling has a *dilution effect*: the viral load of an infected sample is diluted by the other samples in the pool, reducing the test's sensitivity (e.g., [8, 32, 76, 137]). As a result, as the pool size increases, the testing cost goes down, but the residual risk increases. Furthermore, tests have less than perfect *specificity* (the probability of correctly identifying a non-infected sample) [24]. False-positive outcomes are also undesirable; as they lead to

infection-free blood being falsely discarded (*waste*). Pooling can also increase waste, through the possibility of discarding an entire pool based on the outcome of one pooled test. Because healthcare resources are limited in both rich and poor countries (e.g., [11, 29, 115]), blood screening decisions often revolve around the trade-offs between the residual risk, testing cost, and waste. Therefore, it is important to study these trade-offs for various *two-stage testing* (i.e., initial testing and re-testing) schemes, considering the realistic aspects of testing, including infection progression, infectivity of the blood unit, and imperfect tests under the dilution effect and measurement errors.

The transfusion literature, with the exception of some recent research that we discuss subsequently, typically estimates the residual risk of a given testing scheme through the simple *Incidence window period model (IWP)*, which relies on quite restrictive assumptions (see, e.g., [24, 33] for details). In particular, IWP ignores, among others, infection progression (e.g., viral load growth in the context of NAT) and the individual variability with which this happens, as well as the stochasticity in test outcomes due to measurement errors, the dilution effect, and imperfect specificity [8, 32, 76, 137]. Indeed, clinical data for HIV-, HBV-, and HCV-infected individuals indicate that viral load progression may differ among individuals in the ramp-up phase due to physiological characteristics not well-understood [25, 52, 61]; and due to measurement errors, the same test may produce different outcomes when used repetitively on the same pool (*in-sample variability*) [97, 137, 138, 139].

Further, IWP estimates only the residual risk, and not the other important metrics. Consequently, IWP may not provide accurate estimates of the costs and benefits of blood screening assays, especially under pooling [138, 139]. However, pooled NAT has become the common practice in blood screening in many parts of the world, including the US and many European countries, e.g., the American Red Cross (ARC) routinely uses pooled NAT, in pools of size 16, for HIV, HBV, HCV, and WNV screening [1, 40]. Operations researchers and

statisticians, on the other hand, approach this problem as a generic pooled testing problem, and make certain modeling assumptions, detailed below, that we relax in this work so as to obtain a more accurate analysis of various pooled NAT schemes in blood screening.

Our contributions to the blood testing problem are multi-fold. First, we develop analytical expressions for the relevant metrics (the residual risk, expected amount of blood wasted, and expected number of tests) and compare them for various two-stage post-donation testing schemes, while taking into account the joint impact of dilution (as a function of pool size), imperfect tests, in-sample variability, and re-testing possibility. Thus, our model expands the earlier works on pooled testing (e.g., [86, 138, 139]). Second, to close the gap between theory and practice, we integrate, into our model, mathematical models of post-infection viral load growth (i.e., *doubling time* model developed by [33]) adopted in the medical literature, but increase the realism of these models by incorporating the stochasticity in individual viral load growth rates and by considering the *infectivity* of the blood sample (infected blood with low viral load may not be infectious when transfused, e.g., [33, 138, 139]). Further, we calibrate the model parameters using published data on NAT characteristics, and prevalence and viral load growth rates for HIV, HBV, and HCV, and perform a case study. Our study generates key insights on how pooled NAT contributes to the safety and cost of blood.

The concept of pooled testing for infectious diseases was first introduced by Dorfman in 1943 for screening military inductees for syphilis in an affordable manner [46]. Dorfman's objective is to determine the optimal pool size that minimizes the testing cost for a particular two-stage testing scheme, commonly referred to as *Dorfman-type testing*: if the master pool tests negative, then all samples in the master pool are declared infection-free; and if the master pool tests positive, then each sample in the master pool undergoes individual testing. Dorfman's analysis relies on several assumptions including, among others, that tests are perfectly reliable and there is no dilution in pooling. Dorfman's seminal paper paved the

way; and numerous extensions of his model, including consideration of imperfect tests and multi-stage pooling strategies, have been studied for both the classification problem that we consider in this chapter (e.g., [8, 20, 73, 80, 86, 97, 137]), and the surveillance problem (e.g., [39, 117, 122, 123, 141, 142]).

An interesting alternative to traditional hierarchical pooled testing, such as Dorfman-type testing, is *array-based testing*, which utilizes the concept of *overlapping* pools [2]. In its most basic form, an $n \times n$ matrix of n^2 samples is constructed, and $2n$ pools, comprised of samples in each column and in each row, are tested. Under perfect tests, the decision is simple in that all samples that lie at the intersection of a positive-testing row pool and a positive-testing column pool are infected [86]. Needless to say, the decision becomes complex in the presence of test error, when it is possible for a row pool to test positive without a column pool testing positive, and vice versa. While array-based testing is used in genetics (e.g., [2, 12, 30]), it has, surprisingly, been under-utilized in blood testing, and limited research exists on the operational characteristics of array-based testing under test error and/or dilution effect. As some examples, [15, 73] derive various performance metrics for array-based testing under perfect tests; [69, 86, 105] consider test error, but without the dilution effect; and [85] studies three-dimensional array-based testing under similar assumptions. More recently, Habtesllassie et al. [66] study array-based testing under both test error and the dilution effect, but their analysis ignores other important aspects of blood screening, such as the infection progression, infectivity of the blood, and in-sample variability.

On the transfusion side, a recent research focus has been on developing mathematical models of post-infection viral load growth [33] and utilizing these models for residual risk estimation in donated blood under pooled NAT [138, 139]. In particular, Weusten et al. [138] consider that the viral load grows in a deterministic manner post-infection (i.e., according to the doubling time model [33]), that is, with identical growth rates for all infected individuals.

Recently, Weusten et al. [139] partially relax this restriction by modeling the viral load in each time period as a Poisson distribution, which allows the calibration of the first moment of viral load growth. However, the Weusten model [139] uses the Poisson distribution solely for the derivation of the probability that a blood sample is infectious; in other words, the test's sensitivity is still derived using the deterministic viral load model. More importantly, both models [138,139] rely on other restrictive assumptions, including perfect specificity, and do not consider array-based testing and the other important metrics, including the expected number of tests and amount of blood wasted. Our research builds upon and substantially expands these models for a more realistic representation of the various trade-offs incurred among the different pooling schemes. Specifically, we relax the various assumptions used in [138,139] to account for the test's specificity and individual variability in viral load growth; consider various two-stage pooling schemes, including array-based testing; derive expressions for the important metrics, including the residual risk, expected number of tests and waste, and analytically compare the performance of the different pooling schemes, and finally study the trade-offs incurred for each pooling scheme within a cost-based objective.

The remainder of this chapter is organized as follows. Section 2.2 presents the notation and assumptions, and provides an overview of the model. Section 2.3 provides an analytical comparison of the performance metrics for various pooling schemes. Then, Section 2.4 discusses findings from a case study for South Africa, a region with one of the highest TTI rates in the world; and Section 2.5 complements the case study with a cost-based analysis to derive the least-cost pooling scheme for each infection. Finally, Section 2.6 summarizes our findings and provides suggestions for future research. To facilitate the presentation, all proofs, and some tables and figures are relegated to the appendix.

2.2 Notation, Preliminaries, and Model

2.2.1 Notation

Each test (pooled or individual) provides a binary outcome, with a "positive" outcome indicating an infection, and a "negative" outcome indicating otherwise. To simplify the notation, we omit the infection or test index for parameters, random variables, and events throughout Sections 2.2-2.3, and provide infection- and test-specific values in Section 2.4.

Parameters

n_{max}**:** maximum pool size possible (due to technology availability or regulations)

τ**:** average time between two consecutive donations for repeat donors who have sero-converted

v**:** average volume of blood transfused per patient

l_0**:** starting viral load at time of infection, in number of viral particles in genome equivalent (geq) per one mL of blood

χ**:** number of nucleic acid copies per viral particle

Random Variables

D**:** donation time, from time of infection, of an infected donor, where $D \sim \text{Uniform}[0, \tau]$

L**:** viral load in blood sample (geq per mL), with support in $[0, \infty]$

Λ**:** doubling time parameter describing the post-infection viral load growth rate, with mean μ and support in $[0, \infty]$

Events

$T^+(n,m)$**:** event that the outcome of the test, with pool size n, is positive under a given decision rule when the test is repeated m times on the same pool, $\forall n, m \in \mathbb{Z}^+$ $\big($with complement $T^-(n,m)\big)$

A^+**:** event that a random donor is infected (with complement A^-)

I**:** event that the blood sample of volume v is *infectious*, i.e., it contains at least one viral particle that is is infectious

To simplify the notation, we denote $T^+(n,1)$ by $T^+(n)$. Let $Se(n) \equiv P(T^+(n)|A^+)$ and $Sp \equiv P(T^-(n)|A^-)$ respectively denote the sensitivity and specificity of a test with pool size $n \in \mathbb{Z}^+$. While the sensitivity depends on the pool size due to the dilution effect, the specificity is independent of the pool size.

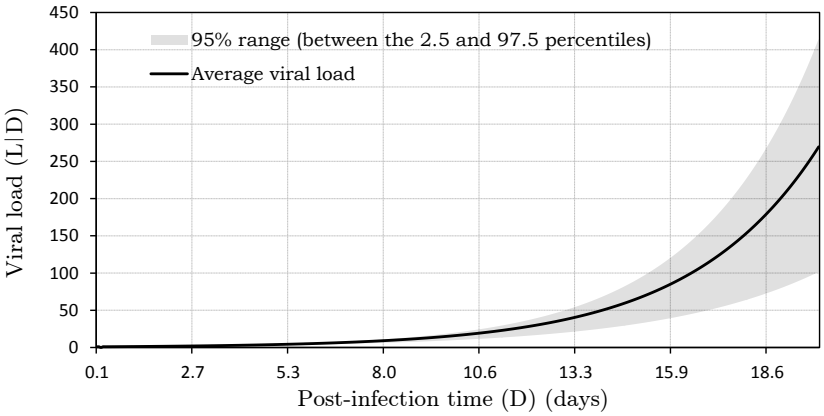
Following the transfusion literature, we define the window period, t_w, as the post-infection time at which the individual's viral load becomes high enough to achieve a test sensitivity of at least 0.999 for all pool sizes, that is, $t_w \equiv \inf\{t \geq 0 : P\big(T^+(n_{max})|A^+, D = t\big) = 0.999\}$, which is infection- and test-specific [79, 138, 139]. Thus, the sensitivity, of 0.999, is achieved exactly for a pool size of n_{max}, and is exceeded for all other pool sizes, $n \leq n_{max}$. To simplify the subsequent analysis, we make the following approximation.

Assumption 2.1. The test has perfect sensitivity for detecting an infected sample from a donor outside of the window period for all pool sizes, i.e., $Se(n)|D > t_w = 1, \forall\, n \leq n_{max}$.

2.2.2 Assumptions and Preliminaries

Our model is based on the following concepts:

Figure 2.1: Viral load (geq per mL) for an HBV-infected individual as a function of post-infection time when $\Lambda \sim \mathcal{N}(\mu, \sigma^2)$, with $l_0 = 1$, $\mu = 2.5$, and $\sigma = 0.122$ (values taken from [139])



1. During the window period, the viral load of an infected individual grows at a rate that may vary among the individuals, reaching a plateau at the end of the window period [25,52,61]. Specifically, for an infected donor whose donation time is within the window period, i.e., $D \in [0, t_w]$,

$$L = l_0 \, 2^{D/\Lambda}. \tag{2.1}$$

   Eq. (2.1), with deterministic Λ, is the doubling time viral load growth model in [33]. A non-infected donor has $L = 0$, and L is left unspecified for an infected donor whose donation time is outside of the window period (due to Assumption 2.1). To simplify the notation, let $f_L(.)$ denote the probability density function (pdf) of the viral load for an infected donor within the window period. Figure 2.1 demonstrates the mean and the 95%-range of an infected donor's viral load as a function of post-infection time under one possible pdf (normal) for Λ.

2. Infectivity of the blood sample increases with viral load, as each viral particle can cause infection with probability p_v, independently of the other viral particles. Then, similar

to [139]:

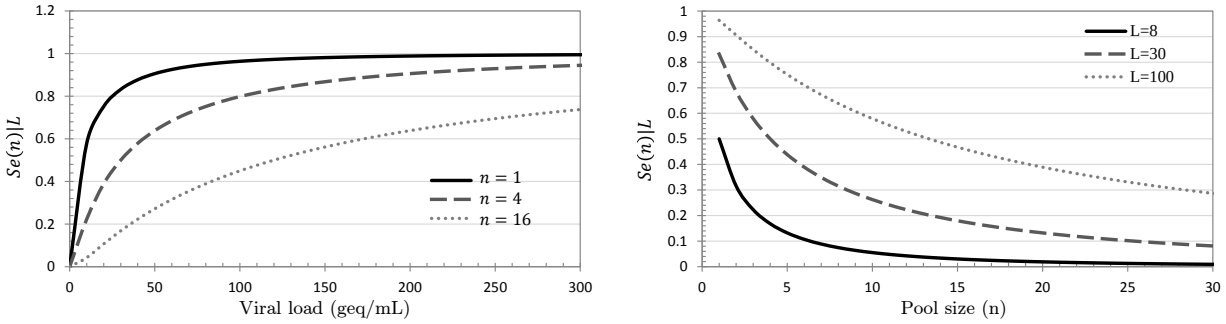
$$P(I|L) = 1 - (1 - p_v)^{v\,L}. \tag{2.2}$$

3. Test sensitivity is a decreasing function of pool size due to the dilution effect; and there is in-sample variability, that is, due to measurement errors, the same test may produce stochastically different outcomes when used repetitively on the same pool (i.e., test outcome is not always positive (negative) when the viral load is above (below) the test's threshold), e.g., [97,137,138,139]. Similar to the transfusion literature, we model these aspects of testing using the probit function (e.g., [138,139]), i.e., the conditional sensitivity for an infected window-period sample is given by:

$$Se(n)|L = P(T^+(n)|A^+, L) = \Phi\left(z\frac{\log\left(\frac{\chi}{x_{50}}\,\frac{L}{n}\right)}{\log(x_{95}/x_{50})}\right), \tag{2.3}$$

where x_{50} and x_{95} are infection- and test-specific parameters, which correspond to the viral load required to achieve a sensitivity of 50% and 95% respectively (i.e., $x_y \equiv \inf\{l \geq 0 : Se(1)|(L = l) = y\}$, for $y = 0.50, 0.95$), $\Phi(\cdot)$ denotes the CDF of the standard normal distribution, and $\{z : \Phi(z) = 0.95\}$. Observe that the dilution effect is taken into account through using the *average* viral load in the pool, L/n, similar to [97, 137, 138, 139]. Figure 2.2 plots the conditional sensitivity in Eq. (2.3) as a function of viral load and pool size. As Figure 2.2 demonstrates, the probit function possesses certain properties that make it a good fit for modeling the sensitivity: (1) It is strictly increasing with viral load, asymptotically converging to zero (one) as the viral load goes to zero (infinity). (2) It is strictly decreasing with pool size, asymptotically converging to zero as the pool size goes to infinity. (3) With respect to viral load, the rate of change in sensitivity per unit change in viral load is much more pronounced (i.e., higher) at lower viral loads (at high viral loads, there are diminishing returns).

Figure 2.2: Conditional test sensitivity for window-period samples as a function of viral load (left) and pool size (right) for ULTRIO HBV



Due to these monotonic and asymptotic properties, along with the ability to calibrate the function based on infection- and test-specific parameters (x_{50} and x_{95}), the probit function is commonly used in the transfusion literature to model test sensitivity.

Our model relies on the following additional assumptions:

Assumption 2.2. The probability that more than one infected sample is present in any pool is negligible.

Assumption 2.3. Test outcomes and infectivity of sample are conditionally independent given the viral load, that is, events $T^+(n)|L$ and $I|L$ are conditionally independent.

Both assumptions are reasonable and are common in the transfusion literature (e.g., [78, 87, 131, 138, 139]). Assumption 2.2 generally holds because TTI prevalence rates are typically low (see Section 2.4), and the maximum pool size used in blood screening, n_{max}, is around 16 [40]. Therefore, the probability that more than one infected sample is present in a pool is negligible.

Assumption 2.3 states that, given the viral load, test outcomes and infectivity of the sample can be considered independent, as they mainly depend on the viral load. Outcomes of the same test, when repetitively performed on the same pool, are still dependent when not

conditioned on the viral load. That is, a high (low) viral load is more likely to produce a positive (negative) outcome in all tests performed on a given pool. Note, however, that even when conditioned on the viral load, outcome of each test is still stochastic due to in-sample variability. Consequently, our approach, of modeling the sensitivity as a function of both pool size and viral load (see Eq. (2.3)), overcomes the limitations of existing approaches, which do not model sensitivity as a function of viral load, and hence need to assume independence among subsequent test outcomes (e.g., [86, 97]). Alternatively, one can use empirically-derived pooled sensitivity values (published only for a small set of pool sizes, e.g., [119]); however, this modeling does not consider the viral load, and in the absence of empirical data on the conditional sensitivity given prior test outcomes, one again will need to assume independence among test outcomes. Thus, Eq. (2.3) allows us to explicitly model the dependence of the test's outcome on the viral load, providing an improvement over the current literature.

To understand the impact of Assumptions 2.1 and 2.2 (as well as the other major assumptions made in our study), we perform a simulation study, which indicates that all assumptions, other than the distribution of donation time, D, have a minor impact on the performance metrics; see Appendix A.1.

In light of Assumption 2.2, we use $P\big(A^+(n)\big)$ to denote the probability that there is an infected sample in a pool of size $n, n \in \mathbb{Z}^+$ $\big($with complement $P\big(A^-(n)\big)\big)$, that is, we model the prevalence rate in a pool as a function of pool size (see Section 2.4).

Under these assumptions, the probability of a positive test outcome for a pool of size $n \in \mathbb{Z}^+$ follows:

$$\begin{aligned} P\big(T^+(n)\big) = P\big(A^+(n)\big) \Big[& P\big(T^+(n)|A^+(n), D \le t_w\big) P\big(D \le t_w | A^+(n)\big) \\ & + P\big(T^+(n)|A^+(n), D > t_w\big) P\big(D > t_w | A^+(n)\big) \Big] + P\big(T^+(n)|A^-(n)\big) P\big(A^-(n)\big), \end{aligned} \tag{2.4}$$

where

$$P\Big(D\leq t_w|A^+(n)\Big)P\Big(T^+(n)|A^+(n),D\leq t_w\Big)=\tfrac{t_w}{\tau}\int_0^\infty P\Big(T^+(n)|A^+(n),D\leq t_w,L=l\Big)f_L(l)dl, \tag{2.5}$$

$$P\Big(D>t_w|A^+(n)\Big)P\Big(T^+(n)|A^+(n),D>t_w\Big)=\frac{\tau-t_w}{\tau}, \quad \text{by Assumption 2.1,} \tag{2.6}$$

$$P\Big(T^+(n)|A^-(n)\Big)=1-Sp. \tag{2.7}$$

These expressions are utilized in the subsequent derivations.

2.2.3 Testing Schemes

We consider one single-stage testing scheme (i.e., only one pooled test), which serves as a reference point, and various two-stage testing schemes. Let n_i ($\leq n_{max}$) denote the pool size in stage $i = 1, 2$. Following the current practice, the second stage, which we also refer to as the *re-testing stage*, involves repeating a certain test a number of times (m) and determining the overall outcome of the second stage based on a given decision rule; the need to perform the same test multiple times is due to the in-sample variability $\big($see Eq. (2.3)$\big)$. One decision rule we subsequently utilize is the *Believe the Positive* (BP) rule, according to which the second stage outcome is positive (negative) only if at least one of the m tests in the second stage provides a positive outcome (only if all m tests in the second stage provide negative outcomes). This rule is commonly used in blood centers as well as in the literature due to its conservative nature (e.g., [22, 24, 102, 138, 139]).

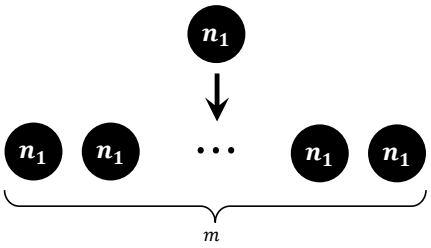
Single-stage testing:

No re-testing (*NR* (n_1)): Only the *master pool*, of size n_1, is tested once. If the master pool "passes" (i.e., the test outcome is negative), then the entire pool is accepted; otherwise, the entire pool is rejected.

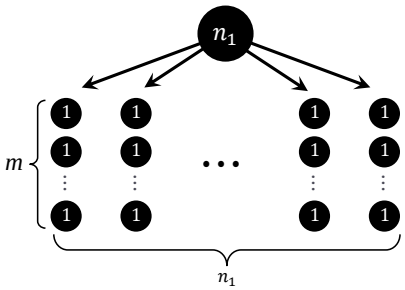
Two-stage testing (initial testing, followed by re-testing):

Figure 2.3: Two-stage testing schemes

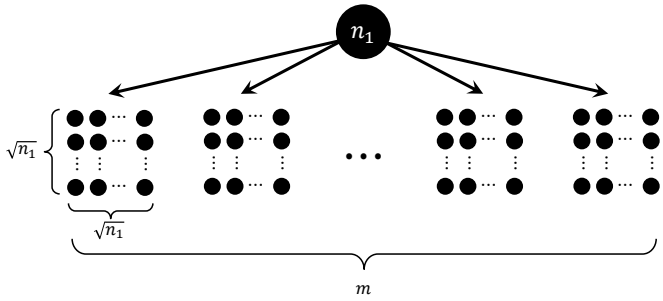
(a) Pooled re-testing (PR)



(b) Individual re-testing (IR)



(c) Array-based re-testing (AR)



All two-stage schemes start with testing of the master pool in the first stage and differ only with respect to their second stage; see Figure 2.3. If the master pool passes, then the entire pool is accepted without further testing; otherwise, the second stage is performed. The sample(s) are rejected only when both stages fail.

(1) Pooled re-testing (PR $(n_1, n_2 = n_1, m)$): In the second stage, the master pool is tested m times under the BP decision rule.

(2) Dorfman-type testing (individual re-testing) (IR $(n_1, n_2 = 1, m)$): In the second stage, each sample in the master pool is tested individually m times under the BP decision rule.

(3) Array-based re-testing (AR $(n_1, n_2 = \sqrt{n_1}, m)$): In the second stage, array-based testing is performed, that is, all samples in the master pool are randomly placed within a $\sqrt{n_1} \times \sqrt{n_1}$ matrix, and $2\sqrt{n_1}$ pools, each of size $\sqrt{n_1}$, are constructed from samples

in each row and each column. Each row pool and column pool is tested m times, and sample (i, j) (i.e., the sample at the intersection of row i and column j) is rejected if both row i and column j fail; and is accepted otherwise. We use the decision rule that a row or a column fails if its pooled test provides a positive result at least once.

Then, the event that both stage 1 and stage 2 fail (i.e., a random sample is rejected), which we denote by $F^+(n_1, n_2, m)$, $n_1, n_2, m \in \mathbb{Z}^+$, and its complement, $F^-(n_1, n_2, m)$, follow:

$$P\Big(F^-(n_1,n_2,m)\Big)=P\Big\{T^-(n_1) \text{ or } \big(T^+(n_1),T^-(n_2,m)\big)\Big\} \tag{2.8}$$

$$\begin{aligned} P\Big(F^+(n_1,n_2,m)|A^+(n_1),D\le t_w\Big)&=P\Big\{\big(T^+(n_1),T^+(n_2,m)\big)|A^+(n_1),D\le t_w\Big\}\\ &=\int_0^\infty P\Big(T^+(n_1)|A^+(n_1),D\le t_w,L=l\Big)\\ &\quad\times P\Big(T^+(n_2,m)|A^+(n_1),D\le t_w,L=l\Big) f_L(l)dl, \quad \text{by Assumption 2.3} \end{aligned} \tag{2.9}$$

$$P\big(F^+(n_1, n_2, m)|A^+(n_1), D > t_w\big) = 1, \quad \text{by Assumption 2.1} \tag{2.10}$$

$$P\big(F^+(n_1, n_2, m)|A^-(n_1)\big) = (1 - Sp)\ P\big(T^+(n_2, m)|A^-(n_1)\big). \tag{2.11}$$

In the next section, we derive the performance metrics for all testing schemes. The superscripts NR, PR, IR, and AR denote the corresponding testing scheme.

2.3 Analysis

2.3.1 Derivation of the Performance Metrics

To facilitate the presentation, we explain the logic behind each derivation, and refer the reader to Appendix A.2 for the derivations.

Residual Risk (R)

An infection will be transmitted to the transfusion recipient only when the blood sample of volume v is infected, is not detected during screening, and is infectious. Then, assuming all blood transfused to a recipient comes from the same donor, we can write:

$$
\begin{aligned}
R &= P\Big(A^+(n_1), I, F^-(n_1,n_2,m)\Big) \\
&= P\Big(A^+(n_1), D \le t_w, I, F^-(n_1,n_2,m)\Big) + \underbrace{P\big(A^+(n_1), D > t_w, I, F^-(n_1,n_2,m)\big)}_{\| \\ 0 \ (by\ Assumption 2.1)} \\
&= P\Big(A^+(n_1)\Big) P\Big(D \le t_w | A^+(n_1)\Big) \int_0^\infty P\Big(I | A^+(n_1), D \le t_w, L = l\Big) P\Big(F^-(n_1,n_2,m) | I, A^+(n_1), D \le t_w, L = l\Big) f_L(l) dl \\
&= P\Big(A^+(n_1)\Big) \tfrac{t_w}{\tau} \int_0^\infty P\Big(I | A^+(n_1), D \le t_w, L = l\Big) \\
&\qquad \times P\Big(F^-(n_1,n_2,m) | A^+(n_1), D \le t_w, L = l\Big) f_L(l) dl, \quad \text{by Assumption 2.3.}
\end{aligned} \tag{2.12}
$$

The expression of the residual risk in (2.12) has two improvements over that in Weusten et al. [139]: It incorporates the individual variability in viral load and it provides a general expression that applies to any two-stage testing scheme, including the array-based testing scheme not considered in [139]. Further, our analysis also incorporates imperfect test specificity (another improvement over Weusten et al. [139]); while imperfect specificity does not alter the residual risk expression, we find that it has substantial impact on the other performance metrics, as discussed in the subsequent sections.

Expected Number of Tests $\big(\mathbb{E}[N]\big)$

We derive:

$$\mathbb{E}[N] = 1 + \begin{cases} 0, & \text{for } NR \\ mP\big(T^+(n_1)\big), & \text{for } PR \\ mn_1P\big(T^+(n_1)\big), & \text{for } IR \\ 2m\sqrt{n_1}P\big(T^+(n_1)\big), & \text{for } AR \end{cases}$$

where $P\big(T^+(n_1)\big)$ is given by Eq. (2.4). Thus, in the no re-testing scheme, only one master pool is tested for all n_1 samples, whereas in the two-stage schemes, the number of tests depends on the outcome of the master pool.

Expected Waste $\big(\mathbb{E}[W]\big)$

No re-testing (NR) and pooled re-testing (PR): In either testing scheme, the entire pool is rejected if both stages fail. Then, for $X \in \{NR, PR\}$, we can write:

$$\mathbb{E}\big[W^X\big] = n_1P\big(A^-(n_1), F^{+X}(n_1, n_2, m)\big) + (n_1 - 1)P\big(A^+(n_1), F^{+X}(n_1, n_2, m)\big). \quad (2.13)$$

Individual re-testing (IR): If the master pool fails, then each sample undergoes individual testing. Letting N_{2+}^{IR} denote the number of infection-free samples that falsely fail in stage 2 of IR, we have that $N_{2+}^{IR}|A^-(n_1)$ is binomial with $\big(n_1, (1 - Sp^m)\big)$ and $N_{2+}^{IR}|A^+(n_1)$ is binomial with $\big(n_1 - 1, (1 - Sp^m)\big)$. Then,

$$\mathbb{E}\big[W^{IR}\big] = (n_1 - 1)(1 - Sp^m)P\big(T^+(n_1)|A^+(n_1)\big)P\big(A^+(n_1)\big) + n_1(1 - Sp^m)(1 - Sp)P\big(A^-(n_1)\big), \quad (2.14)$$

where $P\big(T^+(n_1)|A^+(n_1)\big)$ can be derived using Eq.s (2.5) and (2.6).

Array-based re-testing (AR): The derivation of the expected waste in array-based testing is more involved and detailed in Appendix A.2.

Using these expressions, in the next section we compare the different testing schemes and derive insights.

2.3.2 Comparison of the Performance Metrics

The proofs of the results in this section can be found in Appendix A.3.

Lemma 2.1. *For any master pool of size n_1 and number of re-tests m, we have:*

$$\left.\begin{matrix} R^{PR} \\ R^{AR} \end{matrix}\right\} \geq R^{IR} \geq R^{NR}.$$

Further, R^X is decreasing in m for $X \in \{PR, IR, AR\}$, with $\lim_{m\to\infty} R^X(m) \to R^{NR}$.

Lemma 2.2. *For any master pool size of n_1 and number of re-tests m, we have:*

$$\left.\begin{matrix} \mathbb{E}[N^{IR}] \\ \mathbb{E}[N^{AR}] \end{matrix}\right\} \geq \mathbb{E}[N^{PR}] \geq \mathbb{E}[N^{NR}], \quad \mathbb{E}[N^{AR}] \begin{cases} \leq \mathbb{E}[N^{IR}], & \text{if } n_1 \geq 4 \\ \geq \mathbb{E}[N^{IR}], & \text{otherwise} \end{cases}$$

Lemma 2.3. *For any master pool size of n_1 and number of re-tests m, we have:*

$$\mathbb{E}[W^{NR}] \geq \begin{cases} \mathbb{E}[W^{PR}] \\ \mathbb{E}[W^{IR}] \\ \mathbb{E}[W^{AR}] \end{cases}, \quad \mathbb{E}[W^{PR}] \geq \mathbb{E}[W^{IR}] \geq \mathbb{E}[W^{AR}].$$

Further, $\mathbb{E}[W^X]$ is increasing in m for $X \in \{IR, PR, AR\}$, with $\lim_{m\to\infty} \mathbb{E}[W^X] \to \mathbb{E}[W^{NR}]$.

Thus, the residual risk of the no-retesting scheme is the lowest among all testing schemes. This follows because under any two-stage scheme, a positive master pool is subjected to further testing, and, due to the in-sample variability $\big($see Eq. (2.3)$\big)$, it is given a second chance to pass the test, hence increasing the residual risk. For all the two-stage testing schemes considered in this chapter, the sole purpose of re-testing (the second stage) is to reduce the amount of wasted blood. Of course, one can design other types of re-testing schemes so as to reduce the residual risk, e.g., by re-testing the samples that test negative in the first stage. However, under low prevalence rates, such re-testing schemes will likely lead to a huge increase in the number of tests, and hence, one needs to study the testing design carefully, considering its impact on all the performance metrics.

Finally, it is interesting to note that when the master pool size, n_1, equals 1, the two re-testing schemes, PR and IR, become equivalent, as in this case both schemes reduce to an individual test in the first stage, followed by m individual tests in the second stage.

2.4 Case Study

We consider three chronic infections, HIV, HBV, HCV, for which pooled NAT (ULTRIO HIV, ULTRIO HCV, and two types of NAT for HBV, namely ULTRIO HBV and ULTRIO Plus HBV) and the corresponding data are available. We calibrate our model using published data on test characteristics, viral load progression, and prevalence rates; and perform a case study of South Africa, a region with one of the highest TTI rates in the world [133].

2.4.1 Model Data and Calibration

We calibrate the doubling time parameter, Λ, considering a normal distribution $\big(\Lambda \sim \mathcal{N}(\mu, \sigma^2)\big)$. Our numerical study, which also considers the Poisson distribution used in Weusten [139], indicates that the results of the case study are not highly sensitive to the distribution of the viral load. However, the additional flexibility offered by the normal distribution, of calibrating the first two moments of the distribution, may be important for certain data sets (e.g., for infection-test pairs with long window periods and high variability in viral growth). For each of HIV, HBV, and HCV, we calibrate viral load parameters, μ and σ^2, using the clinical data in [25, 52, 61, 139]; see Table 2.1. The values of τ, χ, p_v, l_0, x_{50}, and x_{95} are from [139] (the reader is referred to [139] for details); the window period for each infection-test pair and test specificity are from [24, 78]; and the average volume of red blood cell transfusion per patient (v) is estimated as 20 mL based on a study conducted by the South African National Blood Service [139]. To derive the value of $P\big(A^+(n)\big)$, the probability that a pool of size $n, n \in \mathbb{Z}^+$, contains an infected sample, we assume that the number of infected samples in the pool follows a binomial distribution $\big(n, P(A^+(1))\big)$. Then, $P(A^+(n)) = 1 - \big[1 - P(A^+(1))\big]^n$, where $P\big(A^+(1)\big)$ values are reported in Table 2.1.

Table 2.1: Data used in the case study (from Weusten et al. [139] unless otherwise noted)

	HBV	HCV	HIV
Epidemiology data			
Prevalence rate $\Big(P\big(A^+(1)\big)\Big)$ (%)	0.030%	0.001%	0.046%
Inter-donation time (τ) (days)	111	149	166
Data on the virion			
Number of nucleic acid copies per viral particle (χ)	1	1	2
Probability that a single viral particle is infectious (p_v)	0.187	0.086	0.217
Parameters for viral load growth			
Viral load at time of infection (l_0) (geq/mL)	1	1	1
Mean doubling time (μ) (days)	2.50	0.45	0.85
Standard deviation of doubling time (σ)	0.122	0.022	0.051

	ULTRIO HBV	ULTRIO Plus HBV	ULTRIO HCV	ULTRIO HIV
NAT parameters				
Specificity (Sp) (%) *	99.93%	99.93%	99.93%	99.93%
Window period (t_w) (days) *	33	29	10	11
Viral load for 50% sensitivity (x_{50}) (geq/mL)	7.5	2.5	2.3	2.7
Viral load for 95% sensitivity (x_{95}) (geq/mL)	80.3	26.7	20.2	18.4

* From [24, 78].

2.4.2 Findings

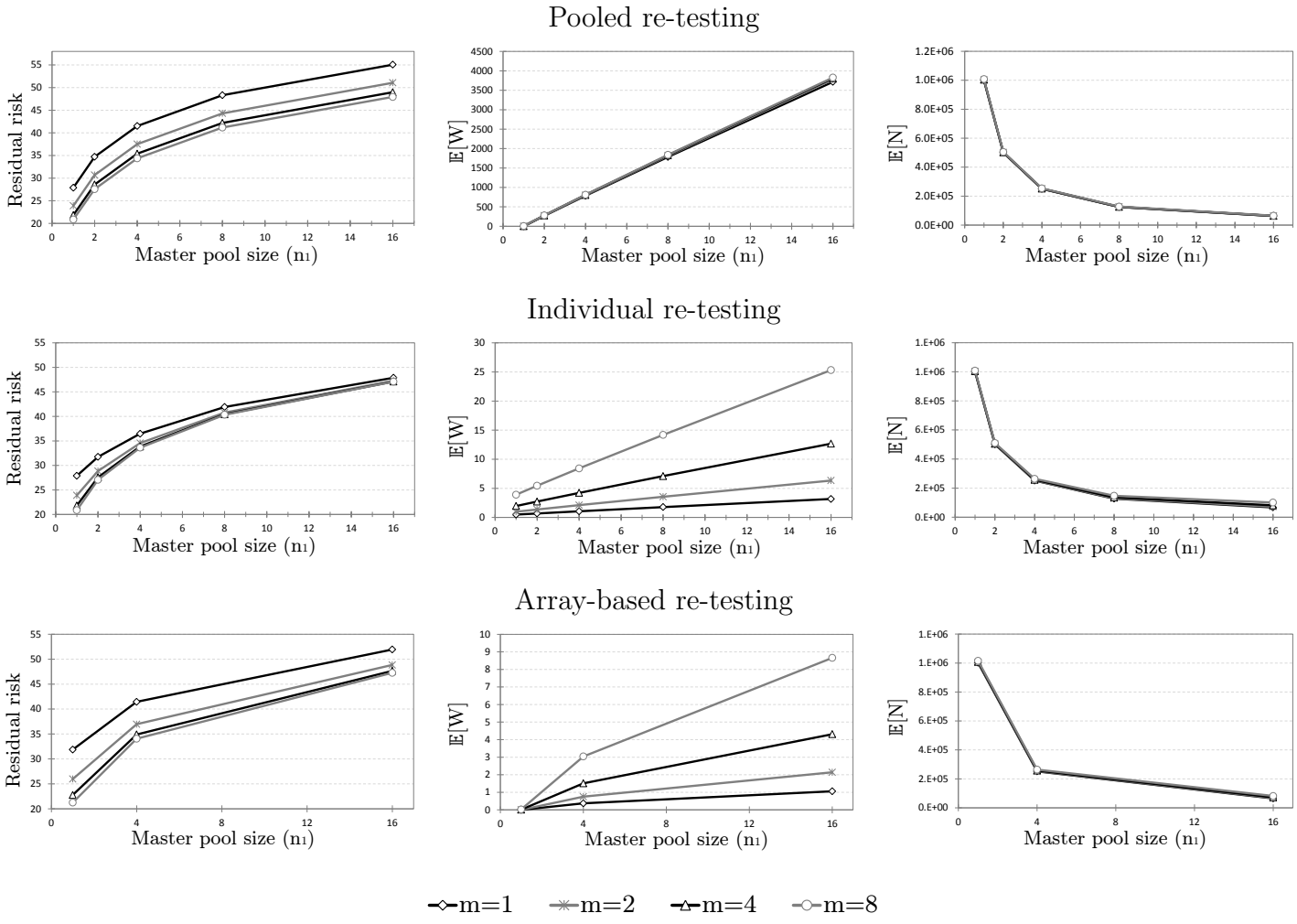
In Table 2.2, we report, per $1,000,000$ donations, the residual risk (expressed as the number of infected blood samples falsely accepted per $1,000,000$ donations, that is, $R \times 1,000,000$), expected number of units wasted $\big(\mathbb{E}[W]\big)$, and expected number of tests needed $\big(\mathbb{E}[N]\big)$. In addition, Figure 2.4 illustrates the change in each metric with respect to the number of re-tests and pool sizes for all testing schemes considered.

The numerical results in Table 2.2 provide some scale for the residual risk relationships de-

tailed in Lemma 2.1. As expected, the largest increase in R is observed for the least accurate test (ULTRIO HBV), and since R decreases with m, this occurs for $m = 1$. The largest increase in R, caused by re-testing, is the release of 11.5 additional infectious donations into the blood supply (over the 20.37 released under the no re-testing scheme), which occurs with array-based re-testing for a pool size of 1, but array-based re-testing is not efficient at such a small pool size. For the pooled re-testing ($m = 1$), around 7.5 extra infectious donations are released for a pool size of 1 (over the no re-testing value of 20.37), while the number of additional infectious donations is 8 for a pool size of 16 (over the no re-testing value of 47.08). Conversely, the R gap between the no re-testing and both the individual re-testing and array-based re-testing schemes reduces as pool size increases. For example, for individual re-testing (at $m = 1$), 7.5 additional infections are released, while for a pool-size of 16, only 0.8 additional infectious donations are released. For pooled re-testing, the number of re-tests decreases in pool size (see Table 2.2), but the dilution causes a significant number of false-negatives, adding considerable risk at $m = 1$ (as m increases, R converges to the no re-testing value, see Lemma 2.1). For individual re-testing, the number of re-tests increases in the pool size (fewer pools need to be re-tested, but these represent more individual re-tests due to the larger pool) and the lack of dilution allows most of the infected donations to be identified. The highest R occurs for the HBV, mainly due to longer window periods (up to 3.3 times longer than HIV and HCV).

Overall, waste in the no re-testing scheme increases with the pool size, as a positive test outcome causes the infection-free samples in the pool to be wasted. This effect is slightly countered by dilution, which decreases waste somewhat by increasing the probability of false-negative outcomes (hence increasing R, see Figure 2.4). This increase in waste with pool size under the no re-testing scheme carries through to all re-testing schemes. Of course, individual re-testing reduces the waste more than the pooled re-testing scheme, by eliminating the waste

Figure 2.4: Residual risk (left), expected waste (middle), and expected number of tests (right) as a function of master pool size (n_1) and number of re-tests (m) for ULTRIO HBV



inherent in pooling. As the number of re-tests (m) increases, so does the waste, due to the likelihood of a false-positive outcome; for large m, all waste figures tend to $\mathbb{E}[W^{NR}]$, but convergence to the no re-testing waste is slow; for instance, when $m = 8$ the waste for all re-testing schemes is still much smaller than the no re-testing waste (except for large pool sizes under pooled re-testing). This tends to encourage a higher number of re-tests, because waste converges (i.e., increases) much slower than R converges (decreases). Array-based re-testing incurs the lowest waste of all testing schemes (see Lemma 2.3). Also, for pool sizes larger than one, the waste is higher for more sensitive tests (e.g., ULTRIO Plus HBV compared

to ULTRIO HBV). However, when the master pool size equals one ($n_1 = 1$), the expected waste does not differ much for the different infections and tests, mainly due to low prevalence rates and the common specificity value used for the different tests. It is also interesting to note that with only one re-test, waste drastically decreases in all schemes (except for large pool sizes under pooled re-testing).

As Figure 2.4 illustrates, for a given pool size and number of re-tests, the expected number of tests does not vary much among the different testing schemes. This is primarily due to low prevalence rates, which imply that in the majority of the cases the blood would not be infected and thus, since test specificity does not depend on the pool size, $\mathbb{E}[N]$ in all schemes would be similar. The subtle differences observed are due to the portion of time the master pool tests positive. Of course, $\mathbb{E}[N]$ decreases with the master pool size and increases with the number of re-tests. Among the two-stage re-testing schemes, pooled re-testing leads to the lowest number of expected tests, while, for $n_1 \geq 4$, individual re-testing incurs the highest (see Lemma 2.2).

Table 2.2 displays the trade-offs among the performance metrics. For example, consider ULTRIO Plus HBV for a master pool size of one ($n_1 = 1$). After the first stage (see the no re-testing scheme), R is 11.27, i.e., out of $1,000,000$ donations, 11.27 infectious blood units are released into the blood supply. Comparing this with pooled re-testing with $m = 1$, R goes up to 17.35 units out of $1,000,000$ donations, but the waste drastically reduces (i.e., from 699.79 wasted units under no re-testing to 0.49 units under pooled re-testing (with $m = 1$) per $1,000,000$ donations). A similar pattern can be observed for any master pool size, any m, and also happens for the other two-stage schemes, individual re-testing and array-based re-testing. Indeed, the waste reduces drastically with any type of re-testing, with the highest reduction occurring for the individual re-testing and array-based re-testing schemes. On the other hand, the number of additional re-tests (from no re-testing to pooled

re-testing with $m = 1$) increases by 992, suggesting that, on average, 992 samples out of the 1,000,000 blood samples failed in the first stage, requiring further tests. Furthermore, the no re-testing waste is 699.79, which implies that out of 992 failed blood samples, 699.79 samples were infection-free and discarded due to false-positive outcomes. The remaining 291.21 samples were, thus, true-positives. When one pooled re-test ($m = 1$) is performed, 6 out of 291.21 samples incorrectly test negative, increasing the risk, but since test specificity is high, the majority of the false-positives are correctly identified as infection-free, reducing the waste to 0.49 donations out of the $1,000,000$ donations. For smaller pool sizes ($n_1 \leq 4$), the relative increase in the expected number of tests, as m increases, is low (the maximum increase is around 8.0%), while for larger pools ($n_1 \geq 8$) the increase is much more drastic (e.g., individual re-testing for HIV with $n_1 = 16,\ m = 8$ the maximum increase is around 100%).

To study the impact of the pooling dilution on the results, we remove the dilution effect from our model by replacing the pooled test sensitivity in Eq. (2.3) with that of individual testing, and analytically re-evaluate the performance metrics. Our results (which are not reported in this dissertation) indicate that failing to model the dilution effect leads to a significant underestimation of the residual risk, but does not alter the expected waste and expected number of tests much. These results encourage the incorporation of the dilution effect, especially for the blood screening context in which the residual risk reduction is the primary objective.

Finally, in order to study the effect of the variability in viral load growth, we extend our case study to two settings: a deterministic setting (with Λ in Eq. (2.1) replaced by its mean, μ) and a high variability setting in which μ remains the same, but $\sigma = \mu/3$, which ensures that Λ is non-negative 99.7% of the time. We find that the differences in the three performance metrics are minor in all three settings. However, for infection-test pairs with long window

periods and high variability in viral load growth, the differences can be large; and our model offers the flexibility to model this variability, unlike the previous models that consider either deterministic or Poisson viral load models [138, 139].

2.5 Cost-based Analysis

One way of incorporating the trade-offs among the various performance metrics in decision-making is by considering a cost-based objective to determine the least-cost testing scheme and its design (i.e., master pool size, n_1, and number of re-tests in the second stage, m - the second stage pool size, n_2, is a function of n_1, and is determined by the testing scheme). The current practice for US blood centers is to perform pooled NAT within pools of 16 for each of HIV, HBV, and HCV. In this section, we consider a maximum pool size of 25 for more flexibility, as much larger pool sizes are utilized in many countries $\big($e.g., pool sizes of up to 96 in some European countries [1]$\big)$. For each infection and each testing scheme, we perform a complete enumeration over (n_1, m), with $n_1 \in \{1, 2, \cdots, 25\}$ and $m \in \{1, 2, \cdots, 8\}$, and determine the least-cost scheme.

Table 2.3 reports the cost data used in our study and the least-cost testing scheme for each infection. Interestingly, for all infections considered, the array-based testing scheme provides the optimal strategy under our data. However, Dorfman-type testing is the strategy of choice for HIV, HBV, and HCV screening of donated blood in many countries, including the US and Europe [1, 40], while array-based testing is common in genetic testing (e.g., [2, 12, 30]). Moreover, according to the South African National Blood Service [111], the current HIV, HBV, and HCV blood screening procedure in South Africa is individual NAT; however, a significant portion of blood donations remains untested (e.g., in 2007, according to the WHO's Global Database on Blood Safety, there were at least 400,000 blood donations in

South Africa that were not tested for HIV, HBV, and HCV [136]). Thus, our study offers important insight into the value of array-based testing in blood screening, especially when the testing cost is high and/or prevalence rates are low. Finally, since the transmission cost of HIV is higher (see Table 2.3), our model recommends performing two re-tests for HIV in order to reduce the residual risk (see Lemma 2.1), and thus the cost of transmission.

Most data used in our study, and especially prevalence rates, are inherently uncertain. In particular, prevalence rates are typically estimated based on small sample sizes and/or sub-populations (e.g., pregnant women) that may not accurately represent the blood donor group, and may vary greatly among the regions (see [49] and the references therein). Further, for emerging and newly recognized TTIs, the sample size may even be more limited, adding to uncertainty [49]. To study the impact that the prevalence rate has on our cost-based function, we perform a one-way sensitivity analysis on the HIV prevalence rate. Specifically, we vary the HIV prevalence rate in the range of [0.01%-1.00%] and determine the least-cost strategy for each scenario; see Table 2.4. Interestingly, for low prevalence rates (which is the case in our study), the array-based testing scheme remains as the least-cost scheme; for higher prevalence rates, however, Dorfman-type testing becomes optimal. Moreover, as the prevalence rate increases, the least-cost master pool size reduces in order to counter the effect of dilution. This analysis highlights the value of studying pooled testing schemes considering infection, test, and regional characteristics, as we do in this chapter.

2.6 Conclusions and Future Research Directions

We derive analytical expressions for various performance metrics (the residual risk, expected waste, and expected number of tests) that are essential for assay selection in blood screening, while explicitly considering the joint impact of dilution, imperfect tests, in-sample variability,

and re-testing possibility. Our model expands upon the earlier works on pooled testing and provides accurate estimates, which can be used within a cost-based framework, such as the analysis in Section 2.5, for decision-making on blood screening strategies.

Interestingly, our analysis indicates that even by re-testing only once, the waste figures are drastically reduced, especially for smaller pool sizes. This is a useful insight, since the minor increase in the residual risk and number of tests resulting from re-testing might be justified by the drastic reduction in waste. The array-based re-testing scheme provides a middle ground between the high-risk, low-cost pooled re-testing and the low-risk, high-cost individual re-testing, and is an interesting alternative to traditional hierarchical testing schemes. Although it is under-utilized in infectious disease settings, it is promising, especially when the testing cost is high or prevalence rates are low. Indeed, this is justified by the cost-based analysis, which indicates that the least-cost strategy for all three infections (HIV, HBV, and HCV) is the array-based testing scheme (see Table 2.3). In summary, our analysis underscores the importance of considering all three metrics simultaneously in assay selection. Further, it indicates that relaxing some of the assumptions made in the literature, such as the perfect specificity assumption, substantially alters the metrics, especially the waste.

Potential improvements to our model include utilizing an expanded viral load model that spans the life-time of an infection to also model chronic or occult phases, studying multi-stage pooling strategies, and investigating other types of re-testing schemes that can reduce the residual risk. We hope that this work motivates and guides future research in this important area.

Table 2.2: Performance metrics for HIV, HBV, and HCV

		Pooled re-testing (PR)				Individual re-testing (IR)				Array-based re-testing (AR)			
		Number of re-tests in the second stage (m)											
Master pool size (n_1)	No re-testing (NR)	1	2	4	8	1	2	4	8	1	2	4	8
ULTRIO HBV						Residual risk (R)							
1	20.37	27.89	23.90	21.83	20.87	27.89	23.90	21.83	20.87	31.87	25.97	22.78	21.25
2	26.84	34.70	30.69	28.58	27.57	31.74	28.86	27.57	27.07	-	-	-	-
4	33.54	41.52	37.51	35.40	34.37	36.47	34.56	33.86	33.63	41.45	36.96	34.90	34.05
8	40.32	48.32	44.31	42.20	41.18	41.92	40.77	40.43	40.34	-	-	-	-
16	47.08	55.07	51.07	48.97	47.94	47.88	47.26	47.11	47.08	51.94	48.84	47.66	47.27
						Expected waste $\mathbb{E}[W]$							
1	699.79	0.49	0.98	1.96	3.91	0.49	0.98	1.96	3.91	0.00	0.00	0.01	0.02
2	976.21	269.26	273.76	276.84	279.81	0.68	1.37	2.73	5.45	-	-	-	-
4	1,508.66	786.08	798.59	805.90	810.92	1.06	2.11	4.22	8.43	0.37	0.75	1.51	3.04
8	2,538.45	1,784.63	1,813.15	1,828.89	1,838.01	1.78	3.55	7.10	14.18	-	-	-	-
16	4,532.89	3,716.89	3,777.27	3,809.84	3,827.13	3.17	6.34	12.68	25.32	1.06	2.14	4.31	8.66
						Expected number of tests $\mathbb{E}[N]$							
1	1,000,000	1,000,983	1,001,966	1,003,932	1,007,864	1,000,983	1,001,966	1,003,932	1,007,864	1,001,966	1,003,932	1,007,864	1,015,727
2	500,000	500,626	501,253	502,506	505,011	501,253	502,506	505,011	510,023	-	-	-	-
4	250,000	250,445	250,889	251,778	253,557	251,778	253,557	257,114	264,228	251,778	253,557	257,114	264,228
8	125,000	125,350	125,700	126,401	127,801	127,801	130,603	136,205	147,411	-	-	-	-
16	62,500	62,799	63,099	63,697	64,894	67,289	72,077	81,655	100,809	64,894	67,289	72,077	81,655
ULTRIO Plus HBV						Residual risk (R)							
1	11.27	17.35	13.62	11.92	11.37	17.35	13.62	11.92	11.37	21.09	15.32	12.46	11.46
2	16.79	23.92	19.98	17.98	17.11	21.04	18.27	17.16	16.84	-	-	-	-
4	23.00	30.69	26.69	24.60	23.61	25.69	23.83	23.19	23.03	30.61	26.13	24.10	23.29
8	29.58	37.49	33.49	31.38	30.36	31.11	29.98	29.66	29.59	-	-	-	-
16	36.29	44.25	40.26	38.16	37.13	37.07	36.45	36.31	36.29	41.12	38.02	36.85	36.46
						Expected waste $\mathbb{E}[W]$							
1	699.79	0.49	0.98	1.96	3.91	0.49	0.98	1.96	3.91	0.00	0.00	0.01	0.02
2	986.27	280.04	284.48	287.46	290.27	0.69	1.38	2.76	5.51	-	-	-	-
4	1,540.29	818.57	831.04	838.29	843.22	1.08	2.16	4.31	8.60	0.39	0.78	1.57	3.16
8	2,613.61	1,860.45	1,888.93	1,904.64	1,913.73	1.83	3.66	7.31	14.60	-	-	-	-
16	4,694.72	3,879.16	3,939.49	3,972.02	3,989.30	3.29	6.57	13.13	26.23	1.11	2.24	4.49	9.03
						Expected number of tests $\mathbb{E}[N]$							
1	1,000,000	1,000,992	1,001,984	1,003,968	1,007,936	1,000,992	1,001,984	1,003,968	1,007,936	1,001,984	1,003,968	1,007,936	1,015,873
2	500,000	500,636	501,273	502,546	505,092	501,273	502,546	505,092	510,184	-	-	-	-
4	250,000	250,455	250,910	251,821	253,641	251,821	253,641	257,283	264,565	251,821	253,641	257,283	264,565
8	125,000	125,361	125,722	126,444	127,887	127,887	130,774	136,549	148,098	-	-	-	-
16	62,500	62,810	63,120	63,740	64,981	67,461	72,423	82,345	102,190	64,981	67,461	72,423	82,345
ULTRIO HCV						Residual risk (R)							
1	0.06	0.09	0.07	0.06	0.06	0.09	0.07	0.06	0.06	0.11	0.08	0.06	0.06
2	0.09	0.13	0.11	0.10	0.09	0.11	0.10	0.09	0.09	-	-	-	-
4	0.13	0.17	0.15	0.13	0.13	0.14	0.13	0.13	0.13	0.16	0.14	0.13	0.13
8	0.16	0.21	0.19	0.17	0.17	0.17	0.17	0.16	0.16	-	-	-	-
16	0.20	0.25	0.23	0.21	0.21	0.21	0.20	0.20	0.20	0.23	0.21	0.21	0.20
						Expected waste $\mathbb{E}[W]$							
1	699.99	0.49	0.98	1.96	3.91	0.49	0.98	1.96	3.91	0.00	0.00	0.01	0.02
2	713.09	13.56	14.07	15.06	17.01	0.50	1.00	1.99	3.98	-	-	-	-
4	739.17	39.57	40.12	41.14	43.11	0.52	1.03	2.07	4.13	0.02	0.04	0.08	0.17
8	791.13	91.40	92.04	93.09	95.09	0.55	1.11	2.21	4.42	-	-	-	-
16	894.69	194.68	195.50	196.64	198.68	0.63	1.25	2.50	5.00	0.05	0.11	0.22	0.46
						Expected number of tests $\mathbb{E}[N]$							
1	1,000,000	1,000,713	1,001,426	1,002,853	1,005,705	1,000,713	1,001,426	1,002,853	1,005,705	1,001,426	1,002,853	1,005,705	1,011,410
2	500,000	500,363	500,726	501,452	502,905	500,726	501,452	502,905	505,810	-	-	-	-
4	250,000	250,188	250,376	250,752	251,504	250,752	251,504	253,009	256,018	250,752	251,504	253,009	256,018
8	125,000	125,101	125,201	125,402	125,804	125,804	126,608	128,217	131,433	-	-	-	-
16	62,500	62,557	62,613	62,727	62,954	63,408	64,315	66,131	69,761	62,954	63,408	64,315	66,131
ULTRIO HIV						Residual risk (R)							
1	2.13	3.49	2.56	2.21	2.13	3.49	2.56	2.21	2.13	4.42	2.92	2.28	2.14
2	3.79	5.62	4.55	4.03	3.84	4.71	4.05	3.83	3.79	-	-	-	-
4	5.82	7.92	6.81	6.24	5.97	6.35	5.95	5.84	5.82	7.67	6.53	6.03	5.86
8	8.06	10.25	9.14	8.55	8.27	8.31	8.11	8.06	8.06	-	-	-	-
16	10.35	12.56	11.45	10.87	10.59	10.45	10.37	10.35	10.35	11.39	10.69	10.45	10.38
						Expected waste $\mathbb{E}[W]$							
1	699.68	0.49	0.98	1.96	3.91	0.49	0.98	1.96	3.91	0.00	0.00	0.01	0.02
2	1,152.99	452.28	453.84	455.34	457.49	0.81	1.61	3.22	6.44	-	-	-	-
4	2,052.87	1,348.34	1,352.15	1,354.86	1,357.61	1.44	2.87	5.74	11.47	0.63	1.26	2.53	5.08
8	3,838.56	3,126.27	3,134.53	3,139.59	3,143.52	2.69	5.37	10.74	21.44	-	-	-	-
16	7,378.92	6,651.33	6,668.44	6,678.17	6,684.36	5.17	10.33	20.64	41.22	1.87	3.75	7.51	15.08
						Expected number of tests $\mathbb{E}[N]$							
1	1,000,000	1,001,155	1,002,310	1,004,620	1,009,241	1,001,155	1,002,310	1,004,620	1,009,241	1,002,310	1,004,620	1,009,241	1,018,481
2	500,000	500,803	501,607	503,213	506,426	501,607	503,213	506,426	512,853	-	-	-	-
4	250,000	250,626	251,252	252,504	255,009	252,504	255,009	260,017	270,034	252,504	255,009	260,017	270,034
8	125,000	125,536	126,072	127,144	129,287	129,287	133,575	142,149	159,298	-	-	-	-
16	62,500	62,989	63,478	64,456	66,412	70,325	78,149	93,798	125,096	66,412	70,325	78,149	93,798

Table 2.3: Cost-based analysis: Data and results

	HBV	HCV	HIV	Source
Costs				
Testing cost per donation*	\$35	\$30	\$30	Jackson et al. [78]
Cost of a symptomatic TTI case†	\$11,288	\$8,355	\$260,193	Marshal et al. [95]
Cost of wasted blood per donation‡	\$625	\$625	\$625	Bish et al. [23], Simon et al. [113]
The least-cost testing scheme				
Testing scheme	AR	AR	AR	
Master pool size (n_1)	25	25	25	
Number of re-tests (m)	1	1	2	
Total cost per donation	\$2.01	\$1.21	\$4.63	

* Cost of single-donation NAT.

† Average life-time medical cost per patient. Estimated based on the average age of the US population, of 37 years [127].

‡ Cost of donor medical evaluation and disposal of blood.

Table 2.4: One-way prevalence sensitivity analysis for the least-cost HIV testing scheme

Prevalence rate	Least-cost testing scheme	Master pool size (n_1)	Number of re-tests (m)	Total cost per donation
0.010%	AR	25	1	\$1.96
0.020%	AR	25	1	\$2.71
0.050%	AR	25	2	\$4.94
0.100%	IR	14	1	\$8.26
0.500%	IR	3	2	\$25.44
1.000%	IR	2	3	\$38.86

Chapter 3

Adaptive Risk-based Pooling in Public Health Screening

3.1 Introduction and Motivation

Screening for diseases is an important, and extensively used, public health tool. The *classification problem* (i.e., classifying each subject as positive versus negative for a disease) involves testing a large number of subjects for infectious or genetic diseases through in-vitro laboratory tests performed on specimens (e.g., blood, urine, tissue swabs) from the subjects so as to measure the concentration (load) of a disease-related bio-marker. Public health screening is performed when early detection can improve clinical outcomes, and/or to reduce the spread of infectious diseases, especially for diseases that have slow to develop and/or initially non-specific symptoms (e.g., AIDS, Zika, hepatitis), and can save lives, reduce suffering, and decrease healthcare expenditures. However, due to limited resources, efficiency is essential. Because screening usually involves large populations and diseases with low prevalence rates, *pooled testing* (testing combined specimens from multiple subjects via a single test) is com-

monly used to improve the efficiency of screening efforts. Pooling schemes studied in the literature test each specimen multiple times, as only a small sample from the collected specimen is required for a test; therefore, multiple *tier* schemes, i.e., two- or three-tier schemes, are common in order to increase the classification accuracy of the schemes.

In designing a pooling scheme, certain issues should be considered: **1)** screening tests are imperfect (e.g., due to biological factors, including the time, post exposure, it takes for the bio-markers to reach levels detectable by the test); and *false positives* (i.e., subjects falsely classified as positive for the disease) and *false negatives* (i.e., subjects falsely classified as negative for the disease) are possible; **2)** pooling may further reduce the classification accuracy, as it leads to the *dilution* of the true-positive specimen's bio-marker load with true-negative specimens in the pool, resulting in a higher false negative probability [32, 76, 137]; and, **3)** the population can often be segmented into sub-populations having different prevalence rates (e.g., based on disease risk factors), that is, the population is *heterogeneous* in terms of the probability of positivity (*risk*) for the disease in question. Consequently, a major public health challenge is to design efficient *screening policies with pooling* so as to accurately classify subjects in a large population with limited resources, considering imperfect tests, dilution effect of pooling, and population heterogeneity; this problem is the focus of this chapter. In our context, a screening policy involves the *testing design* (e.g., pool sizes) as well as the *assignment of subjects*, each with different risk, to the pools.

There are two main types of pooling schemes studied in the literature and adopted in practice: **1)** *Dorfman pooling* [46], which is widely used in infectious disease screening [82, 107], entomology [132], pharmaceuticals and drug discovery [74, 81], and various other industrial applications [114]; and, **2)** *array pooling* [105], which is often used in genetics screening (e.g., [2,12,30]). Dorfman pooling was introduced in 1943 as a way to test military inductees for syphilis in an economical manner [46]. The Dorfman pooling scheme has two tiers: the

first tier is a pooled test; if the pool tests negative, then all subjects in the pool are classified as negative; and if the pool tests positive, then, in a second tier, all subjects in the pool are individually tested (using a new sample from each specimen). Dorfman's idea of pooling (for syphilis screening), using the Wasserman-type antibody blood test, was not used in the 1940's, mainly due to some unrealistic assumptions imposed on the original model, such as no testing errors or dilution, which could be significant for syphilis screening [47]. Since Dorfman's seminal work, variations of the two-tier Dorfman pooling have been studied, and the most restrictive assumptions of Dorfman's original model have been somewhat relaxed to consider imperfect tests (e.g., [3, 4, 59, 62, 80, 86, 92, 122]) and dilution (e.g., [32, 76, 137]). The second type of pooling scheme, array pooling, places samples of specimens from mn subjects into an $m \times n$ matrix, forming $m+n$ overlapping pools (m row pools and n column pools; thus a sample of each subject's specimen lies in a unique pair of pools) that are tested simultaneously. Under perfect tests, all positive subjects will lie at the intersection of a positive-testing row and a positive-testing column. In the realistic case of imperfect tests, however, a decision rule must be constructed, leading to many variations (e.g., [85,86]). Over the years, array pooling has been extended to higher dimensional arrays (e.g., [85]), and has been studied under imperfect tests (e.g., [66, 86, 98]) and dilution (e.g., [66]). While a large number of policies having multi-tier testing designs are possible in both Dorfman and array pooling, complex designs can be very difficult to implement in practice [85, 86, 96, 137], and as a result, most of the extant literature studies two- and three-tier pooling designs (see, e.g., [46, 86, 105, 109]). Therefore, in this chapter, we also restrict our study to three-tier testing designs, as our goal is to provide actionable guidelines for practitioners.

Yet another consideration in designing a pooling scheme is the level of *adaptivity*, i.e., whether or not the testing procedure for subsequent tiers is determined based on the observed outcome of earlier tiers. Two-tier Dorfman pooling is an example of an adaptive scheme, because Tier

2 individual testing is performed only if the Tier 1 pooled test outcome is positive. While the array pooling described above is not adaptive, adaptive array pooling is possible. For example, the row pools can be considered Tier 1, and column pools as Tier 2. The Tier 2 column pool testing can be modified based on Tier 1 results in a number of ways: For instance, in [105], if exactly one row pool tests positive, then all subjects in that row are tested individually in Tier 2; and if more than one row pool tests positive, then all column pools are tested in Tier 2.

The majority of the existing literature on pooled testing assumes a *homogeneous* population, i.e., all subjects have the same risk for the disease in question. In the homogeneous setting, with no risk-based differentiation among the subjects, the only decision is the testing design (i.e., pool sizes in Dorfman pooling, and dimensions of the testing matrix in array pooling), and subjects are assigned to pools randomly. However, many studies show that the prevalence rate of a disease can vary, sometimes significantly, based on demographic and/or clinical risk factors, e.g., 62% of all reported cases for chlamydia, one of the most prevalent sexually transmitted diseases (STDs) in the United States (US), occur in people between 15-24 years of age [35]; the human immunodeficiency virus (HIV) prevalence rate of first-time blood donors is seven times higher than that of repeat donors [143]. Indeed, as we show in this work, incorporating such population level characteristics into the modeling framework is essential for improving both the classification accuracy and efficiency of screening, and is feasible, as various clinical and demographics data are often collected prior to screening; e.g., gender, age, race/ethnicity, reason for testing, and pregnancy status, is collected for STD testing [35]; gender, age, first-time vs repeat donor status is collected from all US blood donors [54]. In models where the heterogeneity of the population is taken into account, in addition to the testing design decision, the decision-maker also needs to determine the *assignment* of subjects, with different risk, to testing pools.

While some papers investigate the testing design for array pooling, most of this work considers homogeneous populations; thus, there is no subject assignment decision, and the only decision variables are the dimensions of the testing matrix. Further, all this research determines the testing design, either via enumeration or heuristically, so as to minimize the expected number of tests (rather than maximize the classification accuracy under limited testing budgets, as we do in this chapter), considering square testing matrices only and for a homogeneous population, and either under perfect tests [73], or imperfect tests but without the dilution effect [98]. On the other hand, research that studies the subject assignment decision in array pooling for heterogeneous populations is extremely limited; this research studies non-adaptive array pooling schemes (i.e., row pools and column pools are tested simultaneously) via solely numerical studies of various heuristics (e.g., [98]), without characterization of the properties of an optimal assignment and without considering the dilution effect of pooling. The assumption of no dilution is indeed restrictive, as classification accuracy may deteriorate substantially with the dilution that comes with pooling. For example, clinical research shows that the sensitivity (i.e., true positive probability) of the HIV Ultrio Plus NAT blood test reduces from near perfect sensitivity, for individual testing, to only 88% when pools of size 16 are used [119]. Such reductions in sensitivity underscore the need to model and study the dilution effect of pooling for certain tests. In particular, the objective of minimizing the expected number of tests is common in the extant literature on both testing design and subject assignment (the latter applies to heterogeneous populations only). In this chapter, we take a different approach, of maximizing the classification accuracy under a testing budget constraint, as this is the main objective of the decision-maker in public health screening.

In particular, we formulate the testing design problem so as to minimize the expected number of false negative classifications under a budget constraint, which includes the testing cost

and the cost of false positive classifications. This formulation applies especially in settings in which false negatives lead to substantially more severe consequences than false positives, and in which false positives are subject to further confirmatory testing that has near perfect sensitivity and specificity. Examples include donated blood screening, as transfusion with infected blood may lead to severe infections, e.g., HIV, hepatitis virus infections, in transfusion recipients, and it is common practice in the US to apply confirmatory testing to all blood specimens that test positive in screening, to appropriately inform the infected donors, but the blood that tests positive during screening is not used in transfusion [41]. This objective is in line with the transfusion literature, which mainly focuses on false negatives, e.g., [4, 138, 139]. However, false positives also carry negative consequences, as they can potentially lead to not only higher costs, due to additional confirmatory tests, but also to anxiety and stress in patients. We account for these negative effects by incorporating the expected number of false positives into the budget constraint, thus penalizing false positives; and through a three-tier testing scheme, in which the third tier consists of individual testing. Our analysis indicates that this third tier substancially reduces the false positives, while having minimal impact on the false negatives, especially when individual testing has almost perfect sensitivity.

Thus, all performance metrics, false negatives, false positives, and testing cost are taken into account in the testing design decision, which is made under uncertainty on subject risk vector. Then, given a testing design, the subjects are assigned to the testing matrix after the subject risk vector is observed for the set of subjects to be screened in a given period (e.g., a day), and in this stage, the assignment decision is made so as to minimize the expected number of false negatives. Due to the complexity of this problem, following the literature we solve the testing design problem under a homogeneous population assumption, but our model differs from the existing literature in that we consider maximization of the

Table 3.1: Summary of the pooled testing literature

Pooled Testing	Homogeneous population	No Dilution	[8, 15, 46, 62, 73, 80, 85, 86, 92, 105, 114, 118, 124, 125]
		With Dilution	[4, 32, 66, 76, 137]
	Heterogeneous population	No Dilution	[20, 21, 26, 27, 31, 75, 96, 98, 109]
		With Dilution	[48]

classification accuracy under a testing budget constraint, as opposed to minimization of the expected number of tests, as discussed above. Then, in the subject assignment problem, we take the heterogeneity of the population into account to make the subject assignment decisions based on their risk.

Table 3.1 provides a summary of the related literature with respect to various important dimensions of the pooled testing problem. The vast majority of the literature studies the pooled testing problem under the assumption of a homogeneous population, with very limited work done on risk-based pooled testing for a heterogeneous population. Moreover, even fewer papers investigate the pooled testing problem for a heterogeneous population under the dilution effect of pooling. However, incorporating the dilution effect and the heterogeneity in the population adds considerable realism to the testing problem. Therefore, motivated by this gap in the literature, in this chapter we investigate risk-based pooled testing schemes for a heterogeneous population, while taking into account the dilution effect of pooling.

Our contributions in this chapter are multi-fold: To our knowledge, our work is the first to study the testing design and subject assignment decisions for an *adaptive risk-based array pooling* scheme, while taking into account important test and population level characteristics, including imperfect tests and an adaptive testing scheme, dilution effect of pooling, and risk profile of subjects; for this purpose, we consider a novel formulation, of maximizing the classification accuracy under a testing budget constraint. From that perspective, our optimization-based model provides a realistic treatment of the important issues surround-

ing pooling, and offers a paradigm shift, from the traditional test minimization approach used in most of the existing literature, to classification accuracy maximization under limited resources. Our analytical results characterize the properties of optimal subject assignment policies. In addition, we perform a case study, using published data, on chlamydia screening in the US. The case study demonstrates that the proposed adaptive risk-based policy substantially reduces both false negative and false positive classifications over screening schemes studied in the literature, while remaining within current testing budgets, underscoring the power of the proposed optimization-based framework and the effectiveness of adaptive risk-based pooling.

The remainder of this chapter is organized as follows. Section 3.2 discusses the decision problem, assumptions, and our modeling. Then, Section 3.3 studies the assignment of subjects to pools and the testing design. Section 3.4 discusses findings from the case study and compares our model to previously proposed policies. Finally, Section 3.5 summarizes our findings and provides suggestions for future research. To facilitate the presentation, all proofs are provided in the appendix.

3.2 The Notation and Model

Throughout, we will use the terms "positive" and "negative" to refer both to subjects (i.e., to respectively denote the presence or absence of the infection in question for the subject) and to test outcomes (i.e., to respectively denote the test outcomes that *indicate* the presence or absence of the infection). To simplify the terminology, we will use "subject" to refer both to a subject and to a specimen taken from the subject. We denote random variables in upper-case letters and their realization in lower-case letters, and vectors in bold face.

In what follows, we first describe the decision problem, and then discuss the modeling of the

dilution effect and the heterogeneity in the population.

3.2.1 The Decision Problem

We consider an adaptive risk-based array pooling scheme in which the subjects are placed in an $m \times n$ testing matrix. The decision-maker (e.g., the lab) needs to determine: (i) the **testing design**, i.e., the dimensions, m and n, of the testing matrix, so as to minimize the expected number of false negative classifications under a budget constraint, which includes the testing cost and the cost of false positives; and (ii) the **assignment of subjects**, with different risk factors, to the pools (i.e., placement of the subjects in the testing matrix). The testing follows a three-tier testing scheme:

Adaptive three-tier array pooling: In Tier 1, all row pools are tested; if the test outcome of at least one row pool is positive, then testing proceeds to Tier 2. In Tier 2, the testing matrix is *reduced* to include the subjects in positive-testing rows only (this reduces dilution in Tier 2), and all column pools of the reduced testing matrix are tested. In Tier 3, all subjects lying at the intersection of a positive-testing row and a positive-testing column are individually tested and are classified based on the outcome of the individual test. All other subjects are classified as negative.

We note here that the main reason for the inclusion of the third tier in our testing scheme is to reduce the false positives. Indeed, our numerical study in Section 3.4 shows that the third tier substantially reduces the number of false positives, while having minimal impact on the false negatives, especially when individual testing has almost perfect sensitivity.

In contrast to the adaptive array scheme described above, the extant literature mainly focuses on non-adaptive array pooling schemes in which row and column pools are tested simultaneously (followed by individual testing of select subjects [73,86,105]). However, adaptive array

schemes, such as the one proposed here, offer several benefits over non-adaptive schemes, including a reduction in the expected number of tests and a reduction in the dilution effect in the second tier column testing. The latter happens because the second tier column testing is performed only on a subset of the subjects, i.e., subjects that belong to positive-testing rows in the first tier row testing. On the other hand, non-adaptive array schemes also offer some benefits, e.g., ease of implementation and shorter overall testing times, as all row and column pools are tested simultaneously (see Section 3.4 for a comparison of our model to non-adaptive array pooling schemes).

The testing design is **static**, i.e., it is made only once and used repetitively each testing period (e.g., day), as it is a tactical decision because equipment setup and process rules are not easy to change on an operational basis. In this chapter, our main focus is on the value of an adaptive testing scheme and risk-based assignment of the heterogeneous subjects to the testing matrix. Towards this end, and following the literature, we determine the testing design (i.e., m and n) under the assumption of a homogeneous population [86,98] (see Section 3.3.2 for the testing design problem).

Let $FN(m,n)$ ($FP(m,n)$) denote the random number of false negatives (positives) incurred for mn subjects tested within an $m \times n$ matrix, with $FN^l(m,n)$ ($FP^l(m,n)$), $l = 1,2,3$, denoting the random number of false negatives (positives) incurred in Tier l, and let $T(m,n)$ denote the random number of total tests required for mn subjects. As discussed in Section 3.1, we consider settings in which false negatives lead to substantially more severe consequences than false positives (e.g., blood screening, STD screening), mainly because a false negative indicates a missed diagnosis, while false positives are discovered through subsequent confirmatory testing [4, 138, 139].

3.2.2 Modeling the Dilution Effect and Heterogeneity of the Population

An important component of our model is the modeling of the *dilution effect of pooling* in a generic manner. Let $Se(n,k)$ denote the conditional probability that the pooled test outcome is positive for a pool of size n given that the pool contains k truly positive subjects (conditional sensitivity of the test), $0 \leq k \leq n,\ k,n \in \mathbb{Z}^+$. We let $Se(n,0) = 1 - Sp(n)$, where $Sp(n)$ denotes the test's specificity (true negative probability, i.e., the probability that the test outcome for a pool of size n is negative given that all subjects in the pool are truly negative). We consider general test sensitivity functions that satisfy only two monotonicity properties related to dilution:

Property 1: $Se(n,k)$ is non-increasing in n, for all $k \leq n,\ k,n \in \mathbb{Z}^+$.

Property 2: $Se(n,k)$ is non-decreasing in k, for all $k \leq n,\ k,n \in \mathbb{Z}^+$.

Not surprisingly, Properties 1 and 2 are satisfied by FDA-licensed blood and STD screening tests (e.g., [119] illustrates how the HIV, HBV, and HCV NAT tests adhere to Properties 1 and 2). Specifically, for a given number of truly positive subjects in a pool, test sensitivity is impaired as pool size increases, since dilution becomes more pronounced (Property 1); and as the number of truly positive subjects in a pool increases, the test will have a higher probability of testing positive due to a higher marker load in the pool, hence a higher sensitivity (Property 2). While test sensitivity is modeled as a function of pool size, test specificity is assumed constant and independent of pool size, i.e., $Sp = Sp(n),\ \forall n \in \mathbb{Z}^+$, as in the absence of any infected specimens in a pool, false positives occur mainly due to technical or human error, and hence are typically not affected by pool size. In addition, we assume that individual testing has perfect sensitivity, i.e., $Se(1,1) = 1$. Indeed, tests that

are utilized in pooled testing are often highly sensitive when conducted individually, e.g., the HIV ULTRIO Plus NAT test has an individual test sensitivity of 0.9998 for HIV testing [6].

To represent the *heterogeneity* in the population, let P_k denote the probability that subject k, with certain risk factors, is truly positive for the disease (hereafter referred to as "risk"). Then, random variable D_k (unobservable by the lab) is 1 if subject k is truly positive, and 0 otherwise, i.e., $D_k \sim \text{Bernoulli}(P_k)$. We assume that random variables $D_k, \forall\ k$, are independent. Observe that in this setting, the probability of having k infected subjects in a pool of size n needs to be derived by conditioning on *which* k subjects are positive.

3.3 Structural Properties of an Optimal Risk-based Assignment

In this section, we first investigate, in Section 3.3.1, the subject assignment problem, for a given configuration, m and n, and risk vector realization, $\boldsymbol{p}$, and establish structural properties of an optimal assignment policy for subjects with different risk profiles. Then, in Section 3.3.2, we formulate the testing design problem that generates a static design considering a homogeneous population.

3.3.1 Assignment of Subjects to Pools

Given an $m \times n$ testing matrix and a risk vector realization $\boldsymbol{p}$ for mn subjects, the subjects need to be assigned to row pools in Tier 1, and to column pools in Tier 2 *given* Tier 1 testing outcome. Note that there is no assignment decision in Tier 3, which corresponds to individually testing select subjects. Towards this end, let $\boldsymbol{x^1} = (x^1_{ik})_{i=1,\cdots,m,\ k\in\Omega}$ and $\boldsymbol{x^2} = (x^2_{jk})_{j=1,\cdots,n,\ k\in\Omega^2}$ respectively denote the first and second tier assignment vectors,

where

$$x^1_{ik} = \begin{cases} 1, & \text{if subject } k \text{ is assigned to row } i \\ & \text{in Tier 1} \\ 0, & \text{otherwise} \end{cases}, \; x^2_{jk} = \begin{cases} 1, & \text{if subject } k \text{ is assigned to column} \\ & j \text{ in Tier 2} \\ 0, & \text{otherwise} \end{cases},$$

where $\Omega = \{1, \cdots, mn\}$ and $\Omega^2 \equiv \{k \in \Omega : x^1_{ik} R_i = 1, i = 1, \cdots, m\}$, with $R_i = 1$ if Row i pool tests positive, and 0 otherwise, that is, Ω^2 is the set of subjects whose assigned row tests positive in Tier 1 (i.e., the set of subjects for which Tier 2 testing needs to be conducted).

Let $\boldsymbol{R} = (R_i)_{i=1,\cdots,m}$ denote the random test outcome vector for Tier 1 row pools, and define counting random variables, $N_d = \sum_{k\in\Omega} D_k$ and $N_r = \sum_{i=1}^{m} R_i$, as the number of truly positive subjects in the testing matrix, and the number of positive-testing rows in Tier 1, respectively. Also let $N^i_{d,r}(\boldsymbol{x^1}) \equiv \sum_{k\in\Omega} D_k x^1_{ik}$ and $N^j_{d,c}(\boldsymbol{x^1}, \boldsymbol{x^2}) \equiv \sum_{k\in\Omega^2} D_k x^2_{jk}$ respectively denote the number of truly positive subjects in row i, $i = 1, \cdots, m$, of the original (Tier 1) testing matrix, and in column j, $j = 1, \cdots, n$, of the reduced (Tier 2) testing matrix. In Tier 2, we relabel the rows of the reduced matrix as $1, \cdots, n_r$, where n_r is a realization of the random variable N_r.

Problem Formulation

The objective is to assign subjects to the testing matrix so as to minimize the total expected number, per subject, of false negatives, i.e., the expected number of false negatives incurred in Tier 1 plus the expected number of false negatives incurred in Tier 2, where the latter needs to be computed for each possible Tier 1 assignment vector $\boldsymbol{x}^1$, via the law of total expectation, i.e., by conditioning on the $\boldsymbol{R}$ vector. However, observe that the probability

mass function of $\boldsymbol{R}$, i.e., $P(\boldsymbol{R}(\boldsymbol{x}^1) = \boldsymbol{r})$, $\forall \boldsymbol{r}$, is a function of the Tier 1 assignment vector, $\boldsymbol{x}^1$, and further, the dimensionality of $\boldsymbol{x}^2$ depends on $\boldsymbol{x}^1$ and the realization of $\boldsymbol{R}$, because not every subject undergoes testing in Tier 2. Consequently, we do not have closed-form expressions on $\mathbb{E}\big[FN^2(\boldsymbol{x}^2)|\boldsymbol{r}\big]$ and $P(\boldsymbol{R}(\boldsymbol{x}^1) = \boldsymbol{r})$ for a given Tier 1 assignment decision. Further, the number of possible assignment decisions in each of Tiers 1 and 2 is huge, e.g., for an $m \times n$ testing matrix, the number of possible Tier 1 assignments is in the order of $(mn)!$, which, even for a moderate matrix size, is huge. Therefore, this alternative formulation is intractable; hence, for analytical tractability, we proceed by minimizing the expected number of false negatives in each tier separately, i.e., $\frac{1}{mn}\mathbb{E}[FN^1|\boldsymbol{p}]$ in Tier 1, and $\frac{1}{mn}\mathbb{E}[FN^2|\boldsymbol{r},\boldsymbol{p}]$ in Tier 2, i.e., the latter is *conditional* on Tier 1 outcome, as given in (3.1) and (3.2):

Tier 1 Assignment Problem:

$$\begin{aligned}
\min_{\boldsymbol{x^1}} \quad & \frac{1}{mn}\mathbb{E}[FN^1(\boldsymbol{x^1}) \mid \boldsymbol{p}] = \frac{1}{mn}\sum_{i=1}^{m}\sum_{k=1}^{n} k\big[1 - Se(n,k)\big]P(N^i_{d,r}(\boldsymbol{x^1}) = k \mid \boldsymbol{p}) \\
\text{s.t.} \quad & \sum_{k\in\Omega} x^1_{ik} = n, \quad \forall\, i = 1, \cdots, m \\
& \sum_{i=1}^{m} x^1_{ik} = 1, \quad \forall\, k \in \Omega \\
& x^1_{ik} \in \{0,1\}, \quad \forall\, i = 1, \cdots, m,\ \forall\, k \in \Omega.
\end{aligned} \tag{3.1}$$

Tier 2 Assignment Problem:

$$\begin{aligned}
\min_{\boldsymbol{x^2}} \quad & \frac{1}{mn}\mathbb{E}[FN^2(\boldsymbol{x^2}) \mid \boldsymbol{r},\boldsymbol{p}] = \frac{1}{mn}\sum_{j=1}^{n}\sum_{k=1}^{n_r} k\big[1 - Se(n_r,k)\big]P(N^j_{d,c}(\boldsymbol{x^1},\boldsymbol{x^2}) = k \mid \boldsymbol{r},\boldsymbol{p}) \\
\text{s.t.} \quad & \sum_{k\in\Omega^2} x^2_{jk} = n_r, \quad \forall\, j = 1, \cdots, n \\
& \sum_{j=1}^{n} x^2_{jk} = 1, \quad \forall\, k \in \Omega^2|\boldsymbol{r} \\
& x^2_{jk} \in \{0,1\}, \quad \forall\, j = 1, \cdots, n,\ \forall\, k \in \Omega^2|\boldsymbol{r}.
\end{aligned} \tag{3.2}$$

Note that mn is a constant in the assignment problem, and hence is omitted from the analysis.

Although the two tiers of the assignment decisions are optimized separately, the two decisions are *linked*, as the second tier assignment decision depends on the outcome of the first tier test (given by $\boldsymbol{r}$) and the subject risk vector updated at the end of the first tier (given by $\boldsymbol{p}'$). Moreover, the second tier column testing is performed on a testing matrix that is modified based on the first tier outcome ($\boldsymbol{r}$). Thus, the dimensionality of the second tier testing is informed by the random outcome ($\boldsymbol{R}$) and the assignment decision ($\boldsymbol{x_1}$) of the first tier. Our modeling approach reflects this dynamic decision-making and determines the optimal Tier 2 assignment given a Tier 1 outcome.

Remark 3.1. $\mathbb{E}[FN^1(\boldsymbol{x^1}) \mid \boldsymbol{p}]$ and $\mathbb{E}[FN^2(\boldsymbol{x^2}) \mid \boldsymbol{r}, \boldsymbol{p}]$ become independent of the subject assignment, $\boldsymbol{x^1}$ and $\boldsymbol{x^2}$, when $m = 1$ or $n = 1$.

To simplify the subsequent notation, hereafter we drop the arguments in parenthesis and omit the dependence on $\boldsymbol{p}$ or $\boldsymbol{r}$ when clear from the context.

In general, the assignment problems in (3.1) and (3.2) are difficult to solve, as their respective objective functions are non-linear and not necessarily well-behaved, and do not have closed-form expressions for general sensitivity functions. As a result, although the constraint sets in both problems possess the total unimodularity property, the binary restrictions on $\boldsymbol{x^1}$ and $\boldsymbol{x^2}$ cannot be relaxed without loss of feasibility. Therefore, in the subsequent sections, we investigate properties of optimal solutions to (3.1)-(3.2), which enable us to characterize the optimal assignment policy.

Given a testing design (m and n), the following assignment policies will be of importance in the subsequent analysis of the assignment problem:

1. **Assignment Row-wise-highest-risk-first (RH)** assigns the n highest risk subjects

(subjects $1, \cdots, n$) to row 1, next n highest risk subjects (subjects $n+1, \cdots, 2n$) to row 2, and so on.

2. **Assignment Column-wise-highest-risk-first (CH)** is similar with respect to columns, i.e., it assigns the m highest risk subjects (subjects $1, \cdots, m$) to column 1, and so on.

In both assignments, ties are broken arbitrarily, as there exist multiple **RH** (**CH**) assignments, including permutations of subjects within each row (column), and permutations of rows (columns).

Given an assignment of the subjects to the testing matrix, we use index (i, j) to denote the subject assigned to cell (i, j) in the matrix (i.e., the ith row and jth column), for all $i = 1, \cdots, m$, and $j = 1, \cdots, n$. The following characterizations will prove to be useful in establishing properties of an optimal assignment. In particular, Corollary 3.1 and the first part of Corollary 3.2 are used in Lemma 3.1 to show that it is sufficient to study a $2 \times n$ matrix to derive properties of an optimal assignment for the original $m \times n$ matrix, and the second part of Corollary 3.2 is utilized in Theorem 3.1 to establish properties of an optimal Tier 1 assignment. All proofs can be found in the appendix.

Corollary 3.1. For an $m \times n$ testing matrix, if an assignment does not follow **RH**, then there exist rows $i_1, i_2 : \ i_1 \neq i_2, \ i_1, i_2 = 1, \cdots, m$, such that:

(a) $\min\limits_{j=1,\cdots,n} \{p_{i_1 j}\} < \max\limits_{j=1,\cdots,n} \{p_{i_2 j}\}$, and **(b)** $\max\limits_{j=1,\cdots,n} \{p_{i_1 j}\} > \min\limits_{j=1,\cdots,n} \{p_{i_2 j}\}$.

Corollary 3.2. For an $m \times n$ testing matrix, if an assignment does not follow **RH**, then there exists a $2 \times n$ sub-matrix of the original $m \times n$ matrix such that: (i) the sub-matrix does not follow **RH**, and (ii) relabeling the rows of the sub-matrix as rows 1 and 2, one can construct an equivalent assignment (i.e., with the same $\mathbb{E}[FN^1|\boldsymbol{p}]$ as the original assignment) such that there exists some subject $k = 1, \cdots, n-1$, with $p_{1j} < p_{2j}$ for all $j = 1, 2, \cdots, k$, and $p_{1j} \geq p_{2j}$ for all $j = k+1, k+2, \cdots, n$, or vice versa.

Corollary 3.2 follows because the number of false negatives in Tier 1 depends only on the set of subjects assigned to each row, and not on their specific location within each row. Hence, in Corollary 3.2, we consider a particular permutation of the original assignment for the $2 \times n$ sub-matrix in which the subjects in row 1 are assigned to columns following a non-decreasing order of their risk, while those in row 2 are assigned following a non-increasing order, e.g., in the new assignment, the subject with a risk of $\min_{j=1,\cdots,n}\{p_{i_1 j}\}$ is assigned to cell (1,1), the subject with a risk of $\max_{j=1,\cdots,n}\{p_{i_2 j}\}$ is assigned to cell (2,1), and so on, or vice versa.

Properties of an Optimal Tier 1 Assignment

We are ready to establish some properties of an optimal Tier 1 assignment.

Lemma 3.1. *If Assignment* **RH** *minimizes* $\mathbb{E}[FN^1|\boldsymbol{p}]$ *for a* $2 \times n$ *testing matrix,* $\forall\ \boldsymbol{p}$*, then Assignment* **RH** *minimizes* $\mathbb{E}[FN^1|\boldsymbol{p}]$ *for all* $m \times n$ *testing matrices, for* $n,\ m \in \mathbb{Z}^+$*, and* $\forall\ \boldsymbol{p}$*.*

In light of Lemma 3.1, in the following we extensively study the properties of a $2 \times n$ matrix. For this purpose, with a slight abuse of the notation, let $\boldsymbol{x^1}$ and N_d respectively denote the Tier 1 assignment and the number of positive subjects in the $2 \times n$ matrix. We define the conditional indicator variable $\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big)$, which equals 1 if there exists a row in the $2 \times n$ matrix with exactly i positive subjects, and 0 otherwise, given a total of n_d truly positive subjects, that is:

$$\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = \begin{cases} 1, & \text{if } \big(N^j_{d,r}|N_d = n_d\big) = i, \text{ for } j = 1 \text{ or } 2 \\ 0, & \text{otherwise} \end{cases} .$$

Observe that, $\forall\ n_d = 0, \cdots, 2n$,

$$P\left(\bigcup_{i=0}^{I(n,n_d)} \Big\{\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = 1\Big\}\right) = \left(\sum_{i=0}^{I(n,n_d)} P\Big\{\ \big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = 1\Big\}\right) = 1,$$

where $I(n, n_d) = \lfloor \min\{n_d, 2n - n_d\}/2 \rfloor$ and $\mathbb{E}\big[Y_i(\boldsymbol{x^1})|N_d = n_d\big] = P\{\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = 1\}$.

Corollary 3.3. For a $2 \times n$ matrix, $\mathbb{E}[FN^1(\boldsymbol{x^1})]$ in (3.1) can be equivalently expressed as:

$$\mathbb{E}[FN^1(\boldsymbol{x^1})] = \sum_{n_d=0}^{2n} \sum_{i=0}^{I(n,n_d)} a(i, n_d)\ \mathbb{E}\big[Y_i(\boldsymbol{x^1})|N_d = n_d\big], \tag{3.3}$$

where $a(i, n_d) \equiv \mathbb{E}\left[FN^1(\boldsymbol{x^1})|\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = 1\right] P(N_d = n_d)$.

Corollary 3.3 follows directly by conditioning on the number of positive subjects, N_d, and on $Y_i(\boldsymbol{x^1})|N_d$, and utilizing the law of total expectation. The representation in Corollary 3.3 is helpful, because only the second component of the right-hand side of Eq. (3.3) is dependent on the assignment decision, $\boldsymbol{x^1}$, and we heavily exploit this structure of the objective function in our analysis.

As stated in Section 3.2.1, we consider a general class of sensitivity functions that satisfy the monotonicity properties given in Properties 1 and 2. Not surprisingly, the form of the sensitivity function impacts the form of the optimal assignment. In order to obtain structural properties of an optimal assignment, in the remainder of the chapter we assume that the sensitivity function satisfies Properties 1, 2, and the following condition:

$$k\frac{\partial^2 Se(n,k)}{\partial k^2} \geq -2\ \frac{\partial Se(n,k)}{\partial k}, \quad \forall\ k \leq n;\ k,\ n \in \mathbb{Z}^+. \tag{3.4}$$

The condition imposed in Eq. (3.4) states that the sensitivity function is either convex, or, loosely speaking, not "too concave" in k, i.e., the number of truly positive subjects in the

pool, $\forall\ k$ (i.e., the second derivative of the sensitivity function is bounded from below by a negative number). This condition is not restrictive, as a large range of dilution dynamics, with different intensities, can be modeled under this condition, as illustrated in Example 3.1.

Example 3.1. Consider the sensitivity function, proposed in [32], which satisfies Eq. (3.4), $\forall\ \alpha \in (0, 1]$:

$$Se(n,k) = 1 - Sp + \Big(Se(1,1) + Sp - 1\Big)\left(\frac{k}{n}\right)^{\alpha}, \quad \forall\ k \leq n;\ k,\ n \in \mathbb{Z}^{+}, \tag{3.5}$$

where $Se(1,1)$ is the sensitivity of individual testing, Sp is the test's specificity, and α is a calibration parameter that governs the intensity of the dilution effect of pooling. For instance, in the case study (see Section 3.4), we consider the Ligase Chain Reaction chlamydia test and set $Se(1,1) = 1.00$, $Sp = 0.98$, and calibrate the sensitivity function and obtain $\alpha = 0.014329$ (see Appendix B.3).

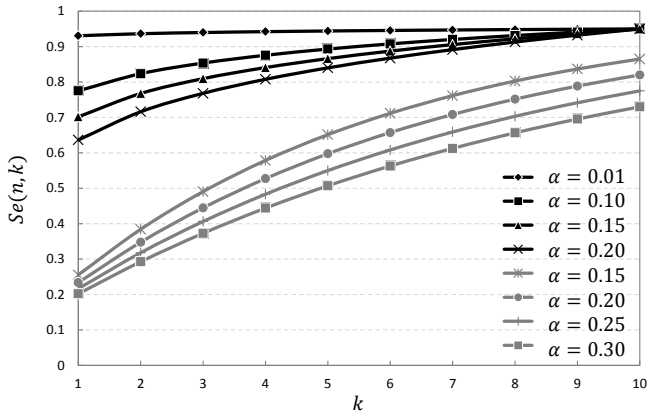
As another example, consider the following sensitivity function derived for the HIV Ultrio Plus NAT blood screening test, using clinical data published in the literature [6]. This sensitivity function also satisfies Eq. (3.4), $\forall\ \alpha \in (e^{-2}, 1)$:

$$Se(n,k) = 1 - Sp\ \alpha^{k/n}, \quad \forall\ k \leq n;\ k,\ n \in \mathbb{Z}^{+}. \tag{3.6}$$

Figure 3.1 plots families of sensitivity functions given in Eq.s (3.5) and (3.6), both of which satisfy Eq. (3.4), for various intensities of the dilution effect (parameter α). As Figure 3.1 demonstrates, one can model a wide range of dilution dynamics under the condition imposed in Eq. (3.4). In the remainder of the chapter, we consider sensitivity functions that satisfy Properties 1, 2, and Eq. (3.4).

Lemma 3.2. *For all sensitivity functions that satisfy Eq.* (3.4)*, $a(i, n_d)$ is increasing in i, $i = 0, \cdots, I(n, n_d)$, for all realizations n_d of N_d.*

Figure 3.1: Example sensitivity functions that satisfy Eq. (3.4), for $n = 10$ and various α value (the black (gray) curves correspond to sensitivity functions of the form in Eq. (3.5) (Eq. (3.6)))



In contrast with the monotonicity result in Lemma 3.2, however, for sensitivity functions satisfying Eq. (3.4) it is not necessarily true that:

$$\mathbb{E}\big[Y_0(\boldsymbol{x}^{\mathbf{1}})|N_d = n_d\big] \geq \mathbb{E}\big[Y_1(\boldsymbol{x}^{\mathbf{1}})|N_d = n_d\big] \geq \cdots \geq \mathbb{E}\big[Y_{I(n,n_d)}(\boldsymbol{x}^{\mathbf{1}})|N_d = n_d\big],$$

that is, the objective function to the Tier 1 Problem (see (3.1) and Corollary 3.3) is not monotone. Therefore, we utilize Corollary 3.2 to identify a sub-matrix of the $2 \times n$ testing matrix such that the risk of each subject in one row is greater than or equal to the risk of each subject in the other row. We note that the second part of Corollary 3.2 guarantees the existence of such a sub-matrix. Then, by conditioning on the number of positive subjects in this sub-matrix, we establish important structural properties of $\mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}})]$. Theorem 3.1 then follows as a result of these properties and the ordering given in Lemma 3.2.

Theorem 3.1. *For all sensitivity functions that satisfy Eq.* (3.4)*, Assignment* **RH** *minimizes* $\mathbb{E}[FN^1|\boldsymbol{p}]$ *in* (3.1)*,* $\forall\ \boldsymbol{p}$*.*

Further, Theorem 3.2 shows another desirable property of the Tier 1 **RH** assignment for a subset of sensitivity functions satisfying Eq (3.4).

Theorem 3.2. *For all sensitivity functions* $Se(n, k)$ *that are concave in* k*,* $\forall\ k$*, Assignment*

RH *minimizes* $\mathbb{E}[N_r|\boldsymbol{p}]$*, the expected number of positive-testing rows in Tier 1,* $\forall\ \boldsymbol{p}$*.*

Thus, for sensitivity functions that satisfy Eq. (3.4) and that are also concave in k, Assignment **RH** minimizes not only the expected number of false negatives in Tier 1, but also the dilution effect in Tier 2, hence improving the testing accuracy in Tier 2 by minimizing the column pool size. Theorems 3.1 and 3.2 demonstrate how well the adaptive and risk-based properties of the proposed assignment policy work together, as Assignment **RH** minimizes the expected number of positive-testing rows, thus taking full advantage of the adaptive array pooling scheme by maximizing the number of rows eliminated in Tier 2 of testing.

Remark 3.2. For all $\alpha \in (0, 1]$ ($\alpha \in (e^{-2}, 1)$), the sensitivity function in Eq. (3.5) (Eq. (3.6)) satisfies Eq. (3.4), and is concave in k, $\forall\ k$. Thus, both Theorems 3.1 and 3.2 hold for the sensitivity function in Eq.s (3.5) and (3.6) under the α values provided above.

Properties of an Optimal Tier 2 Assignment

We next study the optimal Tier 2 assignment that minimizes $\mathbb{E}[FN^2(\boldsymbol{x^2})|\boldsymbol{r}, \boldsymbol{p}]$ for all realizations $\boldsymbol{r}$ of the random vector $R(\boldsymbol{x^1})$. Given a Tier 1 assignment (this applies to any one of the possible **RH** permutations), $\boldsymbol{x^1}$, and outcome, $\boldsymbol{r}$, the *updated* positivity probability (risk) of subject (i, j) (i.e., the subject tested in cell (i, j) in Tier 1), $i = 1, \cdots, m, j = 1, \cdots, n$, follows:

$$p'_{ij} \equiv P(D_{ij} = 1|R_i = r_i) = \frac{P(R_i = r_i|D_{ij} = 1)}{P(R_i = r_i)}\, p_{ij}. \tag{3.7}$$

Remark 3.3. Due to the symmetry between Assignment **RH** for Tier 1 row pooling and Assignment **CH** for Tier 2 column pooling with updated probabilities p'_k, $k \in \Omega^2$, one might expect, based on Theorem 3.1, that Assignment **CH** minimizes $\mathbb{E}\big[FN^2(\boldsymbol{x^2})|\boldsymbol{r}, \boldsymbol{p}\big]$ for the reduced testing matrix for all sensitivity functions that satisfy Eq. (3.4), and $\forall\ \boldsymbol{r} \in \boldsymbol{R}$. However, this is not necessarily true due to two important characteristics of the information

obtained at the end of Tier 1:

(i) Conditioned on $\boldsymbol{r}$, the subjects are no longer independent, i.e., $P(D_{ij_1} = 1, D_{ij_2} = 1|R_i = r_i) \neq P(D_{ij_1} = 1|R_i = r_i)P(D_{ij_2} = 1|R_i = r_i)$, for $i = 1, \cdots, m,\ j_1, j_2 = 1, \cdots, n:\ j_1 \neq j_2$.

(ii) While the original ordering of the risk within each row is preserved when conditioned on $\boldsymbol{r}$ (i.e., $p_{ij_1} \geq p_{ij_2} \Leftrightarrow p'_{ij_2} \geq p'_{ij_2}$), this result does not necessarily hold across rows, as the outcome of Tier 1 depends on the set of subjects assigned to each row.

Consequently, in the following we first identify the conditions under which Assignment **CH** is guaranteed to be optimal for Tier 2, and study the value of the Tier 1 information. Then, we provide several examples, including a counter-example for which **CH** is not optimal in Tier 2. These conditions motivate a highly effective Tier 2 assignment heuristic, as demonstrated in Section 3.4.

Definition 3.1. A set of subjects is said to be *risk-order-independent* (ROI) if, upon conditioning on the true positivity status of any subset of subjects, the risk ordering of the remaining subjects in the set remains unchanged over the original risk vector, $\boldsymbol{p}$.

Corollary 3.4. If a set of subjects is ROI for a Tier 1 outcome $\boldsymbol{r} = (1, \cdots, 1)$, then the set is ROI, $\forall\ \boldsymbol{r}$.

Theorem 3.3. *For all sensitivity functions satisfying Eq.* (3.4)*, Assignment* **CH** *minimizes* $\mathbb{E}[FN^2(\boldsymbol{x^2})|\boldsymbol{r}, \boldsymbol{p}]$ *for any testing matrix,* $m \times n$*,* $m,\ n \in \mathbb{Z}^+$*, and* $\forall\ \boldsymbol{r}$*, when, for a Tier 1 outcome* $\boldsymbol{r} = (1, \cdots, 1)$*, the resulting set of subjects is ROI.*

Of course, Assignment **CH** may still be optimal even when the set of subjects is not ROI at the end of Tier 1. In the following lemma, we provide some cases that satisfy the ROI requirement.

Lemma 3.3. *For a Tier 1 outcome* $\boldsymbol{r} = (1, \cdots, 1)$*, the set of subjects is ROI, if Conditions I and II are satisfied, where* $\Omega_j(l)$ *denotes the collection of all subsets of cardinality* l *from set* $\{1, \cdots, j-1, j+1, \cdots, n\}$*:*

Condition I: *For all* $i = 1, \cdots, m$*,* $j = 1, \cdots, n$*,* $l = 1, \cdots, n-1$*, and all subsets* $S_j(l) \in \Omega_j(l)$*:*

$$\begin{aligned} P\left(D_{ij}=1 \middle| R_i=1, \bigcap_{k\in S_j(l)} D_{ik}=0\right) &\geq P\left(D_{ij}=1 \middle| R_i=1, \bigcap_{k\in S_j(l-1)} D_{ik}=0\right), \text{ and} \\ P\left(D_{ij}=1 \middle| R_i=1, \bigcap_{k\in S_j(l)} D_{ik}=1\right) &\leq P\left(D_{ij}=1 \middle| R_i=1, \bigcap_{k\in S_j(l-1)} D_{ik}=1\right). \end{aligned} \tag{3.8}$$

Condition II: *For all* $i_1, i_2 = 1, \cdots, m$*,* $i_1 \neq i_2$*:*

$$\begin{aligned} &\max_{j=1,\cdot\cdot,n}\left\{P\left(D_{i_1 j}=1 \middle| R_{i_1}=1, \bigcap_{\Omega_j(n-1)} D_{i_1 k}=0\right)\right\} \leq \min_{j=1,\cdot\cdot,n}\left\{P\left(D_{i_2 j}=1 \middle| R_{i_2}=1, \bigcap_{\Omega_j(n-1)} D_{i_2 k}=1\right)\right\}, \text{ or} \\ &\max_{j=1,\cdot\cdot,n}\left\{P\left(D_{i_2 j}=1 \middle| R_{i_2}=1, \bigcap_{\Omega_j(n-1)} D_{i_2 k}=0\right)\right\} \leq \min_{j=1,\cdot\cdot,n}\left\{P\left(D_{i_1 j}=1 \middle| R_{i_1}=1, \bigcap_{\Omega_j(n-1)} D_{i_1 k}=1\right)\right\}. \end{aligned} \tag{3.9}$$

Condition I states that, conditioned on the positive test outcome of a row pool, the probability that a subject is positive decreases (increases) if other subjects in the same row are identified as positive (negative). Thus, Condition I implies negative correlation among subjects in the same row: given that one subject is positive, the conditional probability that another subject in the same row is positive is reduced. On the other hand, Condition II ensures, for all possible pairs of rows (i_1, i_2), that the subject with the highest updated risk in one of these rows (say i_1) will have an equal or lower risk than the subject with the lowest updated risk in the other row (hence i_2) in the worst case, i.e., when all other subjects in row i_1 (i_2) are negative (positive), or vice versa. Then, for all realizations $\boldsymbol{r}$, the resulting set of subjects will be ROI. The following example illustrates the implications of Condition

I for all testing matrices having two columns (i.e., $n = 2$).

Example 3.2. An example of a sensitivity function that satisfies both Eq. (3.4) and Condition I for any $m \times 2$ matrix, $m \in \mathbb{Z}^+$, is $Se(n,k) = 1 - Sp\ \alpha^{k/n}$, for $k = 0, \cdots, n$, $Sp > 0$, $\alpha \in (e^{-2}, 1)$ (see Example 3.1). This follows because (see Example 3.1 and Appendix B.1):

$$\text{Condition I} \ \Leftrightarrow \left\{ \big(Se(2,1)\big)^2 \geq \big(1 - Se(2,0)\big) Se(2,2) \right\} \Leftrightarrow Sp\big(1 - \alpha^{1/2}\big)^2 \geq 0.$$

While the inequality is satisfied for all $\alpha \geq 0$, it also must be true that $\alpha \in (e^{-2}, 1)$ for the sensitivity function to satisfy Eq. (3.4) (see Example 3.1).

Next we provide two examples, both of which use the sensitivity function in Example 3.2, i.e., that satisfies Condition I. These examples provide an idea on when a **CH** assignment is optimal in Tier 2 and when it is not.

Example 3.3. Consider the sensitivity function in Example 3.2, $Se(n,k) = 1 - Sp\ \alpha^{k/n}$, $k = 0 \cdots, n$, with $\alpha = 0.15$ (see Figure 3.1) and $Sp = 0.9993$, and two instances of the problem for a 2×2 testing matrix, characterized by the risk vector, $\boldsymbol{p}$. Suppose that the Tier 1 assignment follows the optimal **RH** assignment. In Tier 2, we evaluate $\mathbb{E}[FN^2(\boldsymbol{x^2})|\boldsymbol{r}, \boldsymbol{p}]$ when the Tier 2 assignment follows: (a) the original **RH** assignment (i.e., Tier 1 assignment is unchanged) and (b) the **CH** assignment using updated risk vector, $\boldsymbol{p'}$. By Remark B.1 (see Appendix B.1), it is sufficient to consider the case of $N_r = 2$ (i.e., $\boldsymbol{r} = (1,1)$).

Instance 1.

$$\boldsymbol{p^{RH}} = \begin{bmatrix} 0.10 & 0.15 \\ 0.45 & 0.50 \end{bmatrix} \Rightarrow \boldsymbol{p'^{RH}} = \begin{bmatrix} 0.437 & 0.644 \\ 0.660 & 0.722 \end{bmatrix}, \ \boldsymbol{p'^{CH}} = \begin{bmatrix} 0.437 & 0.660 \\ 0.644 & 0.722 \end{bmatrix}$$

Instance 2.

$$\boldsymbol{p^{RH}} = \begin{bmatrix} 0.001 & 0.002 \\ 0.980 & 0.990 \end{bmatrix} \Rightarrow \boldsymbol{p'^{RH}} = \begin{bmatrix} 0.243 & 0.486 \\ 0.985 & 0.993 \end{bmatrix}, \boldsymbol{p'^{CH}} = \begin{bmatrix} 0.243 & 0.985 \\ 0.486 & 0.993 \end{bmatrix}$$

		Tier 2 assignment		Condition satisfied?	
		RH	**CH**	I	II
Instance 1	$\mathbb{E}[FN^2(\boldsymbol{x^2})\|\boldsymbol{p}, \boldsymbol{r} = (1,1)]$ (per million)	142,082	175,594	Yes	No
Instance 2	$\mathbb{E}[FN^2(\boldsymbol{x^2})\|\boldsymbol{p}, \boldsymbol{r} = (1,1)]$ (per million)	168,578	138,592	Yes	Yes

While Condition I is satisfied for both instances, Condition II is satisfied only for Instance 2. As such, by Theorem 3.3 and Lemma 3.3, **CH** minimizes the Tier 2 expected number of false negatives for Instance 2, but not necessarily for Instance 1.

In summary, the information gained from Tier 1 testing can be partitioned into two categories: (i) information regarding the updated positivity probabilities (i.e., $\boldsymbol{p'}$), and (ii) information regarding the dependencies of subjects within a row. As can be seen in Example 3.3, both pieces of information are crucial for constructing an optimal Tier 2 assignment.

By Theorem 3.3 and Lemma 3.3, for instances where Conditions I and II are satisfied, **CH** is optimal for Tier 2 assignment. While Condition I is realistic (see the discussion after Lemma 3.3), Condition II is quite restrictive and is not satisfied by most realizations of $\boldsymbol{p}$. As such, we next develop a heuristic for sensitivity functions satisfying Eq. (3.4) for cases where Condition II is not satisfied. Our heuristic is motivated by two observations: (i) Condition I implies negative correlation among the updated risk of subjects within the same row, and (ii) the objective function, $\mathbb{E}[FN^2(\boldsymbol{x^2})|\boldsymbol{r}, \boldsymbol{p}]$, depends only on the set of subjects assigned to each column, and not on their row assignment. Consequently, for sensitivity functions

satisfying Eq. (3.4), the proposed heuristic preserves the row assignment of each subject in Tier 2, avoiding the assignment of dependent subjects to the same column. Under this constraint, the assignment that mimics **CH** as much as possible is to place the subjects in each row in non-decreasing order of risk. Thus, the proposed **RH**-based heuristic (**RH-H**) is as follows: Tier 1 assignment follows a specific permutation of **RH**, with subjects in a given row assigned to the matrix in non-decreasing order of risk. This assignment is preserved in the reduced matrix of Tier 2.

3.3.2 The Testing Design

We next study the testing design problem in which the objective is to determine the dimensions of the testing matrix, m and n, so as to minimize the expected number of false negatives per subject, under a per subject budget constraint on the expected number of tests and expected number of false positives. In contrast, the existing literature focuses mainly on non-adaptive array pooling schemes (i.e., row and column pools are tested simultaneously) and uses enumeration to find the testing matrix that minimizes the expected number of tests under perfect tests [73] or imperfect tests but with no dilution effect [98].

Alternatively, one could formulate the testing design problem as a two-stage stochastic programming problem that includes the testing design in Stage 1, under uncertainty on the $\boldsymbol{P}$ vector, and the subject assignment decision (in Tiers 1 and 2) in Stage 2, after a specific realization of the $\boldsymbol{P}$ vector is observed. However, this problem is intractable because one needs to determine, for all possible matrix dimensions, the optimal Tier 1 and Tier 2 assignments of subjects for all possible $\boldsymbol{p}$ vector realizations, which, as discussed above, is already intractable. As a further complication, the objective function for the testing design problem for a heterogeneous population and under a general sensitivity function does not have a

closed-form expression. Hence, and as discussed in Section 3.2.2, we separate the Stage 1 and Stage 2 problems, and we formulate the testing design problem under the assumption of a homogeneous population, i.e., the risk of each subject is deterministic and assumed equal to the population mean prevalence rate, μ_p. While this assumption ignores the heterogeneity of the population in the testing design, it results in a formulation that can be efficiently solved, while resulting in substantial reductions in classification errors (see Section 3.4).

Testing Design Problem:

$$\begin{aligned} \min_{m,n} \quad & \frac{1}{mn}\,\mathbb{E}[FN(m,n)] \\ \text{s.t.} \quad & \frac{1}{mn}\Big\{\mathbb{E}[T(m,n)] + \gamma\mathbb{E}[FP(m,n)]\Big\} \leq B \\ & m \leq M,\ n \leq N, \quad m,n \in \mathbb{Z}^+, \end{aligned} \tag{3.10}$$

where $\gamma \geq 0$ is the ratio of the cost of a false positive classification to the cost of testing, and M and N represent technological upper bounds on pool sizes (if any). Appendix B.2 provides the derivations of the performance measures for both the proposed adaptive array pooling scheme under the homogeneous population assumption, and the non-adaptive array pooling schemes studied in the literature. The latter will serve as a benchmark in the case study of Section 3.4.

The testing design problem is a difficult optimization problem, as m and n are integer decision variables and the objective function and constraint are non-linear and not monotone in m or n.

3.4 Case Study: Chlamydia Screening in the United States

In this section, we perform a case study on chlamydia screening in the US. Various one-way sensitivity analyses are conducted to account for the uncertainty in the data values used in the case study, as discussed subsequently.

Currently, chlamydia is one of the highest prevalent STDs in the US [35], and most screening occurs on a state level via public state laboratories. However, there are no guidelines on screening practices. As a result, screening practices differ significantly among states (e.g., North Carolina individually tests only high risk female subjects [99]; Idaho uses pooled testing on all subjects in pool sizes of four [89], except those who are "exposed to chlamydia" or who need to be "screened after treatment"). The lack of a nationwide screening practice indicates that risk-based pooling schemes, especially for tests for which the dilution effect is significant, are not well-understood. Further, a study conducted by the Centers for Disease Control and Prevention (CDC) shows how the positivity probability of a subject for chlamydia can substantially vary by age and race/ethnicity [35]. Consequently, in this case study, we decompose the population into two age groups (15-24 and other) and three race/ethnicity groups (black, hispanic, other), where the "other" category includes: white, American Indian or Alaska native, and Asian or Pacific islander, leading to a total of six risk groups. In fact, the risk categorization of the population is an important consideration in the testing design and implementation, and in this case study we select a decomposition that captures the heterogeneity of the population relatively well, while resulting in a reasonable number of risk categories, as a large number of risk categories can hinder the implementation of risk-based testing schemes.

The risk data used in our numerical study come from the Centers for Disease Control and Prevention (CDC) [35], which provides data on chlamydia prevalence rates based on seven age groups, five race groups, and two genders groups, leading to a total of 70 possible risk categories. Our analysis of these data indicate that the risk of subjects within the age group of 15-24 is significantly higher than the risk of subjects belonging to other age groups, all of which have comparable risk. As such, defining two age groups, of 15-24 and other, adequately captures the heterogeneity of the population. Similarly, we categorize the population into three race categories (black, hispanic, and other) because significant differences in the risk is observed between these three categories, while all races belonging to the "other" category had comparable risk. Our numerical results on a population having all seventy risk categories led to only minor differences in the performance of the proposed testing scheme, suggesting that this specific decomposition, with six risk categories, adequately captures the heterogeneity of the population in this case study.

In addition, studies show that a large percent of chlamydia cases go undiagnosed and/or unreported (e.g., 75% of women and 50% of men with chlamydia show no symptoms and are likely to be unreported [56]); and the actual number of cases is estimated to be around three times the number of reported cases [64], leading to a mean population prevalence rate of $\mu_p = 0.973\%$. In Table 3.2, we present the number of reported cases and the population for each risk group based on data in [55] for the year 2014 and using an underreporting factor of 3.

We consider the Ligase Chain Reaction (LCR) chlamydia test, a commonly used test for chlamydia screening. We model the sensitivity of the LCR test by the sensitivity function given in Eq. (3.5), with calibration parameter $\alpha = 0.014329$, $Se(1,1) = 1.0$ (by our assumption, see Section 3.2.2), and $Sp = 0.98$. This function was validated using published empirical data, and provides a good fit for the LCR test (see Appendix B.3 for details). As

Table 3.2: Number of chlamydia cases and the population of risk groups for the year 2014 [55]

Race/ethnicity & age group	Reported cases	Population	Risk (p_k)	Proportion in population (q_k)
Black & (15-24)	301,527	6,822,954	13.26%	2.2%
Black & (other age group)	129,411	33,979,132	1.14%	10.7%
Hispanic & (15-24)	125,681	9,274,931	4.07%	2.9%
Hispanic & (other age group)	75,288	44,796,439	0.50%	14.2%
Other race/ethnicity & (15-24)	255,532	27,856,517	2.75%	8.8%
Other race/ethnicity & (other age group)	138,057	193,398,866	0.21%	61.2%

stated above, to account for the uncertainty in data values used in our case study, we conduct various one-way sensitivity analyses on the mean prevalence rate, μ_p, dilution parameter, α, and the individual test sensitivity, $Se(1,1)$. The values of all input parameters, data sources, and values considered in the one-way sensitivity analyses are summarized in Table 3.3.

To quantify the value of the proposed adaptive risk-based array pooling scheme, which we denote by **RP**, we consider a non-adaptive and non-risk based array pooling scheme, which we denote by **NNP**, in which the decision maker: (i) does not utilize an adaptive scheme; i.e., both Tier 1 row pooling and Tier 2 column pooling are performed simultaneously, and negative-testing rows are not removed from the testing matrix in Tier 2; and (ii) does not consider population level characteristics and thus assigns the subjects to the testing matrix randomly. **NNP** corresponds to pooling schemes commonly studied in the literature (e.g., [73,86,98]). In addition, we also compare our model to the two-tier Dorfman scheme, as it is one of the most commonly utilized testing schemes in practice. In the two-tier Dorfman scheme, subjects are first tested in pools in Tier 1; if a pool tests negative, then all subjects in

Table 3.3: Input parameters and data sources

Input parameter	Value	Values considered in sensitivity analysis	Source
Mean prevalence rate (μ_p)	0.973%	0.486%, 1.945%	[35, 64]
Individual test sensitivity $\big(Se(1,1)\big)$	1.000	0.980, 0.990	[82]
Test specificity (Sp)	0.980	-	[82]
Sensitivity function $\big(Se(n,k)\big)$	$1-Sp+\big(Se(1,1)+Sp-1\big)(k/n)^{\alpha}$	-	[32]
Dilution parameter (α)	0.014329	0.007164, 0.028657	[82]
Testing budget (B)	0.25	0.15, 0.20, 0.30, 0.35	-

the pool are classified as negative; and if a pool tests positive, then each subject in the pool is individually tested and classified based on their Tier 2 individual test outcome. We note that the optimal pool size of the two-tier Dorfman pooling scheme depends only on the average risk of subjects, μ_p, because the subjects are in a single pool, hence the subject assignment decision is irrelevant. The testing schemes utilized in the case study are summarized below:

- **RP**: Adaptive risk-based array pooling scheme, in which subject assignment is based on **RH-H** (see Section 3.3.1), and the testing design is based on a homogeneous population, with the expressions given in Appendix B.2.
- **NNP**: Non-adaptive non-risk based array pooling scheme, in which subjects are randomly assigned to the testing matrix, and the testing design is based on a homogeneous population, with the expressions given in Appendix B.2.
- **Two-tier Dorfman**: Two-tier Dorfman scheme, in which subjects are randomly assigned to the pool, and the pool size is determined based on a homogeneous population.

The optimal pooling configurations for all schemes are obtained by enumerating over all

Table 3.4: Results for chlamydia screening in the US

Pooling scheme	B	Design	Expected false classifications (per million) $\mathbb{E}[FN]$ (95% CI)	$\mathbb{E}[FP]$ (95% CI)	% Change over **NNP** $\mathbb{E}[FN]$	$\mathbb{E}[FP]$
Two-tier non-risk based Dorfman pooling	0.15	Infeasible				
	0.20	Infeasible				
	0.25	$n = 6$	238	1,299		
	0.30	$n = 5$	215	1,124		
	0.35	$n = 4$	185	946		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.15	Infeasible				
	0.20	$m = 10$, $n = 13$	625	247		
	0.25	$m = 8$, $n = 10$	567	164		
	0.30	$m = 6$, $n = 9$	519	119		
	0.35	$m = 6$, $n = 6$	469	85		
Proposed adaptive risk-based array pooling scheme (RP)	0.15	Infeasible				
	0.20	$m = 8$, $n = 9$	312 (307-318)	119 (116-121)	-50%	-52%
	0.25	$m = 2$, $n = 6$	232 (222-242)	31 (27-34)	-59%	-81%
	0.30	$m = 1$, $n = 5$	213 (201-227)	23 (20-28)	-59%	-82%
	0.35	$m = 1$, $n = 4$	183 (169-196)	18 (14-22)	-61%	-79%

possible configurations, with the technological upper bounds on pool sizes, M and N, both set to 16 [40].

Having determined the testing design, the performance measures are determined via a Monte Carlo simulation, which generates realizations of the random risk vector following the discrete distribution presented in Table 3.2. Based on the realized risk vector, the subjects are assigned to the testing matrix, and the true random status of each subject is generated from the corresponding Bernoulli distribution, and the numbers of both false negative and false positive classifications are computed. In Table 3.4, we report both the expected value (per 1 million) and the 95% confidence interval (in parenthesis) for both the expected number of false negatives and false positives, as it is important to evaluate the testing schemes on both performance measures, due to the negative consequences associated with each type of

classification error, see Section 3.1.

In our analysis, we consider a set of budget levels that are representative of realistic per-subject testing budgets, see Table 3.4. While other budget levels are possible, our numerical results on different budget levels lead to similar observations. Specifically, the budget value represents the ratio of the maximum number of tests the testing facility can conduct (due to a testing budget) to the number of tests needed for individually testing each subject (i.e., one test per subject). For example, a budget value of 0.20 indicates that the testing facility has 20% of the budget required to perform individual testing, while a budget level of 1, or greater, represents the case where the testing facility can afford individual testing. Table 3.4 leads to several interesting insights: For a budget of 0.20, there is no feasible two-tier Dorfman solution, while **RP** reduces $\mathbb{E}[FN]$ and $\mathbb{E}[FP]$ by 50% and 52% over **NNP**, respectively. For the two higher budgets, **NNP** outperforms the two-tier Dorfman scheme with respect to $\mathbb{E}[FP]$, but more than doubles $\mathbb{E}[FN]$. On the other hand, **RP** matches the $\mathbb{E}[FN]$ of the two-tier Dorfman scheme, and substantially reduces the $\mathbb{E}[FP]$ by an average of 98%. **RP** does this by performing as well as the Dorfman scheme in the number of false negatives using the first two tiers, and then using Tier 3 to reduce the false positives. **RP** also reduces each of $\mathbb{E}[FN]$ and $\mathbb{E}[FP]$ over **NNP** by an average of 59% and 81%, respectively. In addition, notice that **RP** consistently has smaller testing matrices (smaller m and n) over **NNP**; this is due in part, to the adaptivity of **RP**, which lowers the expected number of tests over **NNP**, and hence, smaller pool sizes become budget feasible. Moreover, our results suggest that array pooling testing designs are often non-square matrices (i.e., $m \neq n$), as opposed to the literature that often limits the analysis to square matrices only (e.g., [66, 86, 98]). In summary, **RP** not only offers a more flexible testing scheme that can provide feasible solutions at lower budget levels, but also outperforms, in terms of classification accuracy, the commonly studied testing schemes, the **NNP** and two-tier Dorfman pooling.

The results from our sensitivity analysis, shown in Tables 3.5, 3.6, and 3.7, confirm that substantial benefits can be realized with risk-based testing, i.e., through explicitly accounting for the population heterogeneity in the assignment decision, in a variety of settings that are representative of practical situations, i.e., with varying dilution levels, mean population prevalence rates, and sensitivity of the individual test. Specifically, Tables 3.5 and 3.6 indicate that risk-based testing continues to yield substantial benefits at different intensities for the dilution effect of pooling (i.e., for various values of the dilution parameter, α) and for a range of mean prevalence rates of the population. In particular, these results indicate that the number of false negatives can be reduced by an average of 55% (57%) and the number of false positives reduced by an average of 70% (66%) over the different values of α (mean prevalence rates of the population).

On the other hand, Table 3.7 shows that risk-based testing works best when $Se(1,1)$ is high. For lower $Se(1,1)$ values, **RP** still outperforms **NNP** for both false negatives and false positives. On the other hand, when there is a feasible Dorfman solution, it outperforms **RP** in terms of the false negatives, but not false positives. Interestingly, the extra false negatives for **RP** all stem from the third tier test. Using the same matrix designs, a two-tiered **RP** has fewer false negatives compared to the Dorfman solutions, but higher false positives, thus the **RP** designs in Table 3.7 rely on the third tier to reduce the number of false positives. If false negatives are a main concern and individual test sensitivity ($Se(1,1)$) is relatively low, then the two-tier Dorfman or two-tiered **RP** scheme might be preferred, depending on the trade-offs between false negatives and false positives. However, as we state in the chapter, in settings that we consider, the individual test sensitivity is typically close to being perfect (otherwise pooling would have a very low sensitivity due to dilution, and would not be considered as a viable option), and false negatives are a primary concern.

Table 3.5: Results for chlamydia screening in the US, sensitivity analysis on μ_p

Pooling scheme	B	Design	Expected false classifications (per million) $\mathbb{E}[FN]$ (95% CI)	$\mathbb{E}[FP]$ (95% CI)	% Change over **NNP** $\mathbb{E}[FN]$	% Change over **NNP** $\mathbb{E}[FP]$
$\mu_p = 0.486\%$						
Two-tier non-risk based Dorfman pooling	0.20	$n = 7$	130	945		
	0.25	$n = 5$	108	766		
	0.30	$n = 4$	93	676		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	$m = 10$, $n = 11$	307	79		
	0.25	$m = 8$, $n = 9$	280	58		
	0.30	$m = 6$, $n = 8$	255	44		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	$m = 2$, $n = 7$	127 (121-134)	20 (18-23)	-59%	-75%
	0.25	$m = 1$, $n = 5$	106 (97-115)	10 (7-13)	-62%	-83%
	0.30	$m = 1$, $n = 4$	95 (86-105)	14 (11-18)	-63%	-68%
$\mu_p = 1.945\%$						
Two-tier non-risk based Dorfman pooling	0.20	Infeasible				
	0.25	Infeasible				
	0.30	$n = 6$	466	2,146		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	Infeasible				
	0.25	$m = 10$, $n = 10$	1,158	593		
	0.30	$m = 7$, $n = 9$	1,052	391		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	Infeasible				
	0.25	$m = 11$, $n = 8$	628 (620-636)	386 (382-390)	-46%	-35%
	0.30	$m = 4$, $n = 6$	468 (456-479)	110 (105-114)	-56%	-72%

3.5 Conclusions and Future Research Directions

In this chapter, we study the classification problem in the context of public health screening, where the objective is to classify each subject as positive or negative for an infection. We propose and study a three-tier adaptive risk-based array pooling scheme that incorporates imperfect tests, the dilution effect of pooling, and the risk profile of subjects. Our analytical

Table 3.6: Results for chlamydia screening in the US, sensitivity analysis on α

Pooling scheme	B	Design	Expected false classifications (per million) $\mathbb{E}[FN]$ (95% CI)	$\mathbb{E}[FP]$ (95% CI)	% Change over **NNP** $\mathbb{E}[FN]$	% Change over **NNP** $\mathbb{E}[FP]$
$\alpha = 0.007164$						
Two-tier non-risk based Dorfman pooling	0.20	Infeasible				
	0.25	$n = 6$	119	1,311		
	0.30	$n = 5$	108	1,132		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	$m = 10$, $n = 13$	318	254		
	0.25	$m = 8$, $n = 10$	288	168		
	0.30	$m = 6$, $n = 9$	263	121		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	$m = 9$, $n = 9$	158 (154-161)	131 (128-133)	-50%	-48%
	0.25	$m = 3$, $n = 6$	123 (117-129)	42 (39-45)	-57%	-75%
	0.30	$m = 1$, $n = 5$	113 (103-122)	24 (19-28)	-57%	-80%
$\alpha = 0.028657$						
Two-tier non-risk based Dorfman pooling	0.20	Infeasible				
	0.25	$n = 6$	469	1,276		
	0.30	$n = 5$	423	1,107		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	$m = 10$, $n = 13$	1,209	233		
	0.25	$m = 8$, $n = 10$	1,100	156		
	0.30	$m = 7$, $n = 7$	987	105		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	$m = 7$, $n = 9$	600 (592-608)	98 (96-101)	-50%	-54%
	0.25	$m = 2$, $n = 6$	463 (449-477)	30 (27-33)	-58%	-81%
	0.30	$m = 1$, $n = 5$	428 (410-446)	25 (21-30)	-57%	-76%

results that consider a general form of the sensitivity function offer valuable insights on the structural properties of an optimal assignment solution, while our case study demonstrates the effectiveness and power of an adaptive risk-based pooling scheme, with the expected number of false classifications reduced substantially over the previous models proposed in the literature. Our findings underscore the importance of taking into account population level characteristics, as failing to do so can lead to pooling schemes with a high probability of

Table 3.7: Results for chlamydia screening in the US, sensitivity analysis on $Se(1,1)$

Pooling scheme	B	Design	Expected false classifications (per million) $\mathbb{E}[FN]$ (95% CI)	$\mathbb{E}[FP]$ (95% CI)	% Change over **NNP** $\mathbb{E}[FN]$	% Change over **NNP** $\mathbb{E}[FP]$
$Se(1,1) = 0.99$						
Two-tier non-risk based Dorfman pooling	0.20	Infeasible				
	0.25	$n = 6$	426	1,290		
	0.30	$n = 5$	403	1,116		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	$m = 10$, $n = 13$	895	243		
	0.25	$m = 8$, $n = 10$	839	162		
	0.30	$m = 6$, $n = 9$	793	117		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	$m = 8$, $n = 9$	595 (586-603)	113 (111-116)	-34%	-53%
	0.25	$m = 2$, $n = 6$	521 (503-540)	32 (29-36)	-38%	-80%
	0.30	$m = 1$, $n = 5$	512 (484-539)	23 (19-28)	-35%	-80%
$Se(1,1) = 0.98$						
Two-tier non-risk based Dorfman pooling	0.20	Infeasible				
	0.25	$n = 6$	613	1,281		
	0.30	$n = 5$	591	1,109		
Non-adaptive and non-risk based array pooling scheme (*NNP*)	0.20	$m = 10$, $n = 13$	1,160	239		
	0.25	$m = 8$, $n = 10$	1,105	159		
	0.30	$m = 7$, $n = 7$	1,049	106		
Proposed adaptive risk-based array pooling scheme (RP)	0.20	$m = 8$, $n = 9$	869 (858-879)	111 (108-113)	-25%	-54%
	0.25	$m = 2$, $n = 6$	792 (769-814)	33 (30-37)	-28%	-79%
	0.30	$m = 1$, $n = 5$	789 (754-824)	23 (18-27)	-25%	-78%

misclassification. Our model has the potential to make a substantial positive societal impact by reducing misclassification for important infections, such as the chlamydia infection that is considered in the case study.

Potential improvements to our model include expanding the testing design formulation to consider a heterogeneous population; the generalization of the testing scheme into non-universal schemes, where subjects with different risk characteristics can potentially have

different testing designs; the incorporation of potential correlation among certain groups (e.g., correlation among sexual partners and family members) into our modeling; and the consideration of the uncertainty in subject risk estimation, which is prone to errors. Another promising direction is to take into account the continuous nature of tests. Test readings are typically continuous, as the test measures the concentration of a bio-marker in the host (e.g., viral load, antibody concentration). These readings are often converted into a binary outcome with help of pre-set thresholds. Since the threshold significantly affects the classification accuracy of the test, an important direction is to determine the optimal thresholds that strike the ideal balance between false negative and false positive classifications. Integrating threshold optimization with the risk-based pooling scheme studied here can further improve the performance of the proposed scheme. We hope that our work motivates both academic researchers and practitioners to consider adaptive risk-based approaches to pooled testing in public health screening.

Chapter 4

Optimal Risk-based Group Testing

4.1 Introduction and Motivation

Screening a population of subjects so as to classify each subject as *positive* or *negative* for a binary characteristic (e.g., presence of a disease or genetic disorder, a product defect, error in a computer code) is essential in many settings. Individually testing each subject is often very costly, and hence, may not be a viable strategy for classification, especially when the prevalence of the binary characteristic in the population is low and the population size is large. Therefore, in 1943, Dorfman, an economist, [46] proposed the concept of *group testing,* which involves testing multiple subjects simultaneously using a single test, for the purpose of screening military inductees for syphilis in an economical manner. This so-called *Dorfman testing* scheme has two stages: in the first stage, subjects are tested in groups; if a group tests negative, then all subjects in the group are classified as negative; and if a group tests positive, then each subject in the group is individually tested and classified based on the outcome of their individual test. Dorfman testing is one of the most commonly utilized group testing schemes today; for example, in donated blood screening, Dorfman

testing has become the standard practice in the United States (US) and several European countries [1,40]. However, many unrealistic assumptions were imposed in Dorfman's original model, as well as in most of the subsequent research on Dorfman testing. These include the assumptions of *perfect* tests (i.e., no classification errors), *homogeneous* (identical) subjects (i.e., the probability of having the binary characteristic is the same for all subjects), and an infinite testing population (in reality, the number of subjects is finite and known in each testing period).

Specifically, the decision problem is as follows: There is a finite set of subjects to be classified as positive or negative for a certain binary characteristic in each testing period; and there are risk factors that are known to increase a subject's probability of positivity (*risk*) for the binary characteristic in question (i.e., subjects come from a *heterogeneous* population). A screening test, which may be used on individual subjects or groups of subjects, is available to detect the binary characteristic, but the test is imperfect, leading to the possibility of false positive or false negative classifications. The challenge, then, is to design a *risk-based Dorfman testing scheme* (i.e., determining group sizes, and assigning subjects, with different risk, to the groups) so as to classify the set of subjects for the binary characteristic *accurately* (i.e., with minimum classification error), *equitably* (i.e., with a fair and even distribution of misclassification probability across subjects), and *efficiently* (i.e., with minimum resources). Equity (fairness) is an important, and often over-looked, dimension of resource allocation problems (e.g., [18, 19, 93]), and considering the trade-off between accuracy and equity is especially important in public health screening [29, 135]. We identify important structural properties of optimal risk-based Dorfman testing schemes with imperfect tests; use these properties to develop efficient algorithms; and derive key insights through a realistic case study that demonstrates an application of the proposed risk-based testing scheme within a public health screening setting.

Our decision problem applies in a wide variety of settings. As mentioned above, an important application of group testing arises in public health screening. For example, state health laboratories often have programs to screen the sexually active population in the state for sexually-transmitted diseases (STDs) [120], and blood banks screen all donated blood for a set of transfusion-transmittable diseases, including HIV, hepatitis viruses, etc. [4, 53, 139]. Individually testing each subject, within a large population, for a disease is typically not feasible due to limited resources. Another important consideration is that disease prevalence rates may vary, and sometimes substantially, with subject characteristics. For example, in the US, subjects within the 15-24 age group are twelve times more likely to be infected with chlamydia, one of the most prevalent STDs in the US, than subjects from other age groups [55]; first-time blood donors are seven times more likely to be infected with HIV than repeat donors [143]. Group testing can also enable the use of more accurate, yet more expensive, tests that would have been too expensive to be implemented for individual testing (e.g., nucleic acid testing (NAT) technology). An equitable testing scheme is especially important in this setting. For example, in STD screening, the optimal testing solution that minimizes the classification errors may do so by placing the subjects in different size Dorfman groups in the first stage of testing, based, in part, on how the demographics (e.g., age, race/ethnicity) impact risk. It is important that in doing this the solution might unfairly increase the classification errors for a certain subset of subjects (e.g., subjects within a specific age-group or belonging to a certain race/ethnicity). Group testing has also seen wide applications beyond health-care. Consider, for example, a common communication channel (e.g., a satellite connection or a fiber-optic cable) that is shared by a large number of users; if multiple users attempt to transmit a signal during the same time slot, a collision occurs, and must be resolved by identifying the "active" users (i.e., users that are transmitting a signal) during this time slot. Group testing can be utilized to identify these active users efficiently, significantly reducing the conflict resolution time in multi-access communication

networks [16]. In this context, the probability of being active varies depending on user characteristics, e.g., users with a history of heavy signal transmission would have a higher probability of being active. Alternatively, in industrial quality control, a manufacturer can test a group of light bulbs for defects by arranging them in series and applying a voltage across the group; or test a group of airtight containers for leaks by filling them with an indicator gas and placing the group in a low pressure chamber, the presence of the gas in the chamber indicates leakage in at least one of the containers [114]. The probability of being defective can vary based, for example, on properties of manufacturing machines, including their age and maintenance schedules. Other examples of group testing applications include, among others, software testing [28], screening of experimental variables [90], data compression [72], compressed sensing [38], and DNA library screening [104].

Dorfman testing has been extensively studied, but mostly under restrictive assumptions, such as perfect tests (e.g., [46,51,75,91,109,114]), which leads to a focus on minimizing the number of tests (i.e., maximizing efficiency), rather than maximizing classification accuracy or equity; infinite populations; and with subjects having identical risk for the binary characteristic (i.e., the testing population is homogeneous) (e.g., [62, 65, 86, 137]). One of the earliest works to incorporate subject-specific risk characteristics in group testing design is by Hwang [75], who studies the problem of determining a risk-based Dorfman testing scheme so as to minimize the expected number of tests for perfect tests. More recent work (e.g., [20,26,27,96,120]) extends the analysis to the realistic case of imperfect tests; these analyses, however, solely rely on heuristics that attempt to reduce the expected number of tests, rather than maximize the classification accuracy or equity under a testing budget constraint, as we do in this chapter. In particular, [96] states that determining an optimal risk-based Dorfman testing scheme that minimizes the expected number of tests (i.e., an extension of Hwang's [75] model to the case of imperfect tests) "appears to be intractable;" hence, the paper develops various

heuristics, which range from restricting all group sizes to be equal; to testing the low-risk subjects (determined via a pre-set risk threshold) in groups of equal size, while testing the high-risk subjects individually; to varying group sizes but under the assumption that group sizes reduce as subject risk increases. Although some of these properties may seem intuitive, we show in this chapter that an optimal solution does not necessarily satisfy any of these properties; thus, none of the greedy heuristics in [96] necessarily converge to the optimal solution. Further, we show that the aforementioned extension of Hwang's model to the case of imperfect tests (i.e., the problem of determining a risk-based Dorfman testing scheme so as to minimize the expected number of tests under imperfect tests) is in fact tractable, resolving the conjecture in the relevant literature. Our model is quite general, and is able to incorporate subject-specific risk characteristics into the testing design, and relax the perfect test and infinite population assumptions, thus enabling us to consider all important dimensions of testing: classification accuracy, efficiency, and equity.

Specifically, we consider a number of objective functions, as in practice there are different goals depending on the context of the problem. In particular, we explore: (1) minimizing a weighted sum of the expected number of false negative and false positive classifications, and number of tests (i.e., *the system's problem* and the first best solution), a special case of which reduces to the minimization of the expected number of tests (i.e., our model extends the earlier works of [75, 96]); and (2) minimizing a weighted sum of the expected number of false negative and false positive classifications under a testing budget constraint (i.e., *the budget-constrained problem*). Further, we explore an equity-based formulation, which aims to capture the trade-off between accuracy and equity under a testing budget constraint. These formulations may arise in various settings. For instance, in STD screening, minimizing classification errors and maximizing equity, especially with respect to false negative classifications, are important objectives. In this setting, false positive classifications may

only lead to further confirmatory testing, while false negative classifications may lead to medical complications and further spread of the disease; and a testing design that yields a much higher probability of a false negative classification for a subset of the subjects than the rest of the population is not desirable from a societal perspective. In industrial quality control, both false negatives (which result in defective products shipped to customers) and false positives (which result in unnecessary wastage) are of importance; thus, minimizing a weighted sum of false negative, false positive, and testing costs would be an appropriate objective.

Our contributions in this manuscript are multi-fold. We formulate the aforementioned decision problems as *partitioning problems* and develop key structural properties. These properties allow us to reduce the system's problem to a shortest path problem, and the budget-constrained problem to a constrained shortest path problem. Not surprisingly, the shortest path problem arises in various other contexts, including pricing and inventory management, transportation, supply chain management, and scheduling (e.g., [43, 116, 130, 134]), and our work adds a novel application to this set. The constrained shortest problem is NP-hard [58], and the algorithms proposed in the literature are not polynomial for the general problem (e.g., [14,50,67,77,140]). Depending on the setting, the problem size can be quite large in our context; for example, in STD screening, it is common for a state health laboratory to screen specimens taken from around a hundred subjects every day [89], hence the algorithms developed in the literature become computationally expensive for realistic instances. Towards this end, we utilize the structural properties of our decision problem to improve its tractability; and, for special cases of our decision problem, we develop a polynomial-time algorithm that can solve the corresponding constrained shortest path problem. Further, our study of an equity-based objective provides valuable insight; for example, in our budget-constrained problem, when the objective is to maximize the equity with respect to false negative classifi-

cations, we show that there is no trade-off between classification accuracy and equity, i.e., the price of fairness is zero, and the testing design that minimizes the number of false negative classifications is also the one that maximizes equity. Finally, we demonstrate the effectiveness of the proposed risk-based Dorfman testing scheme through a case study on chlamydia screening in the US using published data. The proposed risk-based Dorfman scheme not only substantially reduces each of the expected number of false negatives, expected number of false positives, and expected number of tests, but also significantly increases the equity of the testing scheme, over optimal non-risk-based schemes and current screening practices. Such significant improvements in all performance measures underscore the value of incorporating subject-specific risk characteristics and realistic assumptions into the testing design.

The remainder of this chapter is organized as follows. Section 4.2 presents the notation, decision problem, and formulations; and Section 4.3 provides derivations of the performance measures. Section 4.4 studies the optimal design of risk-based Dorfman testing schemes in different settings and derives important structural properties of optimal solutions. Then, Section 4.5 discusses findings from the US chlamydia screening case study. Finally, Section 4.6 summarizes our findings and provides directions for future research. To facilitate the presentation, all proofs are relegated to the Appendix.

4.2 The Notation, Decision Problem, and Models

4.2.1 The Notation and Decision Problem

Throughout, we denote random variables in upper-case letters, their realization in lower-case letters, and vectors in bold. We use indices m and i to respectively refer to a subject and to a group, and use the subject index as a superscript and group index as a subscript, i.e.,

X^m versus X_i. Finally, we use the terms positive and negative to refer both to subjects (i.e., to respectively denote the presence or absence of the characteristic) and to binary test outcomes (i.e., to respectively denote the test outcomes that *indicate* the presence or absence of the characteristic).

Consider an ordered set, $S = \{1, \cdots, N\}$, of subjects, ordered with respect to their risk (probability of positivity) for a certain binary characteristic, with their corresponding risk vector given by, $\boldsymbol{p} = (p^1, p^2, \cdots, p^N)$, where $p^1 \leq p^2 \cdots \leq p^N$. Each subject in set S needs to be classified as positive or negative for the binary characteristic through testing. The test is not perfectly reliable, with test *sensitivity* (i.e., true positive probability), denoted by Se, and test *specificity* (i.e., true negative probability), denoted by Sp. Consequently, misclassification, i.e., classifying a truly negative subject as positive (a false positive classification), or classifying a truly positive subject as negative (a false negative classification), is possible. We assume, without loss of generality, that the test's true negative probability is higher than its false negative probability,[1] i.e., $Sp/(1 - Se) \geq 1$. As such, we have that $Se + Sp - 1 \in [0, 1]$, with the special case, of $Se + Sp - 1 = 1$, corresponding to the perfect test case (i.e., false positives and false negatives are not possible), i.e., the case studied in the previous literature [75], see Section 4.1. Both individual testing and group testing are possible, and the test's sensitivity and specificity remain constant with group size. Our modeling also implies that the testing responses are conditionally independent, given the true positivity status of the subjects. This is a common assumption in the related literature, and is mainly for analytical tractability. We discuss the implications of this assumption in Section 4.4.2. For the given set, S, of subjects to be classified, the decision-maker needs to decide whether each subject is to be tested individually, i.e., with one test per subject and with the subject classified based on the individual test outcome; or in groups, and if so, then group

[1]This follows because any test not satisfying this assumption can be transformed into one that satisfies it by interpreting the test outcome in the opposite way.

sizes and assignments. Each group is to be tested following the Dorfman testing scheme: in the first stage, the group is tested with one test; if the group test outcome is negative, then all subjects in the group are classified as negative; and if the group test outcome is positive, then all subjects in the group are individually tested and classified based on their individual test outcome.

Thus, the **decision problem** is to find a feasible *partition* of set S that is optimal with respect to a certain objective function (see Section 4.2.2). We represent a partition by a combination of mutually disjoint sets, $\mathbf{\Omega} = (\Omega_i)_{i=1,\cdots,g}$, each with cardinality $n_i \equiv |\Omega_i|$, for some $g \in \{1, \cdots, N\}$, such that $\bigcup_i \Omega_i = S$, $\Omega_i \cap \Omega_j = \emptyset$, for all $i, j \in \{1, \cdots, g\}$:$i \neq j$; and each subject in Ω_i:$n_i = 1$ is individually tested, and each set of subjects in Ω_i:$n_i > 1$ is tested according to Dorfman testing scheme with a group size of n_i. We define $\Omega^I \equiv \bigcup_{i:n_i=1} \Omega_i$ and $\Omega^G \equiv \bigcup_{i:n_i>1} \Omega_i$, i.e., the set of subjects to be tested individually and to be tested in groups, respectively.

In this chapter, our focus is on testing facilities that are capable of dynamically changing the testing scheme on a frequent basis, i.e., each period (e.g., day), based on the risk vector realization of the testing population in each period. This type of testing is possible by automated testing machines. For example, in public health screening, many testing facilities use automated molecular testing machines (e.g., [71] and [128]) to conduct screening tests for many diseases and viruses (e.g., chlamydia, gonorrhea, HIV). These testing machines can handle both individual and group testing, and are programmable to be able to handle such dynamic testing schemes.

The objective functions in Section 4.2.2 are based on the following random variables: number of false positive classifications ($FP(\mathbf{\Omega})$), number of false negative classifications ($FN(\mathbf{\Omega})$), and number of tests to be performed ($T(\mathbf{\Omega})$) for a partition $\mathbf{\Omega}$ of set S. Let I^m denote the indicator random variable corresponding to the true positive status of subject $m \in S$; and

for a partition $\mathbf{\Omega}$, let $FN^m(\mathbf{\Omega})$ and $FP^m(\mathbf{\Omega})$, $m \in S$, denote the indicator random variables, respectively corresponding to the false negative classification and false positive classification of subject m, i.e., $I^m, FN^m(\mathbf{\Omega}), FP^m(\mathbf{\Omega}) = 1$, if subject m is, respectively, truly positive, classified falsely as negative, or classified falsely as positive; and 0 otherwise. Similarly, let $N_i^+(\Omega_i)$, $FN_i(\Omega_i)$, and $FP_i(\Omega_i)$ respectively denote the counter-parts of these random variables for group $i, \forall i$, i.e., number of true positive subjects, number of false negative classifications, and number of false positive classifications in group i, that is,

$$N_i^+(\Omega_i) = \sum_{m \in \Omega_i} I^m, \quad FN_i(\Omega_i) = \sum_{m \in \Omega_i} FN^m, \text{ and } \quad FP_i(\Omega_i) = \sum_{m \in \Omega_i} FP^m, \ \forall i.$$

We also let $T_i(\Omega_i)$ denote the random number of tests performed for group $i, \forall i$. Then, the performance measures, corresponding to a partition $\mathbf{\Omega}$ of set S , can be expressed as:

$$FN(\mathbf{\Omega}) = \sum_i FN_i(\Omega_i), \quad FP(\mathbf{\Omega}) = \sum_i FP_i(\Omega_i), \text{ and } \quad T(\mathbf{\Omega}) = \sum_i T_i(\Omega_i).$$

To simplify the subsequent notation, we drop the arguments in parentheses when clear from context.

4.2.2 Models

As discussed above, we consider the decision problem, of finding an optimal partition, $\mathbf{\Omega}^* = (\Omega_i^*)_i$, under different objective functions and in different settings; the latter is characterized by the presence or absence of a constraint on the testing budget.

System-optimal Model

In the System-optimal Model (**SM**), we consider the problem from a system's perspective, with an objective of minimizing the system-wide cost associated with the binary characteristic, that is, we consider a weight (cost) associated with each test, each false negative classification (e.g., consequences of the disease when not detected), and each false positive classification (e.g., follow-up testing cost or hassle, which is unnecessary), i.e., the goal is to identify a partition that minimizes a weighted sum of both types of classification errors and the testing cost. Such an objective function has been analyzed before (e.g., [94]), but not within a heterogeneous population framework. Problem **SM** applies in a wide variety of settings, for example, in the context of a single-payer health-care system or a centrally managed production system.

System-optimal Model (SM):

$$\underset{\mathbf{\Omega}}{\text{minimize}} \quad \lambda_1 \mathbb{E}[FN(\mathbf{\Omega})] + \lambda_2 \mathbb{E}[FP(\mathbf{\Omega})] + (1 - \lambda_1 - \lambda_2)\mathbb{E}[T(\mathbf{\Omega})], \tag{4.1}$$

where parameters $\lambda_1, \lambda_2 \in [0, 1]$ represent the weight the decision-maker places on each objective, with special cases corresponding to the minimization of the expected number of false negative classifications only ($\lambda_1 = 1$), expected number of false positive classifications only ($\lambda_2 = 1$), and expected number of testing cost only ($\lambda_1 = \lambda_2 = 0$); as discussed in Section 4.1, the last case is the case most studied in the literature (e.g., [46, 75, 96, 109]).

Budget-constrained Model

As opposed to the setting above, in the Budget-constrained Model (**BM**), we consider a decision-maker that must perform testing under a testing budget constraint, and the objective is to minimize a weighted sum of both types of classification errors. This applies, for

example, in the context of a testing laboratory that is constrained by the available resources, e.g., a testing budget, which we represent in terms of parameter B, corresponding to the number of tests that can be conducted.

Budget-constrained Model (BM):

$$\begin{aligned} \underset{\mathbf{\Omega}}{\text{minimize}} \quad & \lambda \mathbb{E}[FN(\mathbf{\Omega})] + (1-\lambda)\mathbb{E}[FP(\mathbf{\Omega})] \\ \text{subject to} \quad & \mathbb{E}[T(\mathbf{\Omega})] \leq B, \end{aligned} \tag{4.2}$$

where parameter $\lambda \in [0, 1]$ represents the weight the decision-maker places on each type of classification error, with special cases corresponding to the minimization of the expected number of false negatives only ($\lambda = 1$) and expected number of false positives only ($\lambda = 0$).

Remark 4.1. In some settings, additional confirmatory testing is conducted on all subjects that test positive in the initial screening (see Section 4.5.2). This can be easily incorporated into the **BM** formulation by adjusting the budget constraint to include the additional (expected) cost of confirmatory testing; and all the subsequent results continue to hold under this new formulation.

In general, the partitioning problem, of determining $\mathbf{\Omega}$, under an arbitrary objective function is NP-hard [36], and enumeration-based methods may lead to highly inefficient solution techniques even for small problem instances (e.g., when $N = 20$, the number of possible partitions is around 52 trillion, while realistic problem instances often have hundreds of subjects, e.g., see Section 4.5). Therefore, in the remainder of the chapter, we develop important structural properties for each optimization problem. These properties allow us to develop efficient algorithms and analyze their computational complexity.

4.3 Derivations of the Performance Measures

We first derive expressions for the performance measures, including the expected number of false negatives, false positives, and tests. Equity measures are discussed in Section 4.4.3. Recall that, for a partition $\mathbf{\Omega}$, Ω^I and Ω^G respectively correspond to the sets of subjects to be tested individually and in groups, and n_i denotes the size of group i, $\forall i$.

4.3.1 False Negative Classifications

Recall that in individual testing, a truly positive subject is falsely classified as negative if the test outcome is negative, whereas in group testing, a truly positive subject is falsely classified as negative if: (i) the group test outcome is negative, or (ii) the group test outcome is positive and the subject's subsequent individual test outcome is negative. Then, given $\mathbf{\Omega}$, for any subject $m \in S$, we have:

$$\begin{aligned}\mathbb{E}[FN^m] =& \mathbb{E}[FN^m|I^m = 1]P(I^m = 1) + \mathbb{E}[FN^m|I^m = 0]P(I^m = 0)\\ =& \begin{cases} (1 - Se)p^m + 0, & \text{if } m \in \Omega^I,\\ \Big(Se(1 - Se) + (1 - Se)\Big)p^m + 0, & \text{if } m \in \Omega^G, \end{cases}\end{aligned}$$

leading to:
$$\mathbb{E}[FN^m] = \begin{cases} (1 - Se)p^m, & \text{if } m \in \Omega^I,\\ (1 - Se^2)p^m, & \text{if } m \in \Omega^G. \end{cases}$$

Then, the expected number of false negative classifications for group i is given by:

$$\mathbb{E}[FN_i(\Omega_i)] = \begin{cases} (1-Se)\sum_{m\in\Omega_i} p^m, & \text{if } n_i = 1, \\ (1-Se^2)\sum_{m\in\Omega_i} p^m, & \text{otherwise,} \end{cases}$$

and the expected number of false negative classifications for all subjects in S is given by:

$$\begin{aligned} \mathbb{E}[FN(\mathbf{\Omega})] &= \sum_i \mathbb{E}[FN_i(\Omega_i)] = \sum_{i:n_i=1} \mathbb{E}[FN_i(\Omega_i)] + \sum_{i:n_i>1} \mathbb{E}[FN_i(\Omega_i)] \\ &= (1-Se)\sum_{m\in\Omega^I} p^m + (1-Se^2)\sum_{m\in\Omega^G} p^m. \end{aligned} \tag{4.3}$$

Interestingly, for a grouped subject, m, $\mathbb{E}[FN^m]$ is independent of the risk of the remaining subjects in the group. This behavior follows due to two reasons: (i) subjects are independent of one another (i.e., knowledge of the true status of one subject does not alter the risk of another), and (ii) conditioned on subject m, in group i, being positive, the probability that group i tests positive is Se, regardless of the status of the remaining subjects in the group. This follows under our assumption that Se and Sp are independent of the group size, which implicitly implies that, conditional on the true status of subject m, $m \in \Omega^G$, the grouped and individual test outcomes of subject m are independent of one another. This is a common assumption in the group testing literature, and to relax this assumption, one can model the dilution effect of grouping (e.g., [137]); this is an interesting research direction, but is beyond the scope of this chapter. These observations lead to an important property, discussed in Remark 4.2.

Remark 4.2. For any partition $\mathbf{\Omega}$, the expected number of false negative classifications corresponding to the set of subjects that are grouped, i.e., in set Ω^G, depends only on set Ω^G, and not on *how* the subjects are grouped.

Remark 4.2 will allow us to develop a polynomial-time algorithm for a special case of the problem; see Section 4.4.2.

4.3.2 False Positive Classifications

Recall that in individual testing, a truly negative subject is falsely classified as positive if the test outcome is positive, whereas in group testing, a truly negative subject is falsely classified as positive if the group test outcome is positive and the subject's subsequent individual test outcome is positive. Then, given a partition $\mathbf{\Omega}$, for any individually tested subject $m \in \Omega^I$, we can write:

$$\begin{aligned}\mathbb{E}[FP^m] =& \mathbb{E}[FP^m|I^m = 1]P(I^m = 1) + \mathbb{E}[FP^m|I^m = 0]P(I^m = 0)\\ =& 0 + (1 - Sp)(1 - p^m),\end{aligned}$$

and for any subject $m \in \Omega^G$ grouped in some set Ω_i:$n_i > 1$, $i \in \{1, \cdots, g\}$, i.e., $m \in \Omega_i$, we have:

$$\begin{aligned}\mathbb{E}[FP^m] =& \mathbb{E}[FP^m|I^m = 1]P(I^m = 1) + \mathbb{E}[FP^m|I^m = 0]P(I^m = 0)\\ =& 0 + \left[(1 - Sp)^2 \prod_{k\in\Omega_i\setminus\{m\}} (1 - p^k) + Se(1 - Sp)\left(1 - \prod_{k\in\Omega_i\setminus\{m\}} (1 - p^k)\right)\right](1 - p^m)\\ =& (1 - Sp)Se(1 - p^m) - (1 - Sp)(Se + Sp - 1)\prod_{k\in\Omega_i} (1 - p^k),\end{aligned}$$

leading to:

$$\mathbb{E}[FP^m] = \begin{cases} (1-Sp)(1-p^m), & \text{if } m \in \Omega^I, \\ (1-Sp)Se(1-p^m) - (1-Sp)(Se+Sp-1)\prod_{k\in\Omega_i}(1-p^k), & \text{if } m \in \Omega^G. \end{cases}$$

Then, the expected number of false positive classifications for group i is given by:

$$\mathbb{E}[FP_i(\Omega_i)] = \begin{cases} (1-Sp)\sum_{m\in\Omega_i}(1-p^m), & \text{if } n_i = 1, \\ (1-Sp)Se\sum_{m\in\Omega_i}(1-p^m) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_i}(1-p^m), & \text{otherwise,} \end{cases}$$

and the expected number of false positive classifications for all subjects in set S is given by $\mathbb{E}[FP(\mathbf{\Omega})] = \sum_i \mathbb{E}[FP_i(\Omega_i)]$.

4.3.3 Number of Tests

Recall that in individual testing, the number of tests per subject is always one, whereas in group testing, the number of tests depends on the outcome of the group test: if the group test outcome is negative, then only one test is performed for the entire group, and if the group test outcome is positive, then an additional individual test is performed for each subject in the group. Given a partition $\mathbf{\Omega}$, the expected number of tests for group i, $i = \{1, \cdots, g\}$, is 1 if $n_i = 1$ (i.e., individual testing), and if $n_i > 1$, we can write:

$$
\begin{aligned}
\mathbb{E}[T_i(\Omega_i)] =& \sum_{k=0}^{n_i} \mathbb{E}[T_i(\Omega_i)|N_i^+(\Omega_i)=k]P(N_i^+(\Omega_i)=k) \\
=& \mathbb{E}[T_i(\Omega_i)|N_i^+(\Omega_i)=0]P(N_i^+(\Omega_i)=0) + \sum_{k=1}^{n_i} \mathbb{E}[T_i(\Omega_i)|N_i^+(\Omega_i)=k]P(N_i^+(\Omega_i)=k) \\
=& \big(Sp+(1-Sp)(1+n_i)\big)P(N_i^+(\Omega_i)=0) + \sum_{k=1}^{n_i} \big(1-Se+Se(1+n_i)\big)P(N_i^+(\Omega_i)=k) \\
=& 1+n_i\left(Se-(Se+Sp-1)\prod_{m\in\Omega_i}(1-p^m)\right).
\end{aligned}
$$

$$
\text{Thus,} \qquad \mathbb{E}[T_i(\Omega_i)] = \begin{cases} 1, & \text{if } n_i = 1, \\ 1+n_i\Big(Se-(Se+Sp-1)\prod_{m\in\Omega_i}(1-p^m)\Big), & \text{otherwise,} \end{cases} \tag{4.4}
$$

and the expected number of tests needed for all subjects in set S is given by $\mathbb{E}[T(\mathbf{\Omega})] = \sum_i \mathbb{E}[T_i(\Omega_i)]$.

4.4 Structural Properties and Algorithms

As discussed earlier, the partitioning problem under an arbitrary objective function is NP-hard [36]. Therefore, in what follows, we develop important structural properties of the two optimization problems, **SM** and **BM**, presented in Section 4.2.2. These properties allow us to reduce the partitioning problem into network flow problems and analyze their computational complexity. In many instances, the resulting network flow problems can be solved with algorithms whose complexity is polynomial in problem size, i.e., N, the number of subjects in set S.

Definition 4.1. A partition, $\mathbf{\Omega} = (\Omega_i)_{i=1,\cdots,g}$, is said to be an *ordered partition* if it follows the ordered set $S = \{1, 2, \cdots, N\}$, that is, $\Omega_1 = \{1, \cdots, n_1\}$, $\Omega_2 = \{n_1 + 1, \cdots, n_1 + n_2\}, \cdots, \Omega_g = \{\sum_{i=1}^{g-1} n_i + 1, \cdots, N\}$, for some $g \in \{1, \cdots, N\}$ and $n_i \in Z^+, i = 1, \cdots, g$.

By this definition, an ordered partition $\mathbf{\Omega} = (\Omega_i)_i$ can be equivalently expressed in terms of the group size vector, $\mathbf{n} = (n_i)_i$, as groups are constructed following the ordered set S. In the following, we first present our main results that hold for both **SM** and **BM**, and then derive additional properties for each problem respectively in Sections 4.4.1 and 4.4.2. All proofs can be found in the Appendix.

Theorem 4.1. *For* **SM** *and* **BM***, the following properties hold in an optimal solution:*

(a) There exists an optimal partition that is an ordered partition of S.

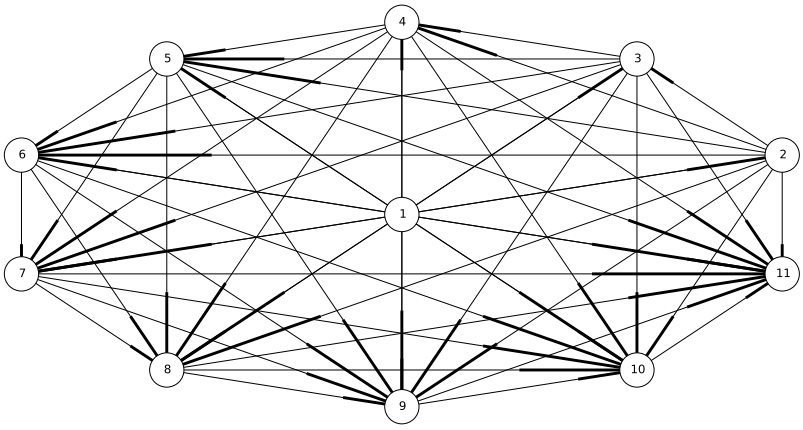
(b) If in the optimal ordered partition, subject m, with risk p^m, is individually tested, then it is optimal to individually test all subjects having a risk higher than p^m.

The first part of Theorem 4.1 allows us to reformulate the partitioning problem as a network flow problem defined on the network in Definition 4.2, while the second part of Theorem 4.1 enables us to improve the computational complexity of the proposed algorithms for certain special cases.

Definition 4.2. For a problem instance with N subjects ($N \in \mathbb{Z}^+$) in set S, let $G = (V, E)$ denote an acyclic directed graph with vertex set $V = \{1, \cdots, N + 1\}$ and edge set $E = \{(i, j) \in V : i < j\}$, with cardinality, $|E| = N(N + 1)/2$.

Figure 4.1 depicts an example of $G = (V, E)$ for $N = 10$, where the bold end of an edge represents its direction, i.e., the flow is directed towards the bold end.

Figure 4.1: $G = (V, E)$ when $N = 10$



Remark 4.3. For a problem instance with N subjects ($N \in \mathbb{Z}^+$) in set S, each path from vertex 1 to vertex $N + 1$ in network $G = (V, E)$ corresponds to an ordered partition of set S, and the number of unique paths is given by 2^{N-1}. Further, $G = (V, E)$ is a dense graph, with the degree of each vertex given by N (i.e., $deg(v) = N$ for all $v \in V$).

To derive the number of paths given in Remark 4.3, let $Path(N)$ denote the number of paths from vertex 1 to vertex $N + 1$ in $G = (V, E)$. We have that:

$$Path(N) = 1 + Path(N-1) + Path(N-2) + \cdots + Path(1), \tag{4.5}$$

which follows since from vertex 1, one can directly go to vertex $N + 1$, or go to vertex 2 and then go to $N + 1$ (in the latter case the number of possible paths from vertex 2 to $N + 1$ equals $Path(N - 1)$), and so on. Rearranging Eq. (4.5) and noting that $Path(1) = 1$, we have:

$$Path(N) = Path(N-1) + \Big(1 + Path(N-2) + \cdots + Path(1)\Big) = 2Path(N-1) = 2^{N-1}.$$

The fact that $G = (V, E)$ is a dense graph follows by definition, i.e., a graph is said to be

dense if $\min_{v \in V}\{deg(v)\} \geq N/2$ [60]; this will play an important role for the construction of an algorithm for a special case of the problem; see Section 4.4.2. Theorem 4.1 leads to the following results.

Property 4.1.

1. **SM** can be formulated as a shortest path (SP) problem defined on $G = (V, E)$, with edge costs given by $c_{ij} = \lambda_1 \mathbb{E}[FN_i(\Omega_{i-j})] + \lambda_2 \mathbb{E}[FP_i(\Omega_{i-j})] + (1 - \lambda_1 - \lambda_2)\mathbb{E}[T_i(\Omega_{i-j})]$, where $\Omega_{i-j} = \{i, \cdots, j-1\}$, i.e., c_{ij} is the cost of utilizing group Ω_{i-j}, for all $(i, j) \in E$.

2. **BM** can be formulated as a constrained-SP problem, having a single constraint, defined on $G = (V, E)$, with edge costs given by $c_{ij} = \lambda \mathbb{E}[FN_i(\Omega_{i-j})] + (1 - \lambda)\mathbb{E}[FP_i(\Omega_{i-j})]$, where $\Omega_{i-j} = \{i, \cdots, j-1\}$, i.e., c_{ij} is the cost of utilizing group Ω_{i-j}, for all $(i, j) \in E$.

Remark 4.4.

1. The SP problem for an acyclic graph can be solved in polynomial time (e.g., via a topological sorting algorithm in $\mathcal{O}(|V| + |E|)$ [37]). As such, a topological sorting algorithm solves **SM** with N subjects in $\mathcal{O}(N^2)$.

2. The constrained-SP problem is, in general, NP-hard [58].

Thus, **SM** can be solved in polynomial time, resolving the intractability conjecture stated in the literature [96]. However, **BM** is a difficult problem. In the remainder of the chapter, we develop structural properties of **SM** and **BM** that enable us to improve their computational efficiency, and to develop an algorithm that can solve an important special case of **BM** in polynomial time.

4.4.1 Analysis of SM

We next study structural properties for important special cases of **SM**, i.e., those that seek to minimize a subset of the expected number of false classifications, or to minimize solely the expected number of tests. Each of these objectives can be important for the decision-maker depending on the setting. For example, [20, 27, 96] exclusively focus on the special case of $\lambda_1 = \lambda_2 = 0$, i.e., minimization of the expected number of tests, and develop various heuristics.

Theorem 4.2. *Consider the following special cases of* **SM** *that respectively minimize the expected number of a weighted combination of both types of classification errors, or number of false negatives only, or number of false positives only.*

1. *For all $\lambda_1, \lambda_2 \in [0, 1] : \lambda_1 + \lambda_2 = 1$, i.e., when minimizing a weighted sum of both types of classification errors:*

   (a) *the optimal ordered partition does not contain a group having more than three subjects, that is, each group is comprised of one, two, or three subjects, i.e., $n_i^* \leq 3$, for all $i = 1, \cdots, g$, for some $g \in \{1, \cdots, N\}$.*

   (b) *If $p^N \leq 1/3$, then the group sizes of the optimal ordered partition are in non-increasing order, i.e., $n_1^* \geq n_2^* \geq \cdots \geq n_g^*$, for some $g \in \{1, \cdots, N\}$.*

2. *For $\lambda_1 = 1$, i.e., when minimizing $\mathbb{E}[FN]$, the optimal partition is to individually test each subject, i.e., $n_i^* = 1$, $i = 1, \cdots, N$.*

3. *For $\lambda_2 = 1$, i.e., when minimizing $\mathbb{E}[FP]$, the optimal ordered partition can have at most one individual test, which, by the second part of Theorem 4.1, has to be for the highest risk subject, i.e., subject N.*

Remark 4.5. For all $\lambda_1, \lambda_2 \in [0,1] : \lambda_1 + \lambda_2 = 1$, by Theorem 4.2, the number of edges in $G = (V, E)$, $|E|$, reduces from $N(N+1)/2$ to $3(N-1)$. As such, a topological sorting algorithm solves **SM** with N subjects in $\mathcal{O}(|V| + |E|) = \mathcal{O}(N)$, that is, in linear time.

Similarly, the following result characterizes properties of the optimal **SM** solution that minimizes the expected number of tests.

Theorem 4.3. *Consider a special case of* **SM** *that minimizes* $\mathbb{E}[T]$*, i.e.,* $\lambda_1 = \lambda_2 = 0$*. If*

$$p^N \leq 1 - \left(\frac{Se - 0.5}{Se + Sp - 1} \right)^{1/2},$$

then the optimal ordered partition can have at most one individual test, which, by the second part of Theorem 4.1, has to be for the highest risk subject, i.e., subject N*.*

We expect the condition imposed in Theorem 4.3 to be satisfied when, for example, the prevalence of the binary characteristic is low and the test specificity is high. As an example, in our case study (see Section 4.5), this condition reduces to $p^N \leq 0.308$, which is satisfied by all subjects in the case study.

Remark 4.6. If $\lambda_1 = \lambda_2 = 0$ and $p^N \leq 1 - \left(\frac{Se-0.5}{Se+Sp-1} \right)^{1/2}$, then the number of edges in $G = (V, E)$, $|E|$, reduces from $N(N+1)/2$ to $1 + N(N-1)/2$, improving the computational complexity of the SP algorithm for **SM**.

Theorem 4.2 establishes that for a special case of **SM** that minimizes the expected number of misclassifications (i.e., $\lambda_1 + \lambda_2 = 1$), and under a certain condition (i.e., $p^N \leq 1/3$), the group sizes for an optimal ordered partition are non-increasing. This property may seem intuitive because it indicates that higher risk subjects are placed in smaller groups than lower risk subjects. Thus, the next question is whether the optimal group sizes continue to be non-increasing when this condition is not satisfied, or when the objective in **SM** contains

the expected number of tests (i.e., $\lambda_1 + \lambda_2 < 1$). The special case of $\lambda_1 = \lambda_2 = 0$, i.e., the minimization of the expected number of tests, is the objective almost exclusively studied in the literature, and various heuristics are proposed that generate ordered partitions with non-increasing group sizes [96]. The following counter-example, which is based on realistic problem parameters, indicates that this property does not necessarily hold in general.

Example 4.1. Consider **SM** with $\lambda_1 = \lambda_2 = 0$, i.e., the objective is to minimize $\mathbb{E}[T]$. Consider a test with $Se = 0.90$ and $Sp = 0.95$, and a set, S, of 100 subjects, i.e., $N = 100$, with an ordered risk vector, $\boldsymbol{p}$, given by $p_{i+1} = \beta + p_i$, $i = 2, \cdots, 99$, where $\beta = 12/3,300$ and $p_1 = 0.01$. The optimal partition that minimizes $\mathbb{E}[T]$ is given by $\boldsymbol{n}^* = (7, 6, 5, 4, 4, 4, 4, 4, 4, 3, 3, 3, 3, 3, 3, 3, 3, 34)$ with $\mathbb{E}[T] = 74.48$, which does not follow a non-increasing ordering of the group sizes.

While placing higher risk subjects in smaller groups seems intuitive, Example 4.1 demonstrates that this is not always the case in an optimal solution.

4.4.2 Analysis of BM

Next, we study structural properties of **BM** in which the objective is to minimize a weighted sum of both types of classification errors under a testing budget constraint; see Eq. (4.2). By Property 4.1, we formulate **BM** as a constrained-SP having a single constraint, which, by Remark 4.4, is NP-hard. Various methods are proposed in the literature to solve the constrained-SP problem, as we briefly discuss below (for a thorough review, see [58]).

One method to solve the constrained-SP problem is the *path ranking method* in which the next unconstrained shortest path is successively generated until the first feasible path, i.e., that satisfies the constraints, is identified. The problem of generating the next shortest path is related to the k-shortest path problem in which the objective is to generate the first k

(unconstrained) shortest paths for a given $k \in Z^+$. When k is fixed, there exist polynomial-time algorithms that generate the k shortest paths [58]. However, when the k-SP problem is used to solve the constrained-SP problem, k is no longer fixed and hence there is no guarantee of a polynomial-time algorithm [58]. This is especially true in our case, as the number of paths grows exponentially with N (see Remark 4.3), rendering this method inefficient and computationally expensive. Alternatively, one can utilize a Lagrangean relaxation based method to solve the constrained-SP problem (e.g., [67]); specifically, when the constraints are relaxed, the problem reduces to an SP problem, which can be solved in polynomial time. In particular, Handler et al. [67] solves the Lagrangean relaxation of the problem in order to determine upper and lower bounds, and then, using a k-SP algorithm (e.g., [140]), closes the gap until optimality or δ-optimality is attained. While such methods are, in general, more efficient than path ranking methods, they may still require a large number of iterations to converge to the optimal solution, especially when the number of paths is large, as in our case.

In what follows, we first analyze an important special case of **BM** that minimizes the expected number of false negative classifications under a testing budget constraint (i.e., $\lambda = 1$). When $\lambda = 1$, Theorem 4.1 and Remark 4.2 enable us to develop an algorithm that can solve **BM** in polynomial time. The algorithm is motivated by the properties that, keeping all else the same, (i) testing any subject individually reduces the objective function value (Eq. (4.3)), (ii) the objective function value is independent of how the subjects in set Ω^G are grouped (Remark 4.2), and (iii) by Theorem 4.1, the subjects in set Ω^I must correspond to the highest risk subjects in set S. Therefore, the proposed algorithm determines the optimal ordered partition by identifying the largest feasible set of subjects that can be tested individually (set Ω^I), and by minimizing the expected number of tests for the remaining subjects (set Ω^G).

Theorem 4.4. *When $\lambda = 1$, the following algorithm solves* **BM** *for N subjects in $\mathcal{O}(N^3)$:*

Step 0: *If $B \geq N$, stop; the optimal solution is to individually test each subject, i.e., $n_i^* = 1$, $i = 1, \cdots, N$.*

Step 1: *Let $\hat{N} = 2$, $S_1 = \{1, 2\}$, and $S_2 = S \setminus S_1$.*

Step 2: *Solve* **SM** *with $S = S_1$ and parameters $\lambda_1 = \lambda_2 = 0$, and let $Z^*(S_1)$ denote the optimal objective function value for set S_1, i.e., $Z^*(S_1, \mathbf{\Omega}^*(S_1)) = \min_{\mathbf{\Omega}} \Big\{ \mathbb{E}[T(S_1; \mathbf{\Omega})] \Big\}$.*

Step 3: *If $Z^*(S_1) + |S_2| \leq B$, stop; the optimal solution is to test the subjects in S_2 individually, and to test the subjects in S_1 according to the optimal ordered partition in Step 2, i.e., $\mathbf{\Omega}^*(S_1)$.*

Step 4: *If $\hat{N} = N$ and $Z^*(S_1) > B$, stop; the problem is infeasible.*

Step 5: *Set $\hat{N} = \hat{N} + 1$, $S_1 = S_1 \cup \{\hat{N}\}$, $S_2 = S \setminus S_1$, and go to Step 2.*

The algorithm provided in Theorem 4.4 depends on Remark 4.2, which in turn depends on the assumption that testing responses are conditionally independent, given the true positivity status of the subjects. In some settings, this assumption might not hold, as there might be a positive correlation among the test outcomes of positive subjects, i.e., if a test outcome of a positive subject is positive, then the probability that the outcome of a sub-sequent test, conducted on the same subject, is positive is higher. This dependency does not have an impact on: (i) the expected number of false positives, as this dependency is typically observed for positive subjects and does not impact the test outcome of negative subjects, and (ii) the expected number of tests, as the number of tests is determined purely from the outcome of the first stage of tests and not from the sub-sequent tests. However, the expected number of false negatives in our model does get impacted, but it provides an upper bound to the expected number of false negatives under a model where this assumption is relaxed. This follows because, by assuming conditional independence, we are underestimating the probability of

a test outcome, in the second stage of individual testing, to be positive. As such, our models are minimizing upper bounds of the objective functions obtained from relaxing this conditional independence assumption, and hence we expect the solutions provided by our model to perform very well even when the conditional independence assumption is relaxed.

Remark 4.7. When $\lambda = 1$, the algorithm presented in Theorem 4.4 not only determines an optimal solution to **BM**, i.e., that minimizes $\mathbb{E}[FN]$, but also provides a solution with the minimum expected number of tests among multiple optimal solutions (if any). This property is not guaranteed by other algorithms, such as Handler's algorithm, which generate any one of the optimal solutions.

Having developed a polynomial-time algorithm for **BM** when $\lambda = 1$, we next explore solving **BM** when $\lambda < 1$. In particular, we formulate **BM** as a binary integer programming problem. Note that the total unimodularity property, present in the integer programming formulation of the unconstrained SP problem, no longer holds with the addition of the budget constraint. Therefore, in the following we exploit the structure of an optimal solution to **BM**. In particular, by Theorem 4.1(b), one can add a set of constraints to the integer programming formulation of **BM** that reduces the feasible region without cutting off the optimal solution, as stated in the following lemma.

Lemma 4.1. *By Theorem 4.1, the following set of constraints do not cut off the optimal solution to* **BM***:*

$$x_{j,j+1} \geq x_{i,i+1},\ \forall\ (i,j) \in E : j > i.$$

In light of Lemma 4.1, the integer programming formulation of **BM** follows:

$$
\begin{aligned}
\underset{\boldsymbol{x}}{\text{minimize}} \quad & \sum_{i=1}^{N} \sum_{j=i+1}^{N+1} \Big(\lambda \mathbb{E}[FN_i(\Omega_{i-j})] + (1-\lambda)\mathbb{E}[FP_i(\Omega_{i-j})] \Big)\, x_{ij} \\
\text{subject to} \quad & \sum_{j=i+1}^{N+1} x_{ij} - \sum_{j=1}^{i-1} x_{ji} = \begin{cases} 1, & \text{if } i = 1 \\ -1, & \text{if } i = N+1 \\ 0, & \text{otherwise} \end{cases} && \forall i \in V \\
& \sum_{j=i+1}^{N+1} x_{ij} \leq 1 && \forall i \in V \\
& x_{j,j+1} \geq x_{i,i+1} && \forall\, (i,j) \in E : j > i \\
& \sum_{i=1}^{N} \sum_{j=i+1}^{N+1} \mathbb{E}[T_i(\Omega_{i-j})]\, x_{ij} \leq B \\
& x_{ij} \in \{0,1\} && \forall (i,j) \in E,
\end{aligned}
\tag{4.6}
$$

where $\Omega_{i-j} = \{i, \cdots, j-1\}$, $\forall i$. Our numerical study shows that, in general, the branch and bound approach used to solve the formulation in (4.6), which includes the additional constraints in Lemma 4.1, outperforms Handler's algorithm [67] in terms of efficiency, allowing us to solve considerably larger problem instances to optimality.

4.4.3 An Equity-based Objective and Properties

As mentioned in Section 4.1, an important consideration in resource allocation problems, especially in public health screening, is the trade-off between classification accuracy and equity. For example, does the most accurate solution unfairly increase the misclassification probability for certain subjects? If so, this solution would be unfair because certain subjects, based on their demographics, which may impact risk, would not benefit from the improved

solution, but instead would be more likely to be misclassified. Therefore, we would like to understand if such inequity occurs in the proposed solutions, and if so, to what degree, i.e., what is the trade-off between accuracy and equity. Towards this end, we capture the trade-off between accuracy and equity by adopting the *α-fairness* measure, commonly used in the literature (e.g., [10,13,19]). The α-fairness measure is a function of parameter $\alpha \geq 0$, known as the *inequality aversion parameter*, that measures the tendency of the model to produce a more equitable solution (over a more accurate solution), see, for example, [19]. Then the equity-based version of the Budget-constrained Model, which we refer to as **BM-E(α)**, follows:

Equity-based Budget-constrained Model (BM-E(α)):

$$\begin{aligned} \underset{\mathbf{\Omega}}{\text{maximize}} \quad & \frac{1}{(1-\alpha)} \sum_{m \in S} \Big(1 - \lambda \mathbb{E}[FN^m(\mathbf{\Omega})] - (1-\lambda)\mathbb{E}[FP^m(\mathbf{\Omega})]\Big)^{1-\alpha} \\ \text{subject to} \quad & \mathbb{E}[T(\mathbf{\Omega})] \leq B. \end{aligned} \tag{4.7}$$

Remark 4.8. Consider the objective function in **BM-E(α)**:

1. When $\alpha = 0$, the objective function reduces to the minimization of a weighted sum of both types of classification errors (i.e., the most accurate solution), that is, **BM-E(α)** reduces to **BM**.

2. As α increases, the objective function assigns more weight to equity [13, 88].

3. As $\alpha \to \infty$, the objective function reduces to the most equitable function [83], i.e., of minimizing the worst-case equity outcome given by,

$$\underset{\mathbf{\Omega}}{\text{minimize}} \quad \max_{m \in S} \{\lambda \mathbb{E}[FN^m(\mathbf{\Omega})] + (1-\lambda)\mathbb{E}[FP^m(\mathbf{\Omega})]\}.$$

Definition 4.3. Following [18], we define the *Price of Fairness*, denoted by $PoF(\alpha)$, as

the relative increase in the weighted sum of classification errors under the optimal equitable solution, with fairness level α, compared to the most accurate solution (i.e., when $\alpha = 0$), that is:

$$PoF(\alpha) = \frac{\lambda\Big(\mathbb{E}[FN(\boldsymbol{\Omega}^*(\alpha))] - \mathbb{E}[FN(\boldsymbol{\Omega}^*(0))]\Big) + (1-\lambda)\Big(\mathbb{E}[FP(\boldsymbol{\Omega}^*(\alpha))] - \mathbb{E}[FP(\boldsymbol{\Omega}^*(0))]\Big)}{\lambda\mathbb{E}[FN(\boldsymbol{\Omega}^*(0))] + (1-\lambda)\mathbb{E}[FP(\boldsymbol{\Omega}^*(0))]}.$$

By Remark 4.8, **BM-E($\alpha = 0$)** reduces to **BM**, and all results of Section 4.4.2 follow. Therefore, in what follows we discuss the case where $\alpha > 0$. The following example shows that when $\alpha > 0$ and $\lambda < 1$, i.e., the objective is to maximize an equity-based objective with respect to either both false negatives and false positives, or false positives only, the optimal partition to **BM-E(α)** need not be an ordered partition, that is, Theorem 4.1 does not necessarily hold under the equity-based objective.

Example 4.2. Consider **BM-E(α)** with $\alpha \to \infty$ and $\lambda = 0$. Suppose that $B = 5$, and consider a test with $Se = 0.90$ and $Sp = 0.95$, and a set, S, of five subjects with the following risk vector:

$$\boldsymbol{p} = (0.10, 0.28, 0.30, 0.40, 0.45).$$

The optimal partition is to have two groups, with the first group containing the lowest and highest risk subjects (i.e., subjects 1 and 5), and the second group containing the remaining three subjects, i.e., $\Omega^* = \big\{\{1,5\},\{2,3,4\}\big\}$. Clearly, the optimal partition is not ordered. Table 4.1 reports the performance of the optimal partition with two ordered partitions that have the same group sizes as the optimal partition (i.e., $\boldsymbol{n} = (2,3)$ and $\boldsymbol{n} = (3,2)$), with $\boldsymbol{n} = (3,2)$ corresponding to the best solution among all ordered partitions.

Example 4.2 demonstrates that the optimal partition need not be an ordered partition. To explain this, first note the following observation.

Table 4.1: Performance of various partitions in Example 4.2

Partition ($\mathbf{\Omega}$)	$\mathbb{E}[FP^m]$					$\max_{m\in S}\{\mathbb{E}[FP^m]\}$	$\mathbb{E}[FP]$
	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5		
$\{1,5\},\{2,3,4\}$	0.01946	**0.01955**	0.01865	0.01415	0.00372	0.01955	0.07552
$\{1,2\},\{3,4,5\}$	0.01296	0.00486	**0.02168**	0.01718	0.01493	0.02168	0.07162
$\{1,2,3\},\{4,5\}$	**0.02122**	0.01312	0.01222	0.01298	0.01073	0.02122	0.07027

Remark 4.9. Consider **BM-E(α)** with $\alpha \to \infty$ and $\lambda = 0$. For any given partition $\mathbf{\Omega}$, the highest false positive probability in each group is determined by the lowest risk subject in that group. Therefore, $\max_{m\in S}\{\mathbb{E}[FP^m]\}$ corresponds to the false positive probability of the lowest risk subject of one of the groups.

As such, this example demonstrates how the optimal partition balances the maximum value of the false positive probability by appropriately grouping the subjects, and the optimal grouping does not need to follow an ordered partition.

Remark 4.10. Since **BM-E(α)** no longer has the property that ensures the existence of an optimal partition that is ordered, it is NP-hard [36].

However, for an important case of **BM-E(α)** with $\lambda = 1$ and $\alpha \geq 0$, i.e., the equity-based objective applies only to false negative classifications, we have the following important result.

Theorem 4.5. *For* **BM-E(α)** *with* $\lambda = 1$ *and* $\alpha \geq 0$*, there exists an optimal ordered partition that is independent of* α*.*

When $\lambda = 1$, Theorem 4.5 follows because, for all $\alpha \geq 0$, (i) testing any subject individually reduces the objective function value (Eq. (4.3)), (ii) the objective function value is independent of how the subjects in set Ω^G are grouped (Remark 4.2), and (iii) by Theorem 4.1, the subjects in set Ω^I must correspond to the highest risk subjects in set S. As such,

for all $\alpha \geq 0$, the objective is to determine the largest feasible set of subjects that can be tested individually (set Ω^I), and since the constraint is independent of α, then this set will be identical for all α levels. Theorem 4.5 has important implications, as stated in the following result.

Corollary 4.1. Consider **BM-E(α)** with $\lambda = 1$ and $\alpha \geq 0$, i.e., the equity-based objective applies only to false negative classifications.

1. $PoF(\alpha) = 0$ for all $\alpha \geq 0$, that is, in terms of the false negative classifications, the partition that is the most accurate is also the most equitable.

2. For all $\alpha \geq 0$, an optimal partition can be obtained by solving **BM**, for which a polynomial-time algorithm exists (see Theorem 4.4).

In the next section, we perform a case study to illustrate the effectiveness of the proposed risk-based testing scheme over optimal non-risk-based schemes and current screening practices.

4.5 Case Study: Chlamydia Screening in the United States

In this section, we perform a case study on chlamydia screening. Chlamydia is one of the most prevalent STDs in the US [35], and most chlamydia screening occurs at the state level via public health laboratories. There are no nationwide guidelines on screening practices for chlamydia, and as a result, screening practices differ significantly among states; for example, North Carolina individually screens high-risk female subjects only [99]; while Idaho uses group testing on all subjects in group sizes of four, with the exception of individual testing of subjects who are exposed to chlamydia or who need to be tested after treatment [89]. A study conducted by the Centers for Disease Control and Prevention (CDC) indicates

Table 4.2: Risk for chlamydia and proportion in population by gender, age, and race/ethnicity [55]

Gender	Race/ethnicity	Age group	Risk (prevalence)	Proportion in general population
Female	Hispanic (H)	15-24	6.54%	1.41%
		Other	0.65%	7.01%
	Black (B)	15-24	19.19%	1.07%
		Other	1.22%	5.67%
	Other (O)	15-24	4.38%	4.29%
		Other	0.25%	31.31%
Male	Hispanic (H)	15-24	1.78%	1.53%
		Other	0.36%	7.16%
	Black (B)	15-24	7.45%	1.09%
		Other	1.05%	5.08%
	Other (O)	15-24	1.20%	4.51%
		Other	0.17%	29.87%

how the positivity probability (risk) of a subject for chlamydia can vary substantially by gender, race/ethnicity, and age [35]. Consequently, in this case study, we decompose the US population by gender, three race/ethnicity groups (black (B), hispanic (H), and other[2] (O)), and two age groups (15-24 and other), leading to a total of 12 risk sub-populations. Studies also show that a large percent of chlamydia cases go undiagnosed and/or unreported (e.g., 75% of females and 50% of males with chlamydia show no symptoms, and are likely to be unreported [56]); and the actual number of cases is estimated to be at least three times the number of reported cases [64]. In Table 4.2, we report the risk (prevalence rate) for chlamydia in the US and the proportion, in the general population, of each risk sub-population based on data in [55] for the year 2014 and using an under-reporting factor, denoted by UP, of three. In addition, we conduct a one-way sensitivity analysis on UP, and investigate two

[2]The "other" category includes: white, American Indian or Alaska native, and Asian or Pacific islander.

other cases of $UP = 4$ and $UP = 5$. The mean overall prevalence rate, μ_p , which we use in non-risk based schemes, is equal to 0.97%, 1.29%, and 1.62%, corresponding to $UP = 3, 4$ and 5, respectively.

We consider an amplified DNA assay for chlamydia (Viper ProbeTec Chlamydia Q^x), a commonly used chlamydia screening test that can be utilized for both individual and grouped testing [84]. A number of NAT tests are available with varying sensitivity and specificity values, hence in this case study, we explore a set of sensitivity and specificity values ranging from 0.93 to 0.97. We use testing and cost data from [100, 129]. Specifically, we set the cost of a false negative to the average cost of sequelae (i.e., any complications resulting from not treating a chlamydia patient), estimated as \$2,927; the screening cost, per test (either individual or grouped), to \$55; and the cost of a false positive to the cost of an additional confirmatory test, which we assume equals the cost of the initial screening test.

To illustrate the benefits of the proposed risk-based Dorfman testing, we perform a Monte Carlo Simulation. In particular, we set the number of subjects that need to be tested in a given period (day) to 100 (i.e., $N = 100$), this provides a realistic representation of the problem [89], and for each day, we generate a realization of the random risk vector following the discrete distribution presented in Table 4.2. We perform 3,000 simulation replications for each scenario, characterized by μ_p, Se, and S_p, and determine the sample mean and sample variance for 3,000 replications for each performance measure. All simulation results in the tables are presented in the form, the point estimate $\pm$ and the half width of a 95% confidence interval.

In Sections 4.5.1 and 4.5.2, we compare each risk-based model, **SM** and **BM**, to a corresponding **base-case (BC)** model in which, following the common treatment of the group testing design in the literature, e.g., [46, 86], we assume that the testing population is homogeneous, with mean risk μ_p, and the population size is infinite. Then, the base-case model

generates a *static* group testing design, which is used repetitively every period, while the proposed risk-based policies generate *dynamic* testing designs, i.e., they produce a potentially different testing design each period based on the observed risk vector for the N subjects. Following current practices, in the base-case, if N is not a multiple of the group size, then the remaining subjects form a (smaller) group for testing, and subjects are randomly assigned to the groups. Then in Section 4.5.3, we compare **SM** to the three risk-based heuristic testing designs proposed by [96], in which the objective is to minimize the expected number of tests. We denote the three heuristics by **MC1**, **MC2**, and **MC3**, respectively corresponding to the *Optimal Dorfman*, *Thresholding*, and *Pool-Specific Optimal Dorfman* algorithms discussed in [96].

4.5.1 System-optimal Model (SM)

We first consider the system's problem, of generating a testing design for N subjects so as to minimize the total cost of false negative and false positive classifications and testing. In our risk-based testing policy, this corresponds to **SM**, with the objective of minimizing $\lambda_1\mathbb{E}[FN] + \lambda_2\mathbb{E}[FP] + (1-\lambda_1-\lambda_2)\mathbb{E}[T]$, with weights $\lambda_1 = 0.96$ and $\lambda_2 = 0.02$, which are normalized based on the cost data discussed above. Specifically, $\lambda_1 = \$2,927/\$3,037^3 \approx 0.96$ and $\lambda_2 = \$55/\$3,037 \approx 0.02$. The corresponding base-case, **BC**, is obtained by minimizing the same objective function, but under the homogeneous and infinite population assumptions, i.e., minimizing the objective function per subject. Table 4.3 reports the performance measures for **BC** and **SM** for a range of parameter values.

The results in Table 4.3 indicate the substantial reductions under **SM** for all performance measures over the non-risk based scheme **BC**. Specifically, **SM** reduces each of $\mathbb{E}[FN]$,

[3] $3,037 represents the total cost, i.e., the cost of false negatives ($2,927), false positives ($55), and testing ($55), see Section 4.5 for details.

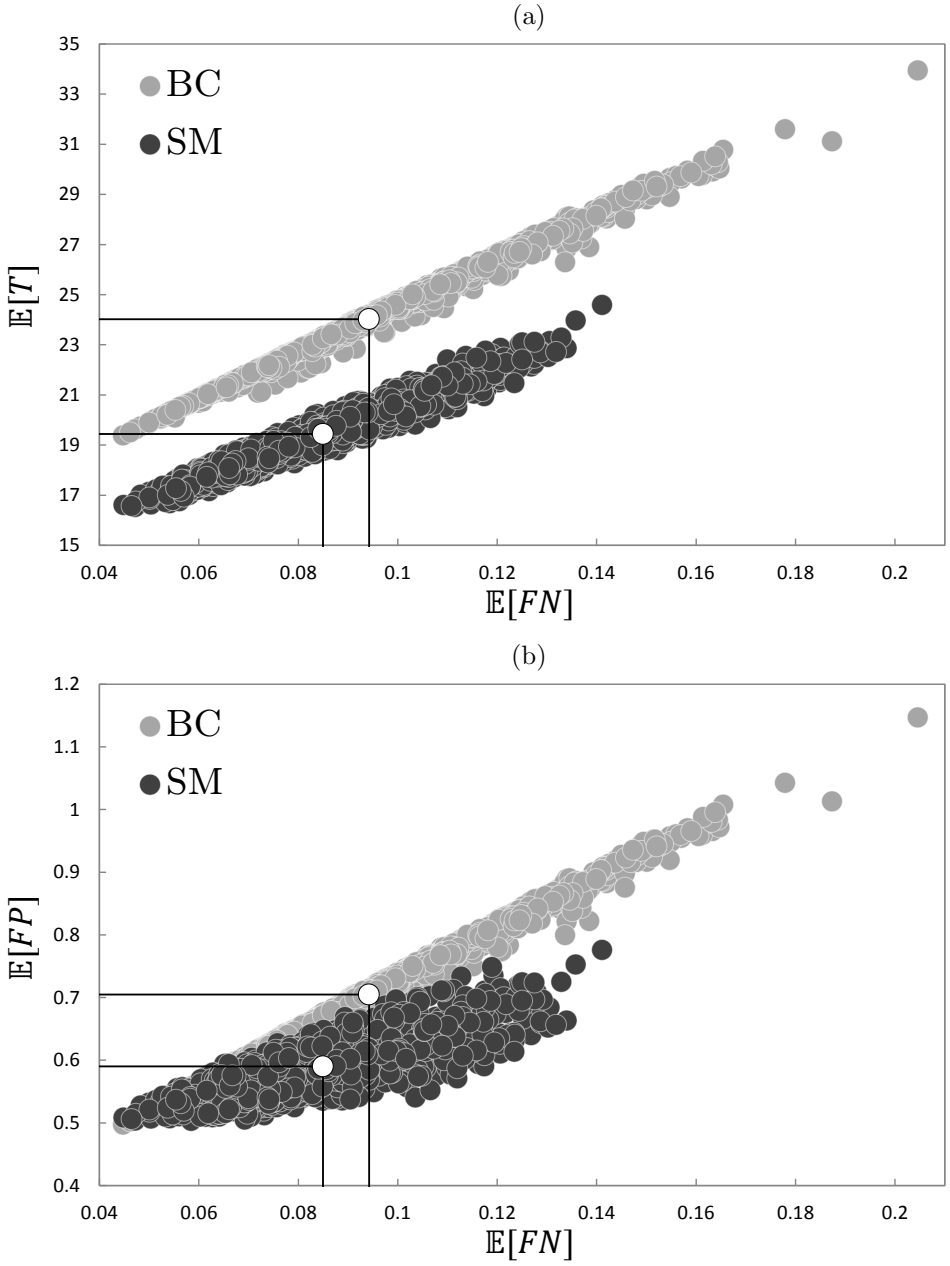
Table 4.3: Performance measures (point estimate ± half width of a 95% confidence interval) for **BC** and **SM**

Model	$\mathbb{E}[FN]$	$\max_{m\in S}\{\mathbb{E}[FN^m]\}$	$\mathbb{E}[FP]$	$\mathbb{E}[T]$	$OF^\dagger$
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.95$				
BC	0.0942 ± 0.0008	0.0146 ± 0.0002	0.7048 ± 0.0034	24.0196 ± 0.0753	0.5850 ± 0.0024
SM	0.0850 ± 0.0006	0.0086 ± 0.0001	0.5901 ± 0.0015	19.4419 ± 0.0441	0.4822 ± 0.0014
%Change	-10%	-41%	-16%	-19%	-18%
	$UP = 4$ ($\mu_p = 1.29\%$), $Se = 0.95$, $Sp = 0.95$				
BC	0.1266 ± 0.0011	0.0197 ± 0.0003	0.7400 ± 0.0039	26.0331 ± 0.0874	0.6570 ± 0.0028
SM	0.1138 ± 0.0008	0.0116 ± 0.0001	0.6259 ± 0.0014	21.4702 ± 0.0460	0.5512 ± 0.0017
%Change	-10%	-41%	-15%	-18%	-19%
	$UP = 5$ ($\mu_p = 1.62\%$), $Se = 0.95$, $Sp = 0.95$				
BC	0.1570 ± 0.0014	0.0241 ± 0.0003	0.8284 ± 0.0043	29.1062 ± 0.0994	0.7494 ± 0.0034
SM	0.1414 ± 0.0010	0.0143 ± 0.0001	0.6553 ± 0.0014	23.2094 ± 0.0495	0.6131 ± 0.0019
%Change	-10%	-41%	-21%	-20%	-18%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.93$, $Sp = 0.95$				
BC	0.1302 ± 0.0011	0.0202 ± 0.0003	0.6944 ± 0.0032	23.7900 ± 0.0715	0.6147 ± 0.0025
SM	0.1179 ± 0.0008	0.0121 ± 0.0001	0.5863 ± 0.0015	19.2801 ± 0.0422	0.5105 ± 0.0016
%Change	-9%	-40%	-16%	-19%	-17%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.97$, $Sp = 0.95$				
BC	0.0574 ± 0.0005	0.0090 ± 0.0001	0.7158 ± 0.0034	24.2618 ± 0.0753	0.5546 ± 0.0020
SM	0.0516 ± 0.0003	0.0052 ± 0.0001	0.5937 ± 0.0015	19.6080 ± 0.0436	0.4536 ± 0.0012
%Change	-10%	-42%	-17%	-19%	-18%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.93$				
BC	0.0947 ± 0.0008	0.0147 ± 0.0002	1.1135 ± 0.0046	25.8354 ± 0.0738	0.6299 ± 0.0024
SM	0.0851 ± 0.0006	0.0087 ± 0.0001	0.9564 ± 0.0021	21.2879 ± 0.0434	0.5265 ± 0.0014
%Change	-10%	-41%	-14%	-18%	-16%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.97$				
BC	0.0939 ± 0.0008	0.0146 ± 0.0002	0.3688 ± 0.0020	22.2124 ± 0.0756	0.5418 ± 0.0023
SM	0.0844 ± 0.0006	0.0086 ± 0.0001	0.2987 ± 0.0009	17.5682 ± 0.0435	0.4384 ± 0.0014
%Change	-10%	-41%	-19%	-21%	-19%

† OF is the objective function of **SM**, i.e., $OF = \lambda_1\mathbb{E}[FN] + \lambda_2\mathbb{E}[FP] + (1 - \lambda_1 - \lambda_2)\mathbb{E}[T]$.

$\max_{m\in S}\{\mathbb{E}[FN^m]\}$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$ over **BC** by an average of 10%, 41%, 17%, and 19%, respectively. Moreover, the objective function of **SM** is reduced by and average 18% over

Figure 4.2: Performance comparison of **BC** and **SM** with respect to $\mathbb{E}[FN]$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$, when $UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, and $Sp = 0.95$



BC. The one-way sensitivity analysis reveals that the reductions in all performance measures are consistent among the different settings, indicating how risk-based testing can provide substantial benefits for a range of parameter values. Figure 4.2 also plots (a) $\mathbb{E}[T]$ and (b) $\mathbb{E}[FP]$ as a function of $\mathbb{E}[FN]$ for each of **BC** and **SM**; each point in the figure represents

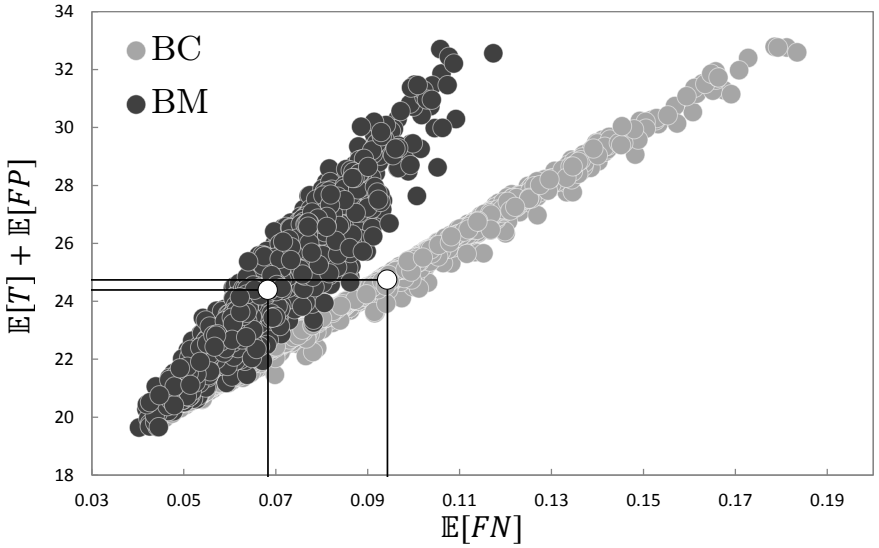
one of the 3,000 simulation replications of the random risk vector. In addition to the reduction of all performance measures under **SM**, interestingly, Figure 4.2 also reveals that **SM** substantially reduces the variance, i.e., the sample variance corresponding to the 3,000 simulation replications, of these measures as well, specifically, by 51%, 80%, and 66% for $\mathbb{E}[FN]$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$, respectively.

4.5.2 Budget-constrained Model (BM)

We next consider the budget-constrained testing problem, of generating a testing design for N subjects so as to minimize the number of false negative classifications under a testing budget constraint. In our risk-based testing policy, this corresponds to **BM**, with $\lambda = 1$. Following common testing practices, we consider that all positive-testing subjects in the initial screening undergo additional confirmatory testing. Consequently, we modify the testing budget constraint in (4.2) to also include the cost of false positives in the initial screening, $\mathbb{E}[T] + \gamma\mathbb{E}[FP] \leq B$, with $\gamma = 1$, i.e., the cost of a false positive is equal to the testing cost. By Remark 4.1, this modification does not impact the analytical results.

In the corresponding base-case, **BC**, under the homogeneous and infinite population assumptions, the per subject expected number of false negatives becomes independent of the group size [7]. As such, for the corresponding base-case, rather than minimizing the per subject expected number of false negatives, we minimize the left-hand side of the budget constraint (i.e., $\mathbb{E}[T]+\gamma\mathbb{E}[FP]$), as this will determine the least costly scheme. In this setting, the optimal group size in **BC** is equal to 11, 10, or 9 corresponding to $\mu_p = 0.97\%, 1.29\%$, and 1.62%, respectively. As stated above, if N is not a multiple of the group size, then the remaining subjects form a (smaller) group for testing, e.g., for $\mu_p = 0.97\%$, all subjects are tested in group sizes of 11, except for one subject (randomly selected) that is tested individually (since

Figure 4.3: Performance comparison of **BM** and **BC** with respect to $\mathbb{E}[FN]$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$, when $UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, and $Sp = 0.95$



$N = 100$). The subjects are randomly assigned to groups.

The per period budgets of **BM** is set to the corresponding testing costs under the **BC** policy, that is, given a risk vector realization in a period, the budget for the risk-based scheme **BM** is set to $B = \mathbb{E}[T] + \mathbb{E}[FP]$ of **BC**. Doing so ensures that the cost of the risk-based scheme does not exceed that of **BC**. Table 4.4 reports the performance measures of **BM** and **BC** for a range of parameter values, and indicates the substantial reductions in all performance measures under **BM**. Specifically, **BM** respectively reduces $\mathbb{E}[FN]$, $\max_{m \in S}\{\mathbb{E}[FN^m]\}$, and $\mathbb{E}[T]+\mathbb{E}[FP]$ by 28%, 48% and 1%, over **BC**. Hence, **BM** generates testing schemes that are substantially more accurate and equitable, in terms of false negatives, than current testings schemes while being cheaper to implement than non risk-based testing schemes. Moreover, the one-way sensitivity analysis reveals that these reductions are consistently observed for a range of parameter values. Figure 4.3 plots $\mathbb{E}[T] + \mathbb{E}[FP]$ as a function of $\mathbb{E}[FN]$, with each point representing one of the 3,000 realizations of the random risk vector. In addition to the reduction of all performance measures under **BM**, interestingly, Figure 4.3 also reveals that **BM** substantially reduces the variance, i.e., the sample variance corresponding to the 3,000

Table 4.4: Performance measures (point estimate ± half width of a 95% confidence interval) for **BC** and **BM**

Model	$\mathbb{E}[FN]$	$\max_{m \in S}\{\mathbb{E}[FN^m]\}$	$\mathbb{E}[FP] + \mathbb{E}[T]$
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.95$		
BC	0.0943 ± 0.0008	0.0147 ± 0.0002	24.7396 ± 0.0756
BM	0.0683 ± 0.0004	0.0077 ± 0.0001	24.3924 ± 0.0759
%Change	-28%	-48%	-1%
	$UP = 4$ ($\mu_p = 1.29\%$), $Se = 0.95$, $Sp = 0.95$		
BC	0.1267 ± 0.0011	0.0196 ± 0.0003	26.7660 ± 0.0935
BM	0.0902 ± 0.0005	0.0102 ± 0.0001	26.4263 ± 0.0933
%Change	-29%	-48%	-1%
	$UP = 5$ ($\mu_p = 1.62\%$), $Se = 0.95$, $Sp = 0.95$		
BC	0.1565 ± 0.0013	0.0242 ± 0.0003	29.9104 ± 0.1006
BM	0.1086 ± 0.0006	0.0125 ± 0.0002	29.5492 ± 0.1011
%Change	-31%	-49%	-1%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.93$, $Sp = 0.95$		
BC	0.1307 ± 0.0011	0.0203 ± 0.0003	24.5217 ± 0.0775
BM	0.0952 ± 0.0006	0.0107 ± 0.0001	24.1705 ± 0.0779
%Change	-27%	-47%	-1%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.97$, $Sp = 0.95$		
BC	0.0566 ± 0.0005	0.0086 ± 0.0001	24.8495 ± 0.0789
BM	0.0409 ± 0.0002	0.0045 ± 0.0001	24.4928 ± 0.0792
%Change	-28%	-48%	-1%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.93$		
BC	0.0941 ± 0.0008	0.0144 ± 0.0002	26.8905 ± 0.0784
BM	0.0683 ± 0.0004	0.0075 ± 0.0001	26.5379 ± 0.0788
%Change	-27%	-48%	-1%
	$UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, $Sp = 0.97$		
BC	0.0942 ± 0.0008	0.0147 ± 0.0002	22.6159 ± 0.0796
BM	0.0681 ± 0.0004	0.0077 ± 0.0001	22.2615 ± 0.0797
%Change	-28%	-48%	-2%

simulation replications, of $\mathbb{E}[FN]$ and $\max_{m \in S}\{\mathbb{E}[FN^m]\}$, specifically by 72% and 77% over **BC**, respectively.

4.5.3 Comparison to Existing Heuristics

In this section, we compare the performance of **SM** to existing heuristics proposed in the literature (see [96]), detailed below:

- *Optimal Dorfman* (**MC1**): All group sizes are restricted to be equal, and the group size is determined by enumerating over all possible values and selecting the one that gives the smallest expected number of tests.
- *Thresholding* (**MC2**): The population is partitioned into two classes, low risk and high risk subjects, based on a risk threshold. The risk threshold is determined as follows: (i) run heuristic **MC1** on all N subjects and determine the best common group size, (ii) using this common group size, and starting with the highest risk subjects, enumerate over the groups of subjects to determine the first group that gives a lower expected number of tests when grouped over individual tests, denote this group by i, (iii) set the risk threshold to the average of the highest risk subject in group i and the lowest risk subject in group $i+1$. All subjects having a risk higher than the risk threshold are classified as high risk subjects, and are individually tested, while all subjects having a risk lower than the risk threshold are classified as low risk subjects, and are tested in groups of common size. The common group size for the low risk subjects is determined by running **MC1** on the set of subjects having a risk lower than the risk threshold.
- *Pool-specific Optimal Dorfman* (**MC3**): Starting with the lowest risk subjects, groups are formed so as to minimize the expected number of tests per subject. Specifically, the groups are constructed as follows: (i) place the lowest risk subject in a group, giving an expected number of test per subject equal to one, (ii) add the second lowest risk subject to this group and measure the expected number of tests per subject, (iii) keep on adding subjects to the group until the group with the lowest expected number of

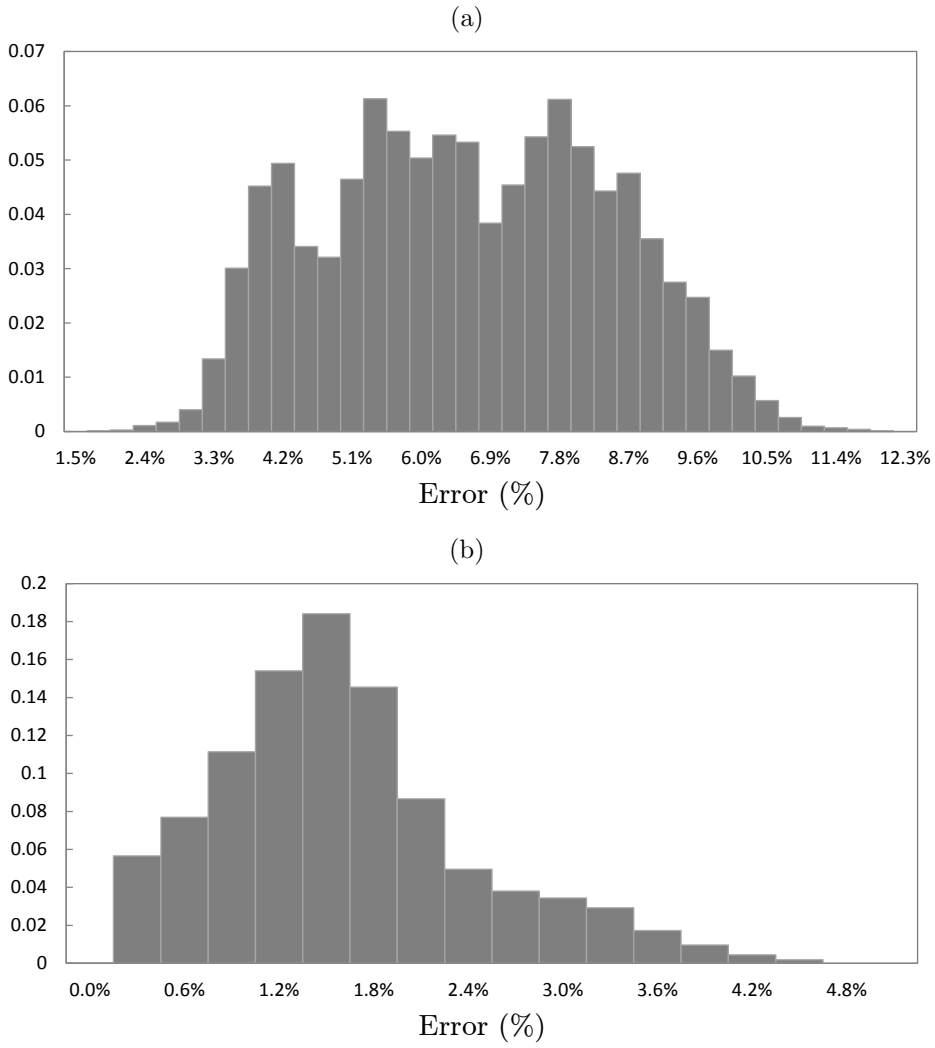
test per subject is identified, (iv) reapply the same steps on subjects that have not yet been assigned to groups.

All three heuristics, **MC1**, **MC2**, and **MC3**, are based on minimizing the expected number of tests. Therefore, for comparison purposes, in **SM** we set λ_1 and λ_2, i.e., the weight of false negatives and positives in the objective function of **SM**, to zero, to also minimize the expected number of tests in **SM**.

To study how the solutions from these three heuristics compare to the optimal solution obtained from **SM**, we perform a Monte Carlo simulation with 10,000 replications. In each replication, we generate a risk vector realization and determine the solutions provided by **SM**, **MC1**, **MC2**, and **MC3**. We demonstrate our results for the case where $UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, and $Sp = 0.95$. (Our extensive numerical study, with various parameter values, yields similar findings.) Figure 4.4 plots the histograms of the error (in percentage), i.e., the deviation (in percentage) of the expected number of tests obtained by the heuristic solution from the optimal expected number of tests obtained by **SM**, for: (a) **MC1&2** and (b) **MC3**. We want to note here that **MC1** and **MC2** heuristics provided identical solutions in all our numerical experiments in this section. This is the case because when implementing **MC2** in our setting, all subjects are identified as low risk subjects, and hence **MC2** reduces to **MC1** (see the details of **MC2** at the beginning of Section 4.5.3). According to Figure 4.4, out of the 10,000 Monte Carlo scenarios, **MC1&2** never attained optimality, and the deviation from the optimal solution can be as high as 12%. On the other hand, **MC3** attained optimality only once out of the 10,000 scenarios, and the deviation from the optimal solution can be as high as 5%.

This case study underscores the substantial benefits of the proposed risk-based policies in both settings (i.e., **SM** and **BM**); risk-based policies substantially reduce the classification errors and improve efficiency and equity over non-risk based policies. We demonstrate how

Figure 4.4: Deviation of (a) **MC1&2** and (b) **MC3** from **SM**, when $UP = 3$ ($\mu_p = 0.97\%$), $Se = 0.95$, and $Sp = 0.95$



heuristic solutions are rarely optimal, and how they can deviate, sometimes substantially, from the optimal solution.

4.6 Conclusions and Future Research Directions

We study the problem of designing an optimal risk-based Dorfman testing scheme to accurately and equitably classify a set of subjects in an efficient manner, while taking into account imperfect tests. Our analytical results enable us to reduce the NP-hard partitioning problems into an SP problem (for **SM**) or a constrained-SP problem (for **BM**). Further, for special cases of **BM**, we develop highly efficient algorithms that exploit the structure of the problem and that are able to solve the constrained-SP problem in polynomial time. Our case study demonstrates the effectiveness of risk-based testing, producing solutions that substantially reduce all performance measures when compared to static, non-risk based models. Our findings highlight the importance of incorporating subject-specific risk characteristics into the modeling framework, as failing to do so can lead to higher classification errors and more costly and less equitable testing schemes.

This research can be expanded in several important directions. In reality, subject risk values are not perfectly observable, hence the decision-maker needs to estimate the risk of each subject given their characteristics. Therefore, an important future research direction would be to consider robust testing schemes that perform well under risk estimation errors, or to consider adaptive strategies that study the exploration (e.g., initial testing for risk estimation) versus exploitation (e.g., testing for classification) trade-off, especially studying the decision of how to allocate a given budget between the efforts of exploration versus exploitation to maximize the classification accuracy.

Another important aspect in group testing is the dilution effect of grouping, i.e., for some tests, the accuracy of the test for detecting positive subjects (i.e., the test's sensitivity) may decrease as group size increases. However, studies have shown that up to certain group sizes, the effects of dilution are negligible. As such, a possible way to incorporate

the dilution effect into our models is to place upper bounds on group sizes; this can be attained by eliminating certain edges from the underlying graph of the partitioning problem. Alternatively, a more accurate, yet more complex, approach is to explicitly model the dilution effect (i.e., the test sensitivity becomes a function of the group size) and incorporate it into the modeling framework. Our analysis also depends on the assumption that different test outcomes performed on the same subject are conditionally independent, given the actual positivity status of the subject. This assumption does not always hold in practice, especially for infection screening tests that measure infection-related bio-markers, because if a subject is infected with the infection in question, then concentrations of several infection-related bio-markers will be higher than infection-free subjects, and tests that measure the related bio-markers will have a tendency to produce a positive test outcome. Therefore, relaxing such outcomes on the test's sensitivity and specificity will increase model realism and may produce better testing schemes.

An important aspect is to consider the operational challenges of changing the testing scheme on a daily basis, as is done here. In some cases, modifying the testing scheme on a frequent basis may not be feasible, or simply not desirable. In this case, the decision-maker may be interested in determining an optimal *static* policy (either static group sizes, or a static threshold vector on subject risk according to which the subjects can be partitioned into groups), that is, the problem is one of a stochastic programming problem, of identifying an optimal static policy under uncertainty on subject risk vector. Finally, our decision problem considers only Dorfman-type testing schemes. There are other, albeit more complicated, group testing schemes, and it will be interesting to study the problem of jointly determining an optimal partitioning and testing scheme. This is a challenging research direction.

It is our hope that this work builds the foundation for more complex risk-based testing schemes and drives future research in any of the aforementioned directions. As we show here,

the benefits of risk-based group testing schemes can be substantial, and we hope our work also motivates the practitioners to consider implementing such risk-based testing schemes.

Chapter 5

Optimal Static Risk-based Group Testing Under Imperfectly Observable Risk

5.1 Introduction and Motivation

Screening a large population so as to classify each subject as positive or negative for a binary characteristic (e.g., presence of a disease or defect) is important in many settings. Individually testing each subject incurs high testing costs, and is often not budget-feasible. Consequently, testing facilities often utilize *group testing*, wherein multiple subjects (or specimens from the subjects, e.g., blood specimens) are grouped and tested together, with one test applied to the entire group. Thus, group testing can offer substantial reductions in testing costs over individual testing, especially when the prevalence of the binary characteristic in the population is low, and is commonly utilized as an integral part of screening/testing schemes across various disciplines, including public health screening, industrial quality control, con-

flict resolution in multi-access communication networks, software testing, and compressed sensing, e.g., [16, 28, 38, 46, 114]. The origins of group testing date back to the 1940's, when Dorfman [46], an economist, introduced this concept as a way to test military inductees for syphilis in an economical manner. Dorfman proposed a simple two-stage testing scheme: in the first stage, a group of subjects are tested with a single test; if the test outcome is negative, suggesting that all subjects within the group are negative for the disease, then the testing stops and all subjects in the group are classified as negative; if, on the other hand, the test outcome is positive, suggesting the presence of at least one positive subject within the group, the testing proceeds to the second stage in which each subject is individually tested and classified according to the outcome of their individual test. Today, this so-called *Dorfman testing* is one of the most commonly adopted schemes in practice due to its simplicity and efficiency, and is the focus of this chapter.

In these settings, the tester needs to determine the various group sizes to be used in testing, along with the assignment of subjects, with different risk estimates (probability of positivity) for the binary characteristic, to the different groups. Moreover, it may not be practical, nor even feasible, to change the testing scheme (e.g., group sizes) each period, as doing so may incur high set-up cost/time and/or operational challenges; thus, "static" testing schemes, which do not change over time, may be highly desirable for practitioners. What complicates the testing decision further is that the test is not perfectly reliable; hence false negative classifications (i.e., falsely classifying positive subjects as negative) and false positive classifications (i.e., falsely classifying negative subjects as positive) are possible. This decision problem arises in many settings, as discussed above. For example, in the context of public health screening, testing laboratories screen donated blood (via a specimen from each donation), received periodically (e.g., with each shipment), for a set of transfusion-transmittable diseases (e.g., human immunodeficiency virus (HIV), hepatitis viruses) [40]. Specimens are

loaded into automated testing machines in "batches" (typically between 40-200 specimens per batch depending on the equipment used [71]). Due to the large number of subjects that need to be tested, testing begins as soon as a sufficient number of subjects to form a complete batch arrive. As another example, consider industrial quality control in which a set of products, received periodically (e.g., with each shipment from the supplier, in each manufacturing shift), needs to be tested for defects; and the batch size may represent the shipment size, or the capacity of the testing machine.

On the population side, the probability of having the binary characteristic (*risk*) may vary, sometimes substantially, with subject-specific characteristics (*risk factors*) that are often known prior to testing. For example, in donated blood screening, first-time blood donors in the United States are around seven times more likely to have an HIV infection than repeat donors [143]; vector-borne infections, such as babesiosis, are endemic in certain areas of the United States [70]. Thus, subjects come from a *heterogeneous* population. However, the process of estimating the subject-specific risk, based on established risk factors for the binary characteristic, and/or informed by sub-population-specific prevalence rate estimates, is far from perfect. This is because risk factors, and their interactions, are often not well-understood; and prevalence rate estimates in the different sub-populations are inherently uncertain, e.g., [9, 63]. Consequently, the true risk of a subject is unobservable, and the tester needs to estimate the risk of each subject and construct an uncertainty set that contains the true risk with a high probability. Under such uncertainty in risk estimation, it is important to determine testing schemes that are not highly sensitive to perturbations in the risk estimates, i.e., robust testing schemes.

The challenge, then, is to determine a *static risk-based Dorfman testing scheme*, comprised of a set of group sizes and a policy to assign subjects, with different risk, to the mutually exclusive groups, under uncertainty on both subject characteristics (hence the estimated risk)

and the actual risk. The goal is to identify a static testing scheme that is used repetitively for every batch, and that is *accurate*, in terms of subject classification, *efficient*, in terms of testing cost, and *robust*, with respect to deviations from the estimated risk vector. Most literature on group testing considers the objective of minimizing the testing cost under perfect tests, with limited focus on misclassification; and robustness is an often overlooked dimension in group testing, as the group testing literature almost exclusively assumes that subject risk is perfectly observable. In this chapter, we explore both expectation-based and robust optimization models to determine optimal static risk-based Dorfman testing schemes, under uncertainty on the subject risk. We characterize key structural properties of optimal static risk-based Dorfman testing schemes. These properties allow us to reduce the resulting optimization problems to network flow problems and solve to optimality. We also perform a case study that demonstrates an application of the proposed static risk-based testing scheme to public health screening, specifically, the donated blood testing setting discussed above.

Dorfman's original model, and the majority of the subsequent research, impose unrealistic assumptions, such as *perfect* tests, i.e., there are no classification errors, a *homogeneous* population, i.e., the probability of having the binary characteristic (risk) is identical across subjects, and infinite testing *batch* sizes (e.g., [46, 114, 118]). While several papers extend the analysis of Dorfman testing schemes to imperfect tests (e.g., [62, 80, 86, 96]), there is very limited work on Dorfman testing for a heterogeneous population, i.e., with subject-specific risk, and the few papers that consider a heterogeneous population (e.g., [5, 75, 96]) mainly do so under restrictive assumptions, including that the subject risk is perfectly observable, or they determine testing schemes heuristically. Specifically, Hwang [75] determines optimal risk-based Dorfman testing schemes for a heterogeneous population, but under the assumption that the test is perfect (hence, the objective is to minimize the number of tests) and the subject risk is perfectly observable. Moreover, Hwang's focus is on "dynamic" testing

schemes, i.e., group sizes and the subject-group assignment policy are allowed to change with each batch, that is, the group testing problem is a deterministic problem, solved after the risk of each batch of subjects is observed. McMahan et al. [96] extend the analysis in [75] to the case of imperfect tests, but conjecture that the problem, of determining risk-based Dorfman testing schemes, under imperfect tests and perfectly observable subject risk, so as to minimize the expected number of tests, is intractable, and develop heuristics. More recently, Aprahamian et al. [5] show that the extension of Hwang's model to the case of imperfect tests, but with perfectly observable subject risk, is in fact tractable, resolving the conjecture in the literature, and develop exact algorithms to determine optimal dynamic risk-based Dorfman testing schemes. While these studies have improved our understanding of optimal risk-based Dorfman testing for a heterogeneous population, they leave out other important aspects of the problem, such as *implementability* of the testing scheme and *uncertainty* in subject risk estimates. For example, both Aprahamian et al. [5] and Hwang [75] assume that the decision-maker can construct an optimal dynamic testing scheme, *customized* for each batch of subjects. While such an assumption may be justified in certain settings, in other settings the decision-maker may not have the flexibility to modify the testing scheme for every batch, as discussed above. McMahan et al. [96] consider a static testing scheme (the same group sizes and assignment policy are used for every batch), which partially resolves the implementability issue, but this is done by: (i) ordering the subjects in non-decreasing order of their risk and simply setting the risk of each subject to the expected risk of the corresponding order statistics, and, (ii) determining testing schemes that attempt to minimize the expected number of tests using heuristics, based on properties that do not necessarily hold in an optimal solution (e.g., group sizes are non-increasing for a risk-ordered batch, see [5]). A lack of properties and algorithms for optimal static Dorfman testing schemes in this setting is not surprising, because various functions of order statistics (for batch sizes that are in the hundreds) arise in an exact formulation, substantially complicating the analy-

sis. Our analysis, of optimal static Dorfman testing schemes for heterogeneous populations, resolves all of the aforementioned issues, and as a by product, provides a novel result on order statistics, which is not limited to the group testing setting. In addition, we investigate the realistic situation in which the true risk of a subject is not known with certainty, but lies within a known uncertainty set, and this aspect of the problem gives rise to a novel *robust* formulation of the problem.

Our contributions in this chapter are multi-fold. **First**, we model important aspects of group testing that are often overlooked in the literature, such as implementability of the testing scheme, the uncertainty in the risk estimates, and objective functions that incorporate the classification accuracy into the modeling framework (as opposed to solely minimizing the expected number of tests). **Second**, we explore novel expectation-based and robust formulations of the aforementioned decision problem, and develop key structural properties of each problem. These properties allow us to reduce the expectation-based and robust formulations to network flow problems, enabling us to solve these problems to optimality, which, to the best of our knowledge, has not been done in the existing literature. Analysis of the expectation-based and robust models further provides valuable insight on the trade-off between classification accuracy and robustness; for example, our numerical study indicates that the *price of robustness* is low in our setting, i.e., the robust model leads to a small increment in the expected value of the objective function (i.e., subject misclassification and testing costs), while substantially improving other aspects of the testing scheme, such as reducing the variability around the objective function value. **Third**, we develop a novel expression on the expected value of the product of some function of a set of consecutive order statistics, which is not limited to the group testing setting. This result substantially improves the computational efficiency of the proposed algorithms, enabling us to solve realistic problem instances to optimality. **Finally**, we demonstrate the effectiveness of the proposed static risk-

based Dorfman testing scheme through a case study on HIV screening in sub-Saharan Africa, an area with one of the highest HIV prevalence rates in the world. The proposed testing schemes substantially reduce the misclassification and testing costs over optimal non risk-based ("uniform") schemes and current screening practices. Further, our numerical study suggests that the performance of static testing schemes, which are easily implementable, are within one percent of the more complicated dynamic testing schemes, i.e., schemes that are customized for each batch. Thus, restricting the testing schemes to static schemes does not hinder the performance of screening in a significant way. Our numerical results also indicate that the performance of static testing schemes comprised of only a small number of group sizes (only two in our setting) is comparable to more complicated static testing schemes comprised of many group sizes. These findings indicate that simple static schemes, with a small number of group sizes, can capture most benefits of risk-based testing, underscoring the value of static risk-based testing schemes studied in this dissertation.

The remainder of this chapter is organized as follows. Section 5.2 presents the notation and the decision problem, and Section 5.3 discusses the expectation-based and robust formulations, and provides derivations of the relevant performance measures. Section 5.4 then studies the optimal design of static risk-based Dorfman testing schemes in different settings and derives important structural properties of optimal solutions. Section 5.5 discusses findings from the HIV screening case study. Finally, Section 5.6 summarizes our findings and provides directions for future research. To facilitate the presentation, all proofs are relegated to the Appendix.

5.2 The Notation and the Decision Problem

In this section, we present the notation and the decision problem. Throughout, we denote random variables in upper-case letters, their realization in lower-case letters, and vectors in boldface. We use the terms *positive* and *negative* to refer to a subject's true status or classification outcome (i.e., to respectively denote the presence or absence of the characteristic, or the classification for the characteristic), or to the binary test outcome (i.e., to respectively denote the test outcome that *indicates* the presence or absence of the characteristic).

Consider a testing facility (e.g., laboratory) where subjects (or specimens collected from subjects) arrive throughout the day. Subjects are tested in batches of size N for a binary characteristic, where the batch size N is determined by the testing equipment. Due to limited testing capacity and throughput requirements, we assume that testing begins when enough subjects arrive to form a batch. For example, most public health screening laboratories have testing equipment dedicated to the screening of a certain condition (i.e., disease or genetic disorder), and most testing machines are highly automated, e.g., the nucleic acid amplification testing machine [71, 128] that we consider in our case study in Section 5.5. These testing machines are loaded in batches (e.g., with batch sizes, N, ranging from 40 to 200), and testing of each batch typically takes 3-4 hours. Thus, whenever a set of N subjects is received, testing is performed. The tester needs to classify each subject as positive or negative for the binary characteristic so as to minimize the costs of misclassification and testing, under imperfectly reliable tests.

The population is *heterogeneous* with respect to *risk* (probability of positivity) for the binary characteristic due to subject-specific demographic and clinical factors. To model population heterogeneity, let D^m denote the true status of subject m for the binary characteristic, with a value of 1 if subject m is a true-positive for the characteristic, and 0 otherwise, that is,

random variable D^m, unknown to the tester, follows a Bernoulli distribution with a subject-specific probability of positivity given by P^m, independently of other subjects. However, the value of P^m, i.e., the "true" risk of subject m, is unobservable by the tester due to potentially unknown or misunderstood risk factors and/or interactions. Therefore, the tester "estimates" the risk of subject m, denoted by $\tilde{P}^m$, based on the subject's characteristics. We let Ξ^m denote the random perturbation (error) term for the risk of subject m, i.e., the deviation of the estimated risk from the true risk. Thus, the true risk of subject m can be expressed as a function of the estimated risk and the random perturbation term. We assume that random variables $\tilde{P}^m, m = 1, \cdots, N$, are independent and identically distributed (iid), following an arbitrary continuous distribution with support in $[a, b]$, for $0 \leq a < b \leq 1$; random variables $\Xi^m, m = 1, \cdots, N$, are iid, following an arbitrary continuous distribution with support in $[-\delta, \delta]$, for some $\delta \geq 0$; and random vectors $\tilde{\boldsymbol{P}}$ and $\boldsymbol{\Xi}$ are independent. Then, the true risk of subject m, conditional on the estimated risk and perturbation term, can be written as, $P^m|\tilde{P}^m, \Xi^m = t\big(\tilde{P}^m, \Xi^m\big)$, for $m = 1, \cdots, N$, where $t(.)$ is some arbitrary continuous function in $[0, 1]$. We do not make any assumptions on function $t(p, \xi)$, other than that it is non-decreasing in each of p and ξ; $\mathbb{E}_{\Xi^m}\big[t\big(\tilde{p}^m, \Xi^m\big)\big] = \tilde{p}^m$, that is, the expectation of the true risk equals the estimated risk; and $t\big(p, 0\big) = p$, for all p, that is, the true risk reduces to the estimated risk when the perturbation term is zero, i.e., the case of no estimation error. Then, $D^m|\tilde{P}^m$ follows a compound Bernoulli distribution with a probability of positivity of $P^m|\tilde{P}^m$, which lies within an uncertainty set, $\big[t\big(\tilde{P}^m, -\delta\big), t\big(\tilde{P}^m, \delta\big)\big] \subseteq [0, 1]$. Notice that the uncertainty set is larger for higher values of δ; thus parameter δ can be interpreted as a "budget of uncertainty" (e.g., [17]) around the estimated risk.

Without loss of generality, we represent the set of subjects in each batch as a *risk-ordered set*, $S \equiv \{1, \cdots, N\}$, that follows a non-decreasing order of the estimated subject risk, i.e., $\tilde{p}^1 \leq \tilde{p}^2 \leq \cdots \leq \tilde{p}^N$, that is, for a given estimated risk vector $\tilde{\boldsymbol{p}} = (\tilde{p}^i)_{i=1,\cdots,N}$, subject 1

corresponds to the subject with the lowest estimated risk, subject 2 with the second lowest estimated risk, and so on. Then $\tilde{\boldsymbol{P}} = (P^{(1)}, P^{(2)}, \cdots, P^{(N)})$ denotes the random *ordered* estimated risk vector, with $P^{(m)}$ denoting the m^{th} order statistic of a random sample of size N.

On the testing side, the test can be used for both individual testing and group testing (i.e., with specimens from multiple subjects combined and tested as a group with a single test). While one test per subject suffices for individual testing, group testing follows the *two-stage Dorfman* testing scheme: in the first stage, the group is tested with a single test; if the group test outcome is negative, then all subjects in the group are classified as negative; and if the group test outcome is positive, then each subject in the group is individually tested and classified according to the outcome of their individual test. In either case, the test is not perfectly reliable, leading to the possibility of *misclassification*. Let $R^m(n)$ denote the random classification outcome for subject m, $m = 1, \cdots, N$, when tested within a group of size n in the first stage, with $R^m(n) = 1$ if subject m is classified as positive, and 0 otherwise. Then, subject m will become a *false negative classification*, i.e., a true-positive subject falsely classified as negative, with probability $Pr\big(D^m(1 - R^m(n)) = 1\big)$, and a *false positive classification*, i.e., a true-negative subject falsely classified as positive, with probability $Pr\big((1 - D^m)R^m(n) = 1\big)$. Let Se and Sp respectively denote the test's *sensitivity* (true positive probability, i.e., the probability that the test outcome is positive, given that the group contains at least one true-positive) and *specificity* (true negative probability, i.e., the probability that the test outcome is negative, given that the group contains all true-negatives), and we assume that the test's sensitivity and specificity are not altered by group size. Without loss of generality, we consider that the test's true negative probability is higher than its false negative probability[1], i.e., $Sp \geq (1 - Se) \Rightarrow Se + Sp - 1 \in [0, 1]$.

[1]This follows because any test not satisfying this assumption can be transformed into one that satisfies it by interpreting the test outcome in the opposite way.

The tester needs to determine a *testing scheme*, comprised of a *set of group sizes* to be used (with a group size of one indicating individual testing) and an *assignment policy* (i.e., a set of rules that specify how each of the N subjects, each with a given risk estimate, is to be assigned to one of the mutually exclusive groups in a batch). Our focus is on *static* testing schemes in which group sizes and the assignment policy remain the same for each batch. Such static schemes are highly desirable from an operational perspective: Testing facilities may not be able to modify group sizes for each batch, or doing so may incur high set-up cost/time; hence, static policies can reduce the operational complexity considerably. We also consider the practical restriction that the tester is able to use a maximum of γ "distinct" group sizes, for some given $\gamma \in \mathbb{Z}^+$; this may be due to the capability of the testing machine, or due to the set up needed to configure the testing machine for the different group sizes.

Then, the **risk-based testing problem** is to determine an optimal static testing scheme, i.e., a set of group sizes and an assignment policy, under uncertainty on both the estimated risk vector, $\tilde{\boldsymbol{P}}$, and the perturbation vector, $\boldsymbol{\Xi}$. We represent the decision variables as a collection of mutually exclusive sets, $\boldsymbol{\Omega} = (\Omega_i)_{i=1,\cdots,g}$, for some $g \in \mathbb{Z}^+$, such that $\bigcup_{i=1}^{g} \Omega_i = S$, and $\Omega_i \cap \Omega_j = \emptyset$, for all $i, j = 1, \cdots, g$: $i \neq j$. Letting $n_i \equiv |\Omega_i|$ denote the cardinality (size) of set $\Omega_i, i = 1, \cdots, g$, we refer to the corresponding vector, $\boldsymbol{n} = (n_i)_{i=1,\cdots,g} : \sum_i n_i = N$, as the *group size* vector. Thus, set Ω_i is the index set of subjects assigned to group i, where a subject's index is determined based on the risk-ordered set, S, that is, index m denotes the m^{th} order statistic for a sample of size N. To represent the constraint on the maximum number of distinct group sizes allowable in any testing scheme, let y_j, $j = 1, \cdots, N$, equal 1 if at least one group of size j is utilized, and 0 otherwise, that is, for a given $\boldsymbol{\Omega}$, and $\forall j = 1, \cdots, N$, $y_j = 1$ only if there exists at least one group $i, i = 1, \cdots, g$, such that $n_i = j$. Then, letting

$$||\boldsymbol{\Omega}|| \equiv \sum_{j=1}^{N} y_j, \tag{5.1}$$

we have that $||\boldsymbol{\Omega}|| \leq \gamma$.

In this setting, the risk vector, $\tilde{\boldsymbol{p}}$, for each subject in a batch is estimated, and testing is conducted following the assignment indicated by $\boldsymbol{\Omega}$, via groups of sizes $\boldsymbol{n} = (n_i)_{i=1,\cdots,g}$: $\sum_i n_i = N$. The objective is to minimize a function of misclassification and testing costs. To express the objective function, we define the following random variables.

For any testing scheme given by $\boldsymbol{\Omega}$, let $FN_i(\Omega_i)$, $FP_i(\Omega_i)$, and $T_i(\Omega_i)$ respectively denote the number of false negative classifications, number of false positive classifications, and number of tests performed for group i, $\forall i$. Then, we have that:

$$FN_i(\Omega_i) = \sum_{m \in \Omega_i} D^m(1 - R^m(n_i)), \quad FP_i(\Omega_i) = \sum_{m \in \Omega_i} (1 - D^m)R^m(n_i), \quad \text{and}$$

$$T_i(\Omega_i) = \begin{cases} 1, & \text{if } n_i = 1 \\ 1 + n_i I(\Omega_i), & \text{if } n_i > 1, \end{cases}$$

where $I(\Omega_i) = 1$, if the test outcome for group i is positive, and 0 otherwise. Then, the total number of false negative classifications, false positive classifications, and tests performed for the set of N subjects under a given testing scheme, $\boldsymbol{\Omega}$, follow:

$$FN(\boldsymbol{\Omega}) = \sum_{i=1}^{g} FN_i(\Omega_i), \quad FP(\boldsymbol{\Omega}) = \sum_{i=1}^{g} FP_i(\Omega_i), \quad \text{and } T(\boldsymbol{\Omega}) = \sum_{i=1}^{g} T_i(\Omega_i).$$

Using these expressions, the total cost for group $i, i = 1, \cdots, g$, and the total cost for the set of N subjects can be respectively written as:

$$Q_i(\Omega_i) \equiv \lambda_1 FN_i(\Omega_i) + \lambda_2 FP_i(\Omega_i) + (1 - \lambda_1 - \lambda_2)T_i(\Omega_i), \text{ and} \tag{5.2}$$

$$Q(\boldsymbol{\Omega}) \equiv \sum_{i=1}^{g} Q_i(\Omega_i) = \sum_{i=1}^{g} \Big[\lambda_1 FN_i(\Omega_i) + \lambda_2 FP_i(\Omega_i)(1 - \lambda_1 - \lambda_2)T_i(\Omega_i)\Big], \tag{5.3}$$

where $\boldsymbol{\lambda} = (\lambda_1, \lambda_2) \in [0,1]^2 : \lambda_1 + \lambda_2 \leq 1$, denotes a normalized weight (cost) vector. In practice, the cost of a false negative classification is typically much higher than the cost of a false positive classification: While false positives are often detected during subsequent confirmatory testing, false negatives may lead to a missed diagnosis, and hence to potentially severe negative outcomes. We discuss the choice of weight parameters in Section 5.5.

To simplify the subsequent notation, we drop the arguments in parentheses when clear from the context. All mathematical proofs can be found in the Appendix.

5.3 Optimization Models and the Objective Function

We first present, in Section 5.3.1, expectation-based and robust formulations of the decision problem. Then, in Section 5.3.2, we provide analytical expressions of the various performance measures that contribute to the objective function.

5.3.1 Optimization Models

We use two different approaches for formulating the decision problem: (i) *an expectation-based optimization model* (**EM**) in which the objective is to minimize the expected value (under uncertainty over both $\tilde{\boldsymbol{P}}$ and $\boldsymbol{\Xi}$) of the objective function, and (ii) *a robust optimization model* (**RM**) in which the objective is to minimize the expected worst-case value of the objective function, that is, for each possible realization of the estimated risk vector, $\tilde{\boldsymbol{P}}$, we determine a realization of the error vector, $\boldsymbol{\Xi}$, that provides the worst-case objective function value, and we minimize the expected worst-case value (under uncertainty over $\tilde{\boldsymbol{P}}$) of the objective function.

Expectation-based Optimization Model (Problem EM):

$$\underset{\boldsymbol{\Omega}=(\Omega_i)_{i=1,\cdots,g},\, g\in\mathbb{Z}^+}{\text{minimize}} \quad \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}_{\boldsymbol{\Xi}}\Big[\mathbb{E}[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}]\Big]\Big]$$

$$\text{subject to} \quad \Omega_i \cap \Omega_j = \emptyset, \quad \forall i,j = 1,\cdots,g\text{: } i \neq j \tag{5.4}$$

$$\bigcup_{i=1}^{g} \Omega_i = \{1,\cdots,N\} \tag{5.5}$$

$$||\boldsymbol{\Omega}|| \leq \gamma, \tag{5.6}$$

where $Q(\boldsymbol{\Omega})$ is as defined in Eq. (5.3), $\gamma \in \mathbb{Z}^+$ represents the maximum number of distinct group sizes allowed, and the operator $||\cdot||$ is as defined in Eq. (5.1).

The following property provides an equivalent expression of the **EM** objective function, and we use it throughout the chapter.

Property 5.1. Problem **EM** can be equivalently formulated as follows:

$$\begin{aligned} \underset{\boldsymbol{\Omega}=(\Omega_i)_{i=1,\cdots,g},\, g\in\mathbb{Z}^+}{\text{minimize}} \quad & \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\mathbf{0},\tilde{\boldsymbol{P}}]\Big] \\ \text{subject to} \quad & (5.4),(5.5),(5.6). \end{aligned} \tag{5.7}$$

Problem **EM** is challenging due to two main reasons: First, the problem, of determining an optimal testing scheme, $\boldsymbol{\Omega}$, that minimizes the objective function reduces to a partitioning problem, which is NP-hard [36]. Hence, for realistic problem sizes in which the number of subjects in each batch, N, is typically in the order of hundreds, the problem quickly becomes computationally expensive. Second, the objective function is non-linear and non-separable, and further, even the evaluation of the objective function for a given solution, $\boldsymbol{\Omega}$, poses some difficulty, as it requires the computation of higher-dimensional integrations (see Sections

5.3.2 and 5.4.1).

We next formulate the robust optimization problem: Under uncertainty on the estimated risk vector, $\tilde{\boldsymbol{P}}$, the tester determines a "robust" static testing scheme that would perform *well* under most perturbations to a realized vector, $\tilde{\boldsymbol{p}}$. For this purpose, we consider a minimax (worst-case) type objective function, commonly adopted in the robust optimization literature, e.g., [17, 57, 103, 110]. Specifically, the objective is to determine a robust static testing scheme that minimizes the worst-case cost, which, for a given realization of the estimated risk vector $\tilde{\boldsymbol{p}}$, and a given testing scheme, is attained by a realization of the error vector, $\boldsymbol{\Xi}$, that maximizes the objective function. Then, the goal is to determine a static testing scheme that minimizes the expectation (under uncertainty over $\tilde{\boldsymbol{P}}$) of the worst-case cost. The formulation of the robust optimization problem follows:

Robust Optimization Model (RM):

$$\begin{aligned} \underset{\boldsymbol{\Omega}=(\Omega_i)_{i=1,\cdots,g},\, g\in\mathbb{Z}^+}{\text{minimize}} \quad & \mathbb{E}_{\tilde{\boldsymbol{P}}}\big[Q^*(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}\big] \\ \text{subject to} \quad & (5.4), (5.5), (5.6), \end{aligned} \tag{5.8}$$

where $Q^*(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}$ is the optimal solution to the following stage 2 problem:

$$\begin{aligned} Q^*(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}} \equiv \underset{\boldsymbol{\xi}}{\text{maximize}} \quad & \mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{\xi}, \tilde{\boldsymbol{P}}\big] \\ \text{subject to} \quad & -\delta \le \xi^m \le \delta, \quad \forall m = 1, \cdots, N. \end{aligned} \tag{5.9}$$

We denote the optimal solution to the stage 2 problem by $\xi^{m*}(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}$, for $m = 1, \cdots, N$.

Remark 5.1. When $\delta = 0$, i.e., when $\boldsymbol{P} = \tilde{\boldsymbol{P}}$, Problem **RM** reduces to Problem **EM**.

Problem **RM** suffers from all the difficulties stated for Problem **EM**; in addition, Problem **RM** faces yet another challenge: Since $\tilde{\boldsymbol{P}}$ is a continuous random vector with an uncountable sample space, to evaluate the expectation in the objective function of (5.8), one needs to solve an infinite number of optimization problems in stage 2 (i.e., (5.9)), to obtain $Q^*(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}$, one for each possible realization of $\tilde{\boldsymbol{P}}$. In the subsequent sections, we characterize key properties of Problem **RM** that will enable us to solve it to optimality.

While a worst-case objective function, similar to the one used in Problem **RM**, is a conservative measure, e.g., [17, 49, 103], one might reduce the value of δ in order to reduce the conservativeness of the solution. Further, we show, in the numerical study of Section 5.5, that the *price of robustness*, i.e., the relative increase in the objective function value under the optimal robust solution (solution to **RM**) compared to the optimal expectation-based solution (solution to **EM**), is low in our setting.

5.3.2 The Objective Function

The objective function is a function of the expected number of false negatives, false positives, and tests. In the following, we provide analytical expressions on each of these performance measures, extending those in [5] to the case where the true risk vector is stochastic and not perfectly observable. We refer the interested reader to [5] for derivation details.

False Negative Classifications: In individual testing, a true-positive subject is falsely classified as negative if the test outcome is negative, whereas in group testing, a true-positive subject is falsely classified as negative if: (i) the group test outcome is negative, or (ii) the group test outcome is positive and the subject's subsequent individual test outcome is negative. Then, conditioned on the estimated risk vector, $\tilde{\boldsymbol{P}}$, and the perturbation vector,

$\boldsymbol{\Xi}$, we can write, for a given $\boldsymbol{\Omega}$:

$$\mathbb{E}\big[FN_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \begin{cases} (1-Se)\sum_{m\in\Omega_i} t\big(\tilde{P}^{(m)},\Xi^m\big), & \text{if } n_i = 1, \\ (1-Se^2)\sum_{m\in\Omega_i} t\big(\tilde{P}^{(m)},\Xi^m\big), & \text{otherwise,} \end{cases} \tag{5.10}$$

$$\text{and } \mathbb{E}\big[FN(\boldsymbol{\Omega})|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \sum_{i=1}^{g}\mathbb{E}\big[FN_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big].$$

False Positive Classifications: In individual testing, a true-negative subject is falsely classified as positive if the test outcome is positive, whereas in group testing, a true-negative subject is falsely classified as positive if the group test outcome is positive and the subject's subsequent individual test outcome is positive. Then, conditioned on the estimated risk vector, $\tilde{\boldsymbol{P}}$, and the perturbation vector, $\boldsymbol{\Xi}$, we can write, for a given $\boldsymbol{\Omega}$:

$$\mathbb{E}\big[FP_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \begin{cases} (1-Sp)\sum_{m\in\Omega_i}\big(1-t\big(\tilde{P}^{(m)},\Xi^m\big)\big), & \text{if } n_i = 1, \\ (1-Sp)Se\sum_{m\in\Omega_i}\big(1-t\big(\tilde{P}^{(m)},\Xi^m\big)\big) & \\ -n_i(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_i}\big(1-t\big(\tilde{P}^{(m)},\Xi^m\big)\big), & \text{otherwise,} \end{cases} \tag{5.11}$$

$$\text{and } \mathbb{E}\big[FP(\boldsymbol{\Omega})|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \sum_{i=1}^{g}\mathbb{E}\big[FP_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big].$$

Number of Tests: In individual testing, the number of tests per subject is always one, whereas in group testing, the number of tests depends on the outcome of the group test: if the group test outcome is negative, then only one test is performed for the entire group,

and if the group test outcome is positive, then an additional individual test is performed for each subject in the group. Then, conditioned on the estimated risk vector, $\tilde{\boldsymbol{P}}$, and the perturbation vector, $\boldsymbol{\Xi}$, we can write, for a given $\boldsymbol{\Omega}$:

$$\mathbb{E}\big[T_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \begin{cases} 1, & \text{if } n_i = 1, \\ 1 + n_i \left(Se - (Se + Sp - 1) \prod_{m \in \Omega_i} \big(1 - t\big(\tilde{P}^{(m)}, \Xi^m\big)\big) \right), & \text{otherwise.} \end{cases} \tag{5.12}$$

$$\text{and } \mathbb{E}\big[T(\boldsymbol{\Omega})|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big] = \sum_{i=1}^{g} \mathbb{E}\big[T_i(\Omega_i)|\boldsymbol{\Xi},\tilde{\boldsymbol{P}}\big].$$

Then, for a given weight vector, $\boldsymbol{\lambda}$, and a testing scheme, $\boldsymbol{\Omega}$, one needs to use the law of total probability to compute the objective functions for each of **EM** and **RM** (see Eq.s (5.2) and (5.3) and the formulations in (5.7)–(5.9)). This, however, requires computations of higher-dimensional integrations (up to N-fold), as we discuss in detail in Section 5.4.1. Moreover, the multiplicative nature of the expressions in Eq.s (5.11) and (5.12) substantially complicates the analysis, as the contribution of a subject to the objective function depends on the set of subjects it is grouped with.

Notice that special cases of the objective function in Eq. (5.3) correspond to the minimization of the expected number of false negative classifications only ($\boldsymbol{\lambda} = (1, 0)$), expected number of false positive classifications only ($\boldsymbol{\lambda} = (0, 1)$), and expected number of tests only ($\boldsymbol{\lambda} = (0, 0)$); the last case is the case most extensively studied in the literature (e.g., [46, 75, 96, 109]), as discussed in Section 5.1. Thus, **EM** and **RM** formulations provide a contribution to the literature by incorporating the classification accuracy into the optimization framework, and by considering a robust formulation.

5.4 Structural Properties and Algorithms

Recall that in its current form, Problem **RM** is intractable, as it requires solutions to an infinite number of optimization problems in stage 2 (see (5.9)), one for each possible realization of the risk vector, $\tilde{\boldsymbol{P}}$, which is continuous. Thus, in what follows, we first provide an equivalent formulation for **RM**. Interestingly, this result also implies that Problems **EM** and **RM** both reduce to an optimization problem with a common structure. Then, in the remainder of this section, we exploit this common structure to develop structural properties and effective solution algorithms for both **EM** and **RM**.

5.4.1 Equivalent Formulations for EM and RM

The following result is essential, as it reduces Problem **RM** from an intractable problem to a problem that is only as difficult as **EM**.

Theorem 5.1.

1. *For all* $\boldsymbol{\Omega}$ *and* $\tilde{\boldsymbol{P}}$*, there exists an optimal solution to* (5.9) *such that* $\xi^{m*}(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}$ *equals either* $-\delta$ *or* δ*, for all* $m = 1, \cdots, N$*.*

2. *If* $\lambda_1(1 - Se) \geq \lambda_2(1 - Sp)$*, then for all* $\boldsymbol{\Omega}$ *and* $\tilde{\boldsymbol{P}}$*, there exists an optimal solution to* (5.9) *such that* $\xi^{m*}(\boldsymbol{\Omega})|\tilde{\boldsymbol{P}}$ *equals* δ*, for all* $m = 1, \cdots, N$*.*

The condition imposed in the second part of Theorem 5.1 is realistic, as the weight (cost) of a false negative in the objective function, i.e., λ_1, is typically much larger than the weight (cost) of a false positive, i.e., λ_2, as discussed in Section 5.2. As such, in the remainder of the chapter, we assume that the condition, $\lambda_1(1 - Se) \geq \lambda_2(1 - Sp)$, is satisfied.

Corollary 5.1. If $\lambda_1(1-Se) \geq \lambda_2(1-Sp)$, then Problem **RM** reduces to the following optimization problem:

$$\begin{aligned} \underset{\boldsymbol{\Omega}=(\Omega_i)_{i=1,\cdots,g},\, g\in\mathbb{Z}^+}{\text{minimize}} \quad & \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{\delta},\tilde{\boldsymbol{P}}\big]\Big] \\ \text{subject to} \quad & (5.4),(5.5),(5.6). \end{aligned} \tag{5.13}$$

Theorem 5.1 is significant, as it eliminates the need to solve an infinite number of optimization problems in (5.9) to determine an optimal solution to **RM**, and reduces the two-stage robust formulation in (5.8)-(5.9) to a single-stage optimization problem. Moreover, notice that the equivalent formulations for Problems **EM** and **RM**, provided respectively in (5.7) and (5.13) (Property 5.1 and Corollary 5.1), have a common structure, in that the random perturbation vector, $\boldsymbol{\Xi}$, is reduced to a constant vector in both cases: in **EM**, $\boldsymbol{\Xi}=\mathbf{0}$, and in **RM**, $\boldsymbol{\Xi}=\boldsymbol{\delta}$. Hence, both **EM** and **RM** reduce to the following form of an optimization problem:

Common-form Optimization Model (CM)

$$\begin{aligned} \underset{\boldsymbol{\Omega}=(\Omega_i)_{i=1,\cdots,g},\, g\in\mathbb{Z}^+}{\text{minimize}} \quad & \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]\Big] \\ \text{subject to} \quad & \Omega_i\cap\Omega_j=\emptyset, \quad \forall i,j=1,\cdots,g\text{: } i\neq j \\ & \bigcup_{i=1}^{g}\Omega_i=\{1,\cdots,N\} \\ & ||\boldsymbol{\Omega}||\leq\gamma, \end{aligned} \tag{5.14}$$

where $\boldsymbol{z}$ is a constant vector, which equals $\mathbf{0}$ for **EM** and $\boldsymbol{\delta}$ for **RM**, and the objective function is given by:

$$\mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]\Big]=\int_a^b\int_{\tilde{p}_1}^b\cdots\int_{\tilde{p}^{N-2}}^b\int_{\tilde{p}^{N-1}}^b\mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}=\tilde{\boldsymbol{p}}\big]f_{\tilde{P}^{(1)},\cdots,\tilde{P}^{(N)}}(\tilde{p}^1,\cdots,\tilde{p}^N)d\tilde{p}^N\cdots d\tilde{p}^1,$$

where

$$\mathbb{E}\big[Q(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]=\lambda_1\mathbb{E}\big[FN(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]+\lambda_2\mathbb{E}\big[FP(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]+(1-\lambda_1-\lambda_2)\mathbb{E}\big[T(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big],$$

and $\mathbb{E}\big[FN(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]$, $\mathbb{E}\big[FP(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]$, and $\mathbb{E}\big[T(\boldsymbol{\Omega})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]$ are given by Eq.s (5.10), (5.11), and (5.12), respectively, and $f_{\tilde{P}^{(1)},\cdots,\tilde{P}^{(N)}}(.)$ denotes the joint probability density function of the ordered random variables $\tilde{P}^{(1)},\tilde{P}^{(2)},\cdots,\tilde{P}^{(N)}$.

As stated earlier, Problem **CM** is challenging due to two main reasons: First, it is at least as hard as the partitioning problem, which is NP-hard [36]; and second, the evaluation of the objective function for a given solution, $\boldsymbol{\Omega}$, requires the computation of up to N-fold integrations, which are computationally expensive. Therefore, in this section, we explore important structural properties of **CM**. Towards this end, consider the following definition.

Definition 5.1. A testing scheme, $\boldsymbol{\Omega}=\big(\Omega_i\big)_{i=1,\cdots,g}$, for some $g=1,\cdots,N$, is said to be an *ordered testing scheme* if it follows the ordered set $S=\{1,2,\cdots,N\}$, that is, $\Omega_1=\{1,\cdots,n_1\}$, $\Omega_2=\{n_1+1,\cdots,n_1+n_2\},\cdots,\Omega_g=\{\sum_{i=1}^{g-1}n_i+1,\cdots,N\}$, where $n_i\in\mathbb{Z}^+, i=1,\cdots,g$, and $\sum_{i=1}^{g}n_i=N$.

By this definition, an ordered testing scheme $\boldsymbol{\Omega}=\big(\Omega_i\big)_i$ can be equivalently expressed in terms of the group size vector, $\boldsymbol{n}=(n_i)_i$, as groups are constructed (i.e., subjects in each batch are assigned to groups) following the risk-ordered set, S.

Our main results for **CM** are given in Theorems 5.2, 5.3, and 5.4.

Theorem 5.2. *For all $N\in\mathbb{Z}^+$ and $\gamma\in\mathbb{Z}^+$, there exists an optimal solution to* **CM** *in which the testing scheme is an ordered testing scheme.*

By Theorem 5.2, to determine an optimal risk-based testing solution, it is sufficient to consider the ordered testing schemes. This result is important in two ways: First, it allows us to reformulate Problem **CM** as a Constrained-Shortest Path (**C-SP**) Problem: While

C-SP is NP-hard [58], the equivalent **C-SP**-type formulation enables us to characterize important structural properties of the risk-based testing problem, allowing us to efficiently solve the problem for realistic problem sizes. Second, recall that the objective function in **CM** includes the expected number of false positive classifications and the number of tests, and the expressions for each term contains products of some function of a set of order statistics (see Eq.s (5.11) and (5.12)). However, Theorem 5.2 indicates that these expressions need to be evaluated for products of functions of *consecutive* order statistics, and not any set of order statistics. This result turns out to be very useful, as we are able to exploit this property in Theorem 5.3 to reduce the higher dimensional (upto N-fold) integrations required to compute those expectations into 3-fold integrations, substantially improving the efficiency with which the **CM** objective function can be evaluated.

As a side note, Theorem 5.2 highlights an additional benefit of optimal static risk-based testing schemes for practitioners: the tester does not need to evaluate the exact risk of each subject, rather it is sufficient to determine a risk-ordering of the subjects. This greatly facilitates the implementation of static risk-based testing schemes.

Theorem 5.3. *Consider N iid continuous random variables, each with a continuous probability density function $f_X(\cdot)$, cumulative distribution function $F_X(\cdot)$, and support $[a,b]$:$0 \leq a < b \leq 1$. Let $X^{(1)} \leq X^{(2)} \leq \cdots \leq X^{(N)}$ denote the order statistics, and let $f_{X^{(i)},\cdots,X^{(j)}}(\cdot)$ and $f_{X^{(i)},X^{(j)}}(\cdot)$ respectively represent the joint probability density functions of the ordered random variables, $X^{(i)} \leq \cdots \leq X^{(j)}$, and of $X^{(i)} \leq X^{(j)}$, $i < j$. Let $g(\cdot)$ denote any continuous function. Then, for all $N \geq 4$ and $i, j = 1 \cdots, N$:$i < j$, we have:*

$$\begin{aligned}\mathbb{E}\left[\prod_{m=i}^{j} g\big(X^{(m)}\big)\right] &= \int_a^b \int_a^{x^j} \cdots \int_a^{x^{i+1}} g(x^i)g(x^{i+1})\cdots g(x^j) f_{X^{(i)},\cdots,X^{(j)}}(x^i,\cdots,x^j)dx^i\cdots dx^j \\ &= \int_a^b \int_a^{x^j} g(x^i)g(x^j)\left[\int_{x^i}^{x^j} \frac{g(x)f_X(x)dx}{F_X(x^j)-F_X(x^i)}\right]^{j-i-1} f_{X^{(i)},X^{(j)}}(x^i,x^j)dx^i dx^j.\end{aligned}$$

Theorem 5.3 follows because, by conditioning on the values of the lowest and highest order statistics, and by exploiting the structure of the integral, we are able to recursively reduce its dimensionality. In the following, we provide an equivalent, **C-SP**-type formulation for **CM**.

Remark 5.2. For a given $\boldsymbol{y} = (y_j)_{j=1,\cdots,N}$, the problem of finding a feasible decomposition, $\boldsymbol{\Omega} = (\Omega_i)_{i=1,\cdots,g}$, that corresponds to vector $\boldsymbol{y}$, i.e., $\forall j = 1, \cdots, N$, $y_j = 1$ only if there exists at least one $i, i = 1, \cdots, g$, such that $n_i = j$, reduces to a Shortest Path (**SP**) Problem defined on an acyclic directed graph $G = (V, E)$, with vertex set $V = \{1, \cdots, N+1\}$, edge set $E = \{(i, j) \in V : y_{j-i} = 1\}$, and edge costs given by:

$$\begin{cases} \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q_i(S_{i-j})|\boldsymbol{\Xi} = \mathbf{0}, \tilde{\boldsymbol{P}}\big]\Big], & \text{for Problem } \mathbf{EM} \\ \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q_i(S_{i-j})|\boldsymbol{\Xi} = \boldsymbol{\delta}, \tilde{\boldsymbol{P}}\big]\Big], & \text{for Problem } \mathbf{RM} \end{cases}$$

Theorem 5.2 and Remark 5.2 lead to the following result.

Theorem 5.4. *Problem* **CM** *can be equivalently formulated as a* **C-SP** *Problem as follows:*

$$
\begin{aligned}
\underset{\substack{\boldsymbol{y}=(y_j)_{j=1,\cdots,N},\\ \boldsymbol{x}=(x_{ij})_{(i,j)\in E}}}{\text{minimize}} \quad & \sum_{(i,j)\in E} \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q_i(S_{i-j})|\boldsymbol{\Xi}=\boldsymbol{z},\tilde{\boldsymbol{P}}\big]\Big]x_{ij} \\
\textit{subject to} \quad & \sum_{j\in V:j>i} x_{ij} - \sum_{j\in V:j<i} x_{ji} = \begin{cases} 1, & \textit{if } i=1 \\ -1, & \textit{if } i=N+1 \\ 0, & \textit{otherwise} \end{cases}, \qquad \forall i\in V \\
& \sum_{j\in V:j>i} x_{ij} \le 1, \qquad \forall i\in V \qquad (5.15) \\
& x_{kl} \le y_{l-k}, \quad \forall (k,l)\in E \qquad (5.15.1) \\
& \sum_{j=1}^{N} y_j \le \gamma \qquad (5.15.2) \\
& y_j \le \sum_{(k,l)\in E:\ l-k=j} x_{kl}, \quad \forall j=1,\cdots,N \qquad (5.15.3) \\
& y_j \in \{0,1\}, \quad \forall j=1,\cdots,N \qquad (5.15.4) \\
& x_{ij}\in\{0,1\}, \quad \forall (i,j)\in E,
\end{aligned}
$$

where $Q_i(\cdot)$ function is as defined in Eq. (5.2)*; $S_{i-j}=\{i,\cdots,j-1\}$, for all $(i,j)\in E$; y_j, $j=1,\cdots,N$, is 1 if a group of size j is utilized, and 0 otherwise; x_{ij}, $(i,j)\in E$, is 1 if edge (i,j) is selected, i.e., the group, comprised of subjects $\{i,\cdots,j-1\}$, is utilized, and 0 otherwise; and $\boldsymbol{z}$ is a constant vector, which equals $\mathbf{0}$ for* **EM** *and $\boldsymbol{\delta}$ for* **RM**.

In the equivalent **CM** formulation provided in Theorem 5.4, each path from vertex 1 to vertex $N+1$ in graph $G=(V,E)$ corresponds to an ordered testing scheme.

Remark 5.3.

1. To construct graph $G=(V,E)$ for the **CM** formulation in Theorem 5.4, one needs to compute $N(N+1)/2$ edge costs, where the cost of each edge $(i,j)\in E$, i.e.,

$\mathbb{E}[Q_i(S_{i-j})]$, requires $(j-i)$-fold integration. Thus, Theorem 5.3 greatly facilitates the construction of this graph by allowing all higher-dimensional integrations, with $j-i \geq 4$, to be computed via 3−dimensional integrations.

2. If Constraints (5.15.1)-(5.15.4), which limit the number of allowable distinct group sizes, are relaxed, then **CM** reduces to an **SP** Problem, which, for an acyclic graph, can be solved in polynomial time via, for example, a topological sorting algorithm in $\mathcal{O}(|V|+|E|) = \mathcal{O}(N^2)$ [37]. While such an algorithm runs in quadratic time, one must still construct the graph by computing all edge costs, and Theorem 5.3 substantially reduces the computational effort required for constructing the graph.

We note here that the total unimodularity property, satisfied for the **SP**, no longer holds with the addition of Constraints (5.15.1)-(5.15.4). Nevertheless, in what follows, we show that the integrality constraint can still be relaxed for a large set of decision variables, while preserving the integrality of the optimal solution.

Lemma 5.1. *The integrality constraint for* $\boldsymbol{x}$ *in* (5.15) *can be relaxed without loss of optimality.*

As a result of Lemma 5.1, integrality constraints are needed only on the $\boldsymbol{y}$ variables, and hence, the number of binary decision variables in **CM** grows only linearly with problem size. Thus, Lemma 5.1 has the potential to drastically improve the computational efficiency.

Next, we provide a structural property for an important special case of Problem **CM**, which minimizes the expected number of misclassifications.

Theorem 5.5. *Consider the special case of* **CM** *with* $\lambda_1, \lambda_2 \in [0,1] : \lambda_1 + \lambda_2 = 1$*, i.e., the objective is to minimize the expected costs of classification errors only. Then, there exists an optimal testing scheme that is comprised of groups of size one, two, or three only, i.e.,*

$n_i^* \leq 3$, equivalently, $y_j^* = 0$, for $j \geq 4$. As such, for $\gamma \geq 3$, Constraints (5.15.1)-(5.15.4) become redundant, and **CM** *reduces to an* **SP** *Problem.*

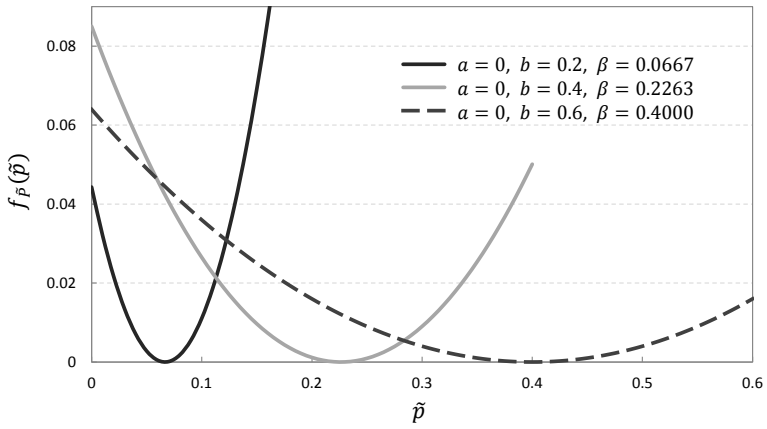
In the next section, we utilize the properties developed in this section to determine optimal testing schemes for our case study, and discuss our findings.

5.5 Case Study: HIV Screening of Blood Donations in Sub-Saharan Africa

In this section, we perform a case study on the screening of donated blood for HIV in sub-Saharan Africa, a region that is home to around 60% of the HIV-infected people worldwide, while containing only 10% of the world's population [44]. Transfusion with HIV-infected blood has been a major contributor to this endemic, with over 95% of transfusions with HIV-infected blood resulting in an infection in the recipient [44]. Consequently, developing a screening strategy with high classification accuracy and low cost is of utmost importance in this setting.

Our objectives in this case study are three-fold: **(1)** To quantify the benefits of risk-based testing (i.e., **EM** and **RM**) over testing schemes that ignore the risk characteristics of the subjects, i.e., that assume that the population is homogeneous with respect to risk ("uniform" testing schemes (**UM**)): such uniform testing schemes, which rely solely on the overall prevalence rate in the population for testing design and randomly assign subjects to testing groups, are common in the existing literature (e.g., [46, 62, 86]). **(2)** To compare the performance of the robust and expectation-based versions of risk-based testing (solutions to **RM** and **EM**), and to quantify the price of robustness for **RM**. **(3)** To compare the performance of the static risk-based schemes, studied in this chapter, to dynamic risk-based

Figure 5.1: Probability density functions of $\tilde{P}$ for different support regions ($[a, b]$) and β values



schemes (**DM**), i.e., testing schemes that are customized (in terms of group sizes and subject assignment) for each testing batch, based on the specific estimated risk vector for that particular batch [5]. Of course, due to the additional flexibility, dynamic testing schemes are expected to outperform static schemes, but this may come at a high operational complexity/cost. Thus, this comparison will shed some light on the degree to which the screening performance is hindered by restriction to static schemes.

The remainder of this section is organized as follows. In Section 5.5.1, we calibrate our models and discuss the data sources. Then, in Sections 5.5.2 and 5.5.3, we discuss the findings from our case study, in terms of the aforementioned objectives.

5.5.1 Model Calibration and Data Sources

We consider a population comprised predominantly of high and low risk subjects. To model this setting, we assume that subject risk estimates, $\tilde{P}$, follow a generalized form of the U-quadratic distribution, with a probability density function given by (see Figure 5.1):

$$f_{\tilde{P}}(\tilde{p}) = \begin{cases} \dfrac{3(\tilde{p}-\beta)^2}{(b-\beta)^3-(a-\beta)^3}, & \text{if } a \leq \tilde{p} \leq b \\ 0, & \text{otherwise} \end{cases} \tag{5.16}$$

with support in $[a, b]$ and parameter β, and with the first moment given by:

$$\mathbb{E}\big[\tilde{P}\big] = \beta + \frac{3}{4}\frac{(b-\beta)^4-(a-\beta)^4}{(b-\beta)^3-(a-\beta)^3}. \tag{5.17}$$

We use β as a calibration parameter to match the first moment to the data. Note that when $\beta = (a+b)/2$, the distribution reduces to the U-quadratic distribution.

The HIV prevalence rate in sub-Saharan Africa varies by country, from 2% to 26% [126]; in this study, we use 15% as a representative prevalence rate for this region. Data on population risk characteristics in sub-Saharan Africa is limited, hence we set the lower bound of the support of the estimated risk variable, a, to zero, while exploring a range of upper bound, b, values in $\{0.2, 0.4, 0.6\}$. For each scenario, we calibrate the parameter β to match the first moment of $\tilde{P}$ (see Eq. (5.17)) to 0.15.

We model the relationship between the true (unobservable) risk, P, and the estimated risk, $\tilde{P}$, through a multiplicative model, i.e., $P|\tilde{P}, \Xi = t(\tilde{P}, \Xi) = \tilde{P}(1+\Xi)$, where $\Xi \sim \text{Uniform}[-\delta, \delta]$, and δ, which represents the degree of uncertainty in the estimated risk with respect to the true risk, is set to 0.667.

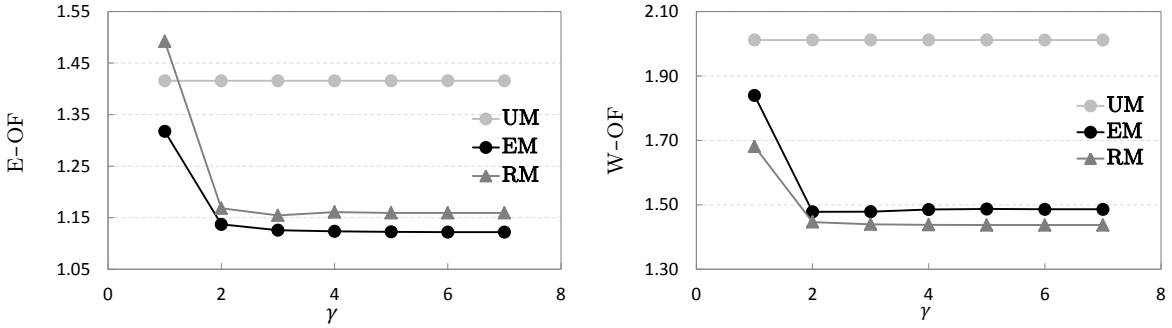
On the testing side, we consider the HIV Nucleic Acid Test (NAT), a commonly used screening test for donated blood that can be conducted on both individual specimens and groups of specimens collected from multiple donors [78], with a sensitivity of $Se = 0.9670$ and a specificity of $Sp = 0.9930$ [22]. For the objective function, which is comprised of the costs of misclassification and testing, we set the unit testing cost to \$15, as reported in [78]. While it is difficult to quantify the costs of false positives and false negatives, the most important

Table 5.1: Performance comparison of **UM**, **EM**, and **RM**

	Problem **UM**					
	$\boldsymbol{n}^*=(3_{(20)})$	E-OF=1.416		W-OF=2.012		
	Problem **EM**			Problem **RM**		
γ	$\boldsymbol{n}^*$	E-OF	W-OF	$\boldsymbol{n}^*$	E-OF	W-OF
	$a=0$, $b=0.6$, $\beta=0.4$					
1	$(5_{(12)})$	1.318	1.840	$(1_{(60)})$	1.492	1.682
2	$(5_{(8)}, 1_{(20)})$	1.137	1.478	$(5_{(6)}, 1_{(30)})$	1.168	1.447
3	$(7_{(2)}, 4_{(7)}, 1_{(18)})$	1.126	1.479	$(8_{(1)}, 4_{(6)}, 1_{(28)})$	1.155	1.440
4	$(9_{(1)}, 5_{(2)}, 4_{(6)}, 1_{(17)})$	1.124	1.486	$(8_{(1)}, 5_{(2)}, 4_{(3)}, 1_{(30)})$	1.161	1.438
5	$(9_{(1)}, 6_{(2)}, 4_{(4)}, 3_{(2)}, 1_{(17)})$	1.123	1.487	$(8_{(1)}, 5_{(1)}, 4_{(3)}, 3_{(2)}, 1_{(29)})$	1.159	1.437
≥ 6	$(9_{(1)}, 6_{(1)}, 5_{(2)}, 4_{(3)}, 3_{(2)}, 1_{(17)})$	1.122	1.486	$(8_{(1)}, 5_{(1)}, 4_{(3)}, 3_{(2)}, 1_{(29)})$	1.159	1.437
	$a=0$, $b=0.4$, $\beta=0.226$					
1	$(5_{(12)})$	1.320	1.824	$(1_{(60)})$	1.492	1.682
2	$(5_{(8)}, 1_{(20)})$	1.104	1.427	$(5_{(7)}, 1_{(25)})$	1.110	1.399
3	$(9_{(2)}, 4_{(5)}, 1_{(22)})$	1.093	1.407	$(7_{(2)}, 4_{(5)}, 1_{(26)})$	1.107	1.389
4	$(11_{(1)}, 6_{(2)}, 4_{(4)}, 1_{(21)})$	1.089	1.412	$(8_{(1)}, 5_{(2)}, 4_{(4)}, 1_{(26)})$	1.106	1.387
5	$(10_{(1)}, 7_{(1)}, 5_{(2)}, 4_{(3)}, 1_{(21)})$	1.088	1.410	$(8_{(1)}, 5_{(2)}, 4_{(3)}, 3_{(1)}, 1_{(27)})$	1.113	1.387
≥ 6	$(10_{(1)}, 7_{(1)}, 5_{(2)}, 4_{(3)}, 1_{(21)})$	1.088	1.410	$(8_{(1)}, 6_{(1)}, 5_{(1)}, 4_{(3)}, 3_{(1)}, 1_{(26)})$	1.105	1.386
	$a=0$, $b=0.2$, $\beta=0.067$					
1	$(3_{(20)})$	1.407	1.990	$(1_{(60)})$	1.492	1.682
2	$(4_{(7)}, 1_{(32)})$	1.364	1.705	$(4_{(2)}, 1_{(52)})$	1.401	1.608
3	$(7_{(1)}, 3_{(8)}, 1_{(29)})$	1.358	1.720	$(5_{(1)}, 4_{(1)}, 1_{(51)})$	1.392	1.605
≥ 4	$(6_{(1)}, 4_{(2)}, 3_{(5)}, 1_{(31)})$	1.357	1.704	$(5_{(1)}, 4_{(1)}, 1_{(51)})$	1.392	1.605

consideration in our model is the relationship between these costs and the testing cost. We assume that if the initial screening test indicates that the subject is positive, then additional individual confirmatory testing will be performed, as is the case in practice in many countries [40]. Hence, we set the cost of a false positive to the testing cost of \$15. On the other hand, in donated blood screening, the consequences of a false negative classification are substantially more severe than a false positive classification, as a false negative may lead to the contamination of the blood supply, hence to a potential HIV infection in the transfusion recipient. While an accurate estimate of this cost is difficult to obtain, we set the cost of a false negative to be 55 times the cost of a false positive, as this is in line with published research,

Figure 5.2: Expected cost (E-OF) (left) and worst-case cost (W-OF) (right) for **UM**, **EM**, and **RM**, as a function of γ when $a = 0$, $b = 0.6$, $\beta = 0.4$



e.g., [137]. Normalizing these cost parameters leads to $\lambda_1 = 0.96$ and $\lambda_2 = 0.02$ (hence, $1 - \lambda_1 - \lambda_2 = 0.02$). While these parameter values represent costs in the US, we assume that, proportionally, they reflect the same trade-offs encountered in sub-Saharan Africa. In what follows, we illustrate the benefits of our model by considering a testing batch size, N, of 60. Our extensive numerical study indicates that our model behaves similarly for different values of N.

For each *scenario*, characterized by the support of the estimated risk distribution, given by b, and the maximum number of distinct group sizes allowed, γ, we determine the optimal solutions for Problems **UM**, **EM**, and **RM**. In uniform schemes, generated by **UM**, the population is assumed to be homogeneous, i.e., the risk of each subject is the same, and equals the mean prevalence rate of the population, which is 0.15. For both **EM** and **RM**, we determine an optimal testing scheme that is an ordered testing scheme (see Theorem 5.2). Thus, for all models, we can represent the testing scheme in terms of its group size vector, $\boldsymbol{n} = (n_i)_i$, as in **EM** and **RM** groups are constructed (i.e., subjects in each batch are assigned to groups) following the risk-ordered set, S; and in **UM** groups are constructed in a random fashion (i.e., subjects, which are assumed identical, are assigned to groups randomly). To simplify the presentation of the group size vector, we use the notation $x_{(y)}$ to represent y groups each of size x. We also let E-OF denote the expected cost of a testing scheme, i.e.,

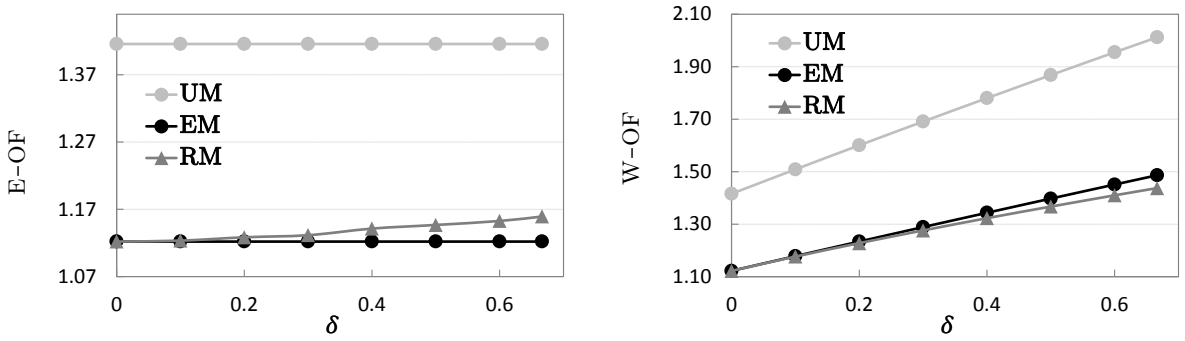
$\mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q|\boldsymbol{\Xi}=\mathbf{0},\tilde{\boldsymbol{P}}\big]\Big]$, and W-OF denote the worst-case expected cost of a testing scheme, i.e., $\mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}\big[Q|\boldsymbol{\Xi}=\boldsymbol{\delta},\tilde{\boldsymbol{P}}\big]\Big]$. Similarly, we let CE-OF denote the expected cost of a testing scheme *conditioned* on a given realization of the estimated risk vector, i.e., $\mathbb{E}\big[Q|\boldsymbol{\Xi}=\mathbf{0},\tilde{\boldsymbol{P}}\big]$, and CW-OF denote the worst-case cost of a testing scheme *conditioned* on a given realization of the estimated risk vector, i.e., $\mathbb{E}\big[Q|\boldsymbol{\Xi}=\boldsymbol{\delta},\tilde{\boldsymbol{P}}\big]$.

5.5.2 Risk-based Schemes versus Non Risk-based Schemes

In this section, we compare the performance of **EM** and **RM** to non risk-based (uniform) testing schemes, i.e., solutions to Problem **UM**, for various scenarios, see Table 5.1. Note that the performance of **UM** is identical in all scenarios, as the **UM** solution is based only on the mean prevalence rate of the population, which remains constant across the scenarios. Also observe that for scenarios with $\gamma = 1$ (i.e., with only one group size allowed), the optimal group sizes in **EM** and **UM** are not necessarily equal (e.g., when $b = 0.6$ and $\gamma = 1$, the single group size in **UM** is equal to 3, while the single group size in **EM** is 5). This difference in group sizes arises due to the ordering of the estimated risk vector in **EM**, that is, the optimal group size under a random assignment policy (in **UM**) differs from the optimal group size under an ordered assignment policy (in **EM**). However, when the heterogeneity of the population reduces (i.e., the support region shrinks, e.g., the scenario with $b = 0.2$), the optimal group sizes in **EM** and **UM** converge. Also observe that when the maximum number of distinct group sizes exceeds six (i.e., $\gamma \geq 6$), no additional benefits are realized in **EM** and **RM** solutions, i.e., the solutions converge to the solution with $\gamma = 6$ (and in some scenarios, this convergence happens quicker, i.e., for $\gamma \geq 4$); see Table 5.1.

The results in Table 5.1 highlight several important properties. First, both **EM** and **RM** substantially reduce both the expectation and the worst-case of the cost over **UM** (with

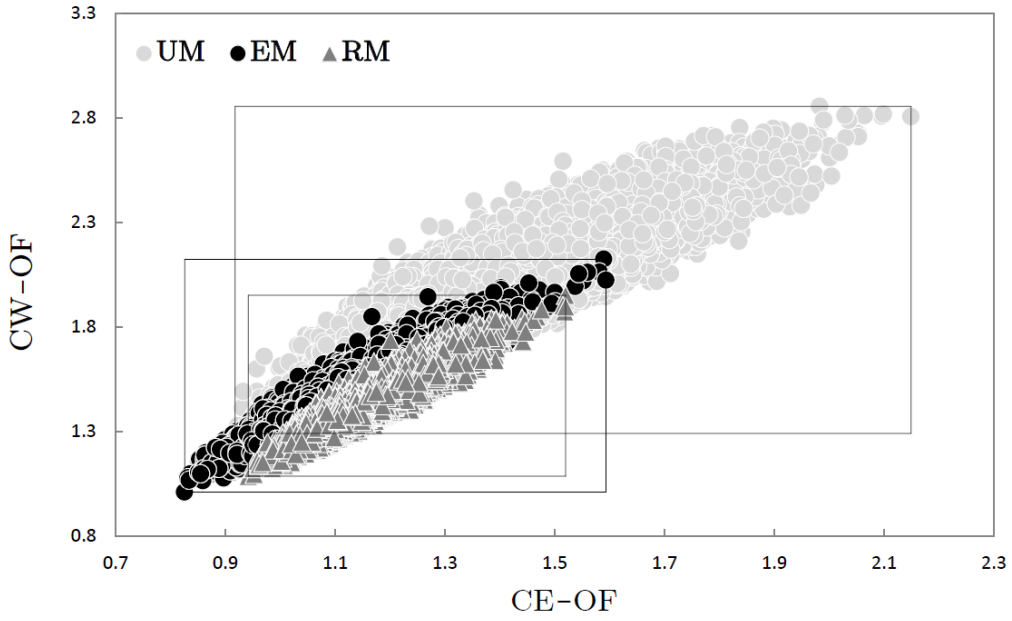
Figure 5.3: Expected cost (E-OF) (left) and worst-case cost (W-OF) (right) for **UM**, **EM**, and **RM**, as a function of δ when $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$



the exception of the expected cost for **RM** when $\gamma = 1$). For example, when $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$, comparing **EM** (**RM**) with **UM**, we observe substantial reductions in both the expected cost and the worst-case cost, respectively by 21% (18%) and 26% (29%) over **UM**. Even for the most restrictive case of $\gamma = 1$, i.e., with only one group size allowed, **EM** still reports reductions in the expected cost, especially for cases when the support region for the estimated risk is large (i.e., large b values). Also, observe that both the optimal expected cost (optimal solution to **EM**) and the worst-case cost (optimal solution to **RM**) reduce as γ increases, but in both cases, the reductions exhibit diminishing returns, with a substantial reduction occurring when γ increases from one to two, and with all subsequent reductions being much smaller in magnitude (see Figure 5.2). This finding has important implications, as schemes with only two group sizes are easier to implement in practice, making them especially appealing to practitioners.

Next, we study how the testing performance varies with the degree of uncertainty in the estimated risk with respect to the true risk, δ. For this purpose, we conduct a sensitivity analysis on δ and obtain **UM**, **EM**, and **RM** optimal solutions for various δ values in $\{0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.667\}$; see Figure 5.3 for the case with $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$, that is, the case where there is effectively no limit on the number of distinct group sizes (see our discussion above). Our results indicate that both **EM** and **RM**

Figure 5.4: Conditional expected cost (CE-OF) as a function of the conditional worst-case cost (CW-OF) for **UM**, **EM**, and **RM**, when $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$

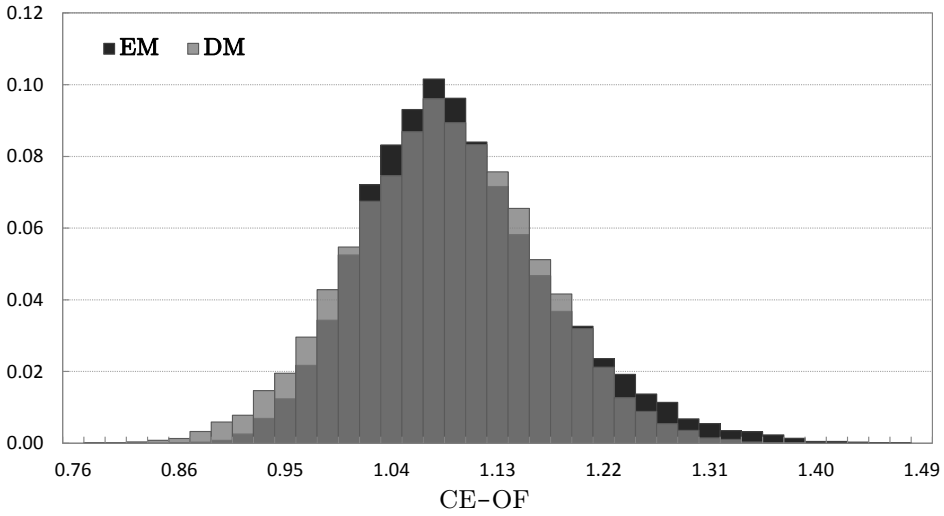


substantially improve both objective functions over **UM** for all values of δ.

Next, we compare the costs incurred in **EM** and **RM** solutions so as to quantify the price of robustness and analyze the trade-off in the expected classification accuracy versus robustness. For this purpose, we analyze the *distributions* of CE-OF versus CW-OF generated by **UM**, **EM**, and **RM** testing schemes. In particular, we use the optimal solutions for **UM**, **EM**, and **RM** within a Monte Carlo simulation with 10,000 replications. In each replication, a random realization of the estimated risk vector is generated following the distribution in Eq. (5.16), the estimated risk vector is perturbed randomly according to the aforementioned multiplicative model (see Section 5.5.1), and the resulting expected and worst-case costs under each testing scheme are computed. Figure 5.4 plots CW-OF versus CE-OF for all replications for the scenario where $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$. (Similar results have been obtained for the other scenarios.)

RM solution has the smallest range for both the objective function value and the worst-

Figure 5.5: Histogram of the expected cost (E-OF) for **EM** and **DM**, when $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$



case value, marked by the range rectangles in Figure 5.4. A smaller range represents a more "robust" solution, one that is less sensitive to perturbations in the estimated risk vector. Specifically, **RM** reduces the range of the expected cost by 53% over **UM** and 25% over **EM**, and also reduces the range of the worst-case cost by 45% over **UM** and 22% over **EM**. Moreover, **RM** solution leads to substantial reductions in the variability of both performance metrics: **RM** reduces the variance of the expected cost by 81% over **UM** and 42% over **EM**, and reduces the variance of the worst-case cost by 76% over **UM** and 38% over **EM**. Further, **RM** reports only a 3% increase in the expected cost over **EM**, leading to a price of robustness of around 3%. Depending on the setting, the added benefits of a robust solution may outweigh this slight increase in the expected cost.

5.5.3 Static Schemes versus Dynamic Schemes

Having quantified the value of risk-based testing, in this section we compare the performance of the static **EM** model to dynamic risk-based schemes **DM** [5], in which the decision-maker

customizes the testing scheme to each batch, that is, in **DM**, the decision-maker first observes the estimated risk vector for the batch, and then optimizes accordingly. The **DM** testing scheme will outperform the **EM** scheme, but we want to quantify the degree to which the testing performance is affected by using a static scheme. Towards this end, we perform a Monte Carlo simulation with 10,000 replications. While the optimal static **EM** solution is computed only once, prior to the simulations (as in the previous section), an optimal **DM** solution is computed for each batch, that is, in each replication, a random realization of the estimated risk vector for a batch is generated following the distribution in Eq. (5.16), the optimal **DM** solution is determined for this specific estimated risk vector, and the resulting expected costs are computed for the optimal **EM** and **DM** solutions. Figure 5.5 depicts the histogram of the expected cost for **EM** and **DM** for the scenario with $a = 0$, $b = 0.6$, $\beta = 0.4$, and for all $\gamma \geq 6$.

Figure 5.5 (and other numerical studies) lead to an interesting finding. In particular, the two histograms almost completely overlap, with only a miniscule difference between the expected costs under **EM** and **DM**; in fact, **EM** and **DM** costs are within only 1% of each other. This implies that a static risk-based testing scheme captures most benefits of dynamic risk-based testing, while greatly simplifying the implementation.

5.6 Conclusions and Suggestions for Future Research

We develop novel models for determining optimal static risk-based Dorfman testing schemes under imperfectly observable subject risk, with the objective of accurately and efficiently classifying a set of subjects as positive or negative for a binary characteristic. Our models take into account important test and population level characteristics, and generate easily implementable risk-based testing schemes. While these problems can be modeled as par-

titioning problems, we derive various key structural properties of their optimal solutions and reduce them into network flow problems; this allows us to obtain optimal risk-based testing schemes for realistic problem sizes. Further, our novel expression on the expected value of the product of a function of a set of consecutive order statistics enables us to substantially improve the efficiency with which the corresponding graph can be constructed. We also explore a novel robust formulation, an important special case of which we are able to solve to optimality. Our case study, on HIV blood donation screening in sub-Saharan Africa, demonstrates the effectiveness of static risk-based testing schemes, which substantially reduce the costs of misclassification and testing over current screening practices, while significantly improving the robustness of the solution.

There are several important extensions of this research effort. We consider a purely static testing scheme, comprised of group sizes and a subject assignment policy that is used repetitively for each testing batch. One might consider various partially dynamic testing schemes in which some components of the testing scheme may be customized for the specific batch. Further research directions may include improving the realism of the model. For example, in certain settings, the sensitivity of the test may reduce as the group size increases. This is known as the *dilution effect*, and it is an interesting future research direction to model the test sensitivity as a function of the group size. One can also expand this work to consider other group testing schemes, such as multi-stage hierarchical schemes or schemes that take advantage of overlapping groups (e.g., array-based grouping schemes [86]). While such schemes may be more complicated to implement, they have the potential to outperform Dorfman testing schemes, and the complexity versus benefit trade-off needs to be studied. Finally, a promising research direction is to utilize group testing for the purpose of risk estimation, where important research questions arise on how the population should be clustered into different risk groups (sub-populations) and what risk value should be assigned to each

of these sub-populations.

We hope that this work, which indicates that the benefits of static risk-based group testing schemes can be substantial, encourages academicians and practitioners to further study static risk-based testing schemes.

Chapter 6

Conclusions and Future Research Directions

Incorporating the heterogeneity of the population into the modeling framework to design *risk-based testing schemes* is of utmost importance for testing facilities, as substantial benefits can be observed by taking into account such additional information. This is evident by our extensive numerical analysis, which demonstrate the value of optimal risk-based testing designs, which are shown to be less expensive, more accurate, more equitable, and more robust than current screening practices.

In Chapter 2, we derive analytical expressions for various performance metrics (the residual risk, expected waste, and expected number of tests) that are essential for assay selection in blood screening, while explicitly considering the joint impact of dilution, imperfect tests, in-sample variability, and re-testing possibility. Our model expands upon the earlier works on pooled testing and provides accurate estimates, which can be used within a cost-based framework for decision-making on blood screening strategies.

In Chapter 3, we propose and study a three-tier adaptive risk-based array pooling scheme that incorporates imperfect tests, the dilution effect of pooling, and the risk profile of subjects. Our analytical results that consider a general form of the sensitivity function offer valuable insights on the structural properties of an optimal assignment solution, while our case study demonstrates the effectiveness and power of an adaptive risk-based pooling scheme, with the expected number of false classifications reduced substantially over the previous models proposed in the literature. Our findings underscore the importance of taking into account population level characteristics, as failing to do so can lead to pooling schemes with a high probability of misclassification. Our model has the potential to make a substantial positive societal impact by reducing misclassification for important infections, such as the chlamydia infection that is considered in the case study.

In Chapter 4, we study the problem of designing an optimal risk-based Dorfman testing scheme to accurately and equitably classify a set of subjects in an efficient manner, while taking into account imperfect tests. Our analytical results enable us to reduce the NP-hard partitioning problems into an SP problem (for **SM**) or a constrained-SP problem (for **BM**). Further, for special cases of **BM**, we develop highly efficient algorithms that exploit the structure of the problem and that are able to solve the constrained-SP problem in polynomial time. Our case study demonstrates the effectiveness of risk-based testing, producing solutions that substantially reduce all performance measures when compared to static, non-risk based models. Our findings highlight the importance of incorporating subject-specific risk characteristics into the modeling framework, as failing to do so can lead to higher classification errors and more costly and less equitable testing schemes.

In Chapter 5, we develop novel models for determining optimal static risk-based Dorfman testing schemes under imperfectly observable subject risk, with the objective of accurately and efficiently classifying a set of subjects as positive or negative for a binary character-

istic. Our models take into account important test and population level characteristics, and generate easily implementable risk-based testing schemes. While these problems can be modeled as partitioning problems, we derive various key structural properties of their optimal solutions and reduce them into network flow problems; this allows us to obtain optimal risk-based testing schemes for realistic problem sizes. Further, our novel expression on the expected value of the product of a function of a set of consecutive order statistics enables us to substantially improve the efficiency with which the corresponding graph can be constructed. We also explore a novel robust formulation, an important special case of which we are able to solve to optimality. Our case study, on HIV blood donation screening in sub-Saharan Africa, demonstrates the effectiveness of static risk-based testing schemes, which substantially reduce the costs of misclassification and testing over current screening practices, while significantly improving the robustness of the solution.

There are several important extensions of this research effort. We consider a purely static testing scheme, comprised of group sizes and a subject assignment policy that is used repetitively for each testing batch. One might consider various partially dynamic testing schemes in which some components of the testing scheme may be customized for the specific batch. Further research directions may include improving the realism of the model. For example, in certain settings, the sensitivity of the test may reduce as the group size increases. This is known as the *dilution effect*, and it is an interesting future research direction to model the test sensitivity as a function of the group size. Our analysis also depends on the assumption that test outcomes performed on the same subject are conditionally independent, given the actual positivity status of the subject. This assumption does not always hold in practice, especially for infection screening tests that measure infection-related bio-markers, because if a subject is infected with the infection in question, then concentrations of various infection-related bio-markers will be higher than infection-free subjects, and tests that measure the

related bio-markers will have a tendency to produce positive test outcomes. Relaxing such assumptions on the test's sensitivity and specificity will increase model realism, and may produce better testing schemes.

Another possible future research direction is to consider other group testing schemes, such as multi-stage hierarchical schemes. While such schemes may be more complicated to implement, they have the potential to outperform Dorfman testing schemes, and the complexity versus benefit trade-off needs to be studied. Finally, a promising research direction is to utilize group testing for the purpose of risk estimation, where important research questions arise on how the population should be clustered into different risk groups (sub-populations) and what risk value should be assigned to each of these sub-populations.

We hope that this work, which indicates that the benefits of risk-based group testing schemes can be substantial, encourages academicians and practitioners to further study risk-based testing schemes.

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Appendix A

Appendix for Chapter 2

A.1 Simulation Results when Modeling Assumptions are Relaxed

We perform several Monte Carlo simulations to study the impact of various modeling assumptions on the performance metrics. For each simulation study, we perform 45,000,000 replications and construct the 95% confidence intervals for each performance metric.

Impact of Assumptions 2.1 and 2.2: Assumption 1 is relaxed by considering the viral load of a non window-period donor to be a constant, which equals the viral load at the end of the window period, i.e., the viral load that achieves a sensitivity of 0.999 for a pool size of n_{max}, see Section 2.2.1. Thus, infected non window-period samples have a non-zero probability of falsely testing negative (i.e., test sensitivity is no longer perfect for non window-period donors). On the other hand, Assumption 2.2 is relaxed by allowing multiple infected samples to be present in a pool.

Relaxing Assumptions 2.1 and 2.2 impacts each performance metrics differently. For example, relaxing Assumption 2.1 increases the residual risk, since infected non window-period samples now have a non-zero probability of being falsely declared as infection-free. On the other hand, relaxing Assumption 2.2 reduces the residual risk, since a larger number of infections within a pool increases the probability of detection (countering the dilution effect). Similarly, while relaxing Assumption 2.1 reduces the probability that the master pool fails, hence leading to a reduction in both the expected number of tests and expected waste, relaxing Assumption 2.2 has the exact opposite effect on these two measures.

Our simulation study indicates that the impact of Assumptions 2.1 and 2.2 is minor: for instance, when only Assumption 2.1 is relaxed, 96% of the analytical results fall within the confidence intervals of the simulation results; and this number becomes 92% when both Assumptions 2.1 and 2.2 are relaxed.

Impact of the distribution of the donation time, D: To study the impact of the distribution of the donation time, D, we perform another simulation study in which we model D as a triangular distribution with the same mean ($\tau/2$) and support in $[0, \tau]$. The triangular distribution is often used under limited information [121]. The simulation results indicate that the distribution of D has a major impact on the performance metrics, especially on the residual risk. However, under no additional information on donation times, the uniform distribution is a good choice.

Impact of the distribution of the viral load, L: Lastly, we perform a simulation study in which the viral load (conditional upon D) follows a Poisson distribution (similar to [139]). Our results reveal only slight differences in all three performance metrics, suggesting that, under our data set, the choice of the distribution of L does not have a significant impact. Similarly, when Λ is replaced by μ (i.e., when L grows deterministically) we also observe minor differences in all performance metrics.

A.2 Derivations of the Performance Metrics

A.2.1 Residual Risk

No re-testing (NR): Substituting

$$P\big(F^{-NR}(n_1,n_2,m)|A^+(n_1),D\leq t_w,L\big)=P\big(T^-(n_1)|A^+(n_1),D\leq t_w,L\big),$$

R^{NR} directly follows from Eq. (2.12).

Pooled re-testing and individual re-testing (PR and IR): Substituting

$$P\big(F^-(n_1,n_2,m)|A^+(n_1),D\leq t_w,L\big)=1-P\big(T^+(n_1)|A^+(n_1),D\leq t_w,L\big)\times\bigg(1-\Big(P(T^-(n_2)|A^+(n_1),D\leq t_w,L)\Big)^m\bigg),$$

where n_2 respectively equals n_1 for PR and 1 for IR, R^{PR} and R^{IR} directly follow from Eq. (2.12).

Array-based testing (AR): We have:

$$P\Big(F^{-AR}(n_1,n_2,m)|A^+(n_1),D\leq t_w,L\Big)=1-P\Big(T^+(n_1)|A^+(n_1),D\leq t_w,L\Big)P\Big(T^+(n_2,m)\Big|A^+(n_1),D\leq t_w,L\Big),\tag{A.1}$$

where $P\big(T^+(n_2,m)\big|A^+(n_1),D\leq t_w,L\big)=\bigg(1-\Big(P\big(T^-(\sqrt{n_1})|A^+(n_1),D\leq t_w,L\big)\Big)^m\bigg)^2$, since the re-test fails only if both the row pool and the column pool containing the infected window-period sample fail at least once during the m re-tests. Then, substituting Eq. (A.1) in Eq. (2.12) leads to the expression for R^{AR}.

A.2.2 Expected Waste

No re-testing (NR): We have that:

$$P\big(A^-(n_1), F^{+NR}(n_1,n_2,m)\big) = P\big(T^+(n_1)|A^-(n_1)\big)P\big(A^-(n_1)\big) = (1-Sp)P\big(A^-(n_1)\big),$$
$$P\big(A^+(n_1), F^{+NR}(n_1,n_2,m)\big) = P\big(A^+(n_1), T^+(n_1)\big) = P\big(T^+(n_1)|A^+(n_1)\big)P\big(A^+(n_1)\big).$$

Noting that

$$P\big(T^+(n_1)|A^+(n_1)\big) = P\big(T^+(n_1)|A^+(n_1), D \le t_w\big)P\big(D \le t_w|A^+(n_1)\big) + P\big(D > t_w|A^+(n_1)\big),$$

and substituting the expressions in Eq.s (2.5) and (2.6) into Eq. (2.13) provides the result.

Pooled re-testing (PR): We have that:

$$\begin{aligned}
P\big(A^-(n_1), F^{+PR}(n_1,n_2,m)\big) &= P\big(A^-(n_1), T^+(n_1), T^+(n_2,m)\big),\\
&= P\big(A^-(n_1)\big)\ P\big(T^+(n_1)|A^-(n_1)\big)\ P\big(T^+(n_2,m)|T^+(n_1), A^-(n_1)\big),\\
&= P\big(A^-(n_1)\big)(1-Sp)(1-Sp^m), \qquad \text{(A.2)}\\
P\big(A^+(n_1), F^{+PR}(n_1,n_2,m)\big) &= P(A^+(n_1))P(D \le t_w|A^+(n_1))P\big(T^+(n_1), T^+(n_2,m)|A^+(n_1), D \le t_w\big)\\
&\quad + P\big(T^+(n_1), T^+(n_2,m)|A^+(n_1), D > t_w\big)P\big(A^+(n_1)\big)P\big(D > t_w|A^+(n_1)\big),\\
&= P\big(A^+(n_1)\big)P\big(D \le t_w|A^+(n_1)\big)\int_0^\infty P\big(T^+(n_1)|A^+(n_1), D \le t_w, L = l\big)\\
&\quad \times \Big(1 - \Big(P(T^-(n_1)|A^+(n_1), D \le t_w, L = l)\Big)^m\Big) f_L(l)dl\\
&\quad + P\big(A^+(n_1)\big)P\big(D > t_w|A^+(n_1)\big). \qquad \text{(A.3)}
\end{aligned}$$

Substituting Eq.s (A.2)-(A.3) into Eq. (2.13) provides the result.

Individual re-testing (IR): Substituting $P\big(T^+(n_1)|A^+(n_1)\big)$, derived in Section 2.2.2, into

Eq. (2.14) provides the result.

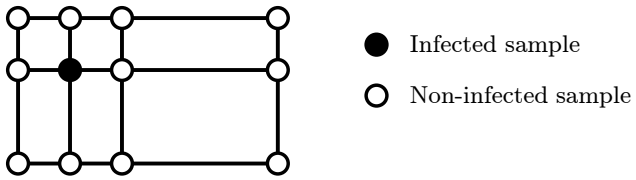
Array-based re-testing (AR): We have:

$$\begin{aligned}\mathbb{E}[W^{AR}] =&\mathbb{E}\big[W^{AR}|A^+(n_1), D > t_w\big]P\big(A^+(n_1), D > t_w\big)\\ &+ \mathbb{E}\big[W^{AR}|A^+(n_1), D \leq t_w\big]P\big(A^+(n_1), D \leq t_w\big)\\ &+ \mathbb{E}[W^{AR}|A^-(n_1)]P\big(A^-(n_1)\big). \end{aligned} \tag{A.4}$$

For the analysis of the first two cases $\big($i.e., $(A^+(n_1), D > t_w)$ and $(A^+(n_1), D \leq t_w)\big)$, assume, without loss of generality, that the infected sample is placed at the intersection of row i and column j in the matrix for some i,$j \in \{1, 2, \cdots, \sqrt{n_1}\}$. We refer to a sample as an *intersection sample* if both its corresponding row pool and column pool have failed in the second stage. Per our decision rule, all intersection samples are discarded. In what follows, we present only the first case in detail, as the derivation of the other cases follow similarly.

Case 1: Event $(A^+(n_1), D > t_w)$*:* If event $(A^+(n_1), D > t_w)$ occurs, that is, the master pool contains one infected sample that is outside of the window period, then by Assumption (A1) the master pool will fail with probability one, that is, $P(T^+(n_1)|A^+(n_1), D > t_w) = 1$. Similarly, in the second stage, both row i and column j will fail with probability one $\big($by Assumption (A1)$\big)$. Let N_{2c}^{AR} and N_{2r}^{AR} respectively denote the additional number of column pools and number of row pools that fail in the second stage (i.e., that produce a positive test outcome at least once in the m re-tests). Then, N_{2c}^{AR} and N_{2r}^{AR} each follow an independent and identical binomial distribution with $\Big(\sqrt{n_1}-1, \big(1-Sp^m\big)\Big)$. Hence, the number of intersection samples equals $(1+N_{2c}^{AR})(1+N_{2r}^{AR})$, of which the infected sample will be correctly discarded and the remaining intersection samples will be wasted (falsely discarded); Figure A.1 depicts an example with $N_{2c}^{AR} = 3$ and $N_{2r}^{AR} = 2$ leading to a waste of $4 \times 3 - 1 = 11$ blood units. Then:

Figure A.1: An example illustrating the number of column pools and row pools that have failed and the corresponding waste in array-based testing



$$\mathbb{E}[W^{AR}|A^+(n_1), D > t_w] = \left[1 + \left(1 - Sp^m\right)(\sqrt{n_1} - 1)\right]^2 - 1. \tag{A.5}$$

Case 2: Event $(A^+(n_1), D \leq t_w)$*:* If event $(A^+(n_1), D \leq t_w)$ occurs, that is, the master pool contains one infected sample within the window period, we condition on the outcome of the master pool:

$$\mathbb{E}[W^{AR}|A^+(n_1), D \leq t_w] = \mathbb{E}[W^{AR}|A^+(n_1), D \leq t_w, T^+(n_1)]P(T^+(n_1)|A^+(n_1), D \leq t_w) + 0. \tag{A.6}$$

Recalling that the infected sample lies at location (i, j) in the matrix, we let random variable N_{ij} denote the total number of failures for row i and column j (i.e., 2 if both row i and column j fail, 1 if only one fails, and 0 if none fail), that is, N_{ij} is binomial with $\Big(2, \Big(1 - \Big(P(T^-(\sqrt{n_1})|A^+(n_1), D \leq t_w\Big)^m\Big)\Big)$. Then:

$$\begin{aligned}\mathbb{E}\big[W^{AR}|A^+(n_1), D \leq t_w, T^+(n_1)\big] = \sum_{x=0}^{2} &\mathbb{E}\big[W^{AR}|A^+(n_1), D \leq t_w, T^+(n_1), N_{ij} = x\big] \\ &\times P(N_{ij} = x|A^+(n_1), D \leq t_w),\end{aligned}$$

which utilizes the following expressions, whose derivations follow similarly to those of Case

1:

$$\mathbb{E}\big[W^{AR}|A^+(n_1), D \le t_w, T^+(n_1), N_{ij} = 2\big] = [1 + \big(1 - Sp^m\big)(\sqrt{n_1} - 1)]^2 - 1,$$
$$\mathbb{E}\big[W^{AR}|A^+(n_1), D \le t_w, T^+(n_1), N_{ij} = 1\big] = [\big(1 - Sp^m\big)(\sqrt{n_1} - 1)][\big(1 + \big(1 - Sp^m\big)(\sqrt{n_1} - 1)\big)],$$
$$\mathbb{E}\big[W^{AR}|A^+(n_1), D \le t_w, T^+(n_1), N_{ij} = 0\big] = \big(1 - Sp^m\big)^2(\sqrt{n_1} - 1)^2.$$

Case 3: Event $A^-(n_1)$: In case of event $A^-(n_1)$, that is, the master pool does not contain any infected sample, we can write:

$$\begin{aligned}\mathbb{E}[W^{AR}|A^-(n_1)] =& \mathbb{E}[W^{AR}|A^-(n_1), T^+(n_1), T^+(n_2, m)]P(T^+(n_1)|A^-(n_1))P(T^+(n_2, m)|T^+(n_1), A^-(n_1)) \\ &+ \mathbb{E}[W^{AR}|A^-(n_1), T^+(n_1), T^-(n_2, m)]P(T^+(n_1)|A^-(n_1))P(T^-(n_2, m)|T^+(n_1), A^-(n_1)) \\ &+ \mathbb{E}[W^{AR}|A^-(n_1), T^-(n_1)]P(T^-(n_1)|A^-(n_1)) \\ =& n_1\ (1 - Sp)\ \big(1 - Sp^m\big)^2 + 0 + 0. \end{aligned} \tag{A.7}$$

Finally, substituting Eq.s (A.5), (A.6), and (A.7) in Eq. (A.4) leads to the expression.

A.3 Proof of Lemmas

Proof of Lemma 2.1. Since $P(T^+(n_1)|A^+(n_1), D \le t_w, L) \ge P(T^+(n_1), T^+(n_2, m)|A^+(n_1), D \le t_w, L)$ for all $n_1, n_2, m \in \mathbb{Z}^+$, it trivially follows that $R^{NR} \le R^X$ for $X \in \{PR, IR, AR\}$. In addition, $P(T^-(n_1)|A^+(n_1), D \le t_w, L)$ is increasing in n_1, which, in turn, implies that $R^{PR} \ge R^{IR}$. Finally, for $n_1 \ge 1$, we have that:

$$\begin{aligned}\Big(1 - \Big(P\big(T^-(\sqrt{n_1})|A^+(n_1), D \le t_w, L\big)\Big)^m\Big)^2 &\le 1 - \Big(P\big(T^-(\sqrt{n_1})|A^+(n_1), D \le t_w, L\big)\Big)^m \\ &\le 1 - \Big(P\big(T^-(1)|A^+(n_1), D \le t_w, L\big)\Big)^m,\end{aligned}$$

leading to $R^{AR} \geq R^{IR}$. For the second part of the lemma, note that R is a function of m only through $P\big(F^{-}(n_1, n_2, m)|A^{+}(n_1), D \leq t_w, L\big)$. Thus, it is sufficient to study how the latter varies in m. Deriving the partial derivative, one can show that:

$$\frac{\partial}{\partial m} P\big(F^{-X}(n_1, n_2, m)|A^{+}(n_1), D \leq t_w, L\big) \leq 0, \;\; \forall\, X \in \{PR, IR, AR\}.$$

Finally, by taking the limit as $m \to \infty$, it trivially follows that R^X for $X \in \{PR, IR, AR\}$ tends to R^{NR}, completing the proof. □

Proof of Lemma 2.2. The first set of inequalities trivially hold, since $mn_1 \geq m \geq 1$ and $2m\sqrt{n_1} \geq m \geq 1$, respectively, for any $n_1 \geq 1, m \geq 1$. For the second set of inequalities, note that $\mathbb{E}[N^{IR}] \geq \mathbb{E}[N^{AR}] \Leftrightarrow n_1 \geq 4$, since then $mn_1 \geq 2m\sqrt{n_1}$, completing the proof. □

Proof of Lemma 2.3. Since $P\big(T^{+}(n_1), T^{+}(n_2, m), A^{+}(n_1)|L\big) \leq P\big(T^{+}(n_1), A^{+}(n_1)|L\big)$, it follows that:

$$\begin{aligned}
\mathbb{E}[W^{NR}|L] &= (n_1 - 1)P\big(T^{+}(n_1), A^{+}(n_1)|L\big) + n_1(1 - Sp)P(A^{-}(n_1)) \\
&\geq (n_1 - 1)P\big(T^{+}(n_1), T^{+}(n_2, m), A^{+}(n_1)|L\big) + n_1(1 - Sp)(1 - Sp^m)P(A^{-}(n_1)) \\
&= \mathbb{E}[W^{PR}|L].
\end{aligned}$$

Similarly, we can show that $\mathbb{E}[W^{NR}] \geq \mathbb{E}[W^{IR}]$. To compare the expected waste of the AR and IR testing schemes, we define the following two terms:

$$\begin{aligned}
(\star) =& (\sqrt{n_1} - 1)\big(1 - Sp^m\big)\Bigg[\Bigg(2\Big(1 - \big(P(T^{-}(n_2)|A^{+}(n_1), D \leq t_w, L)\big)^m\Big) + \big(1 - Sp^m\big)\left(\sqrt{n_1} - 1\right)\Bigg) \\
&\times P(T^{+}(n_1)|A^{+}(n_1), D \leq t_w, L)P(D \leq t_w|A^{+}(n_1)) \\
&+ \Bigg(2 + \big(1 - Sp^m\big)\left(\sqrt{n_1} - 1\right)\Bigg)P(D > t_w|A^{+}(n_1))\Bigg]
\end{aligned}$$

$$(\star\star) = n_1(1-Sp)\big(1-Sp^m\big)^2$$

Then, $\mathbb{E}[W^{AR}|L] = (\star)P(A^+(n_1)) + (\star\star)P(A^-(n_1))$. We have that:

$$(\star) \leq (n_1-1)(1-Sp^m)\Big(1-P\big(D\leq t_w|A^+(n_1)\big)P\big(T^-(n_1)|A^+(n_1),D\leq t_w,L\big)\Big),$$
$$(\star\star) \leq n_1(1-Sp)\big(1-Sp^m\big).$$

Thus,

$$\begin{aligned}
\mathbb{E}[W^{AR}|L] &= (\star)P(A^+(n_1)) + (\star\star)P(A^-(n_1)) \\
&\leq (n_1-1)(1-Sp^m)\Big(1-P\big(D\leq t_w|A^+(n_1)\big)P\big(T^-(n_1)|A^+(n_1),D\leq t_w,L\big)\Big)P(A^+(n_1)) \\
&+ n_1(1-Sp)\big(1-Sp^m\big)P(A^-(n_1)) \\
&= \mathbb{E}[W^{IR}|L],
\end{aligned}$$

proving that $\mathbb{E}[W^{AR}] \leq \mathbb{E}[W^{IR}]$. To show that $\mathbb{E}[W^{PR}] \leq \mathbb{E}[W^{IR}]$, we note that if

$$P\big(F^{+PR}(n_1,n_2,m)|T^+(n_1),A^+(n_1),D\leq t_w\big) \geq (1-Sp^m)P\big(T^+(n_1)|A^+(n_1),D\leq t_w\big),$$

then it can be easily shown that $\mathbb{E}[W^{PR}] \leq \mathbb{E}[W^{IR}]$. However, we have that:

$$\begin{aligned}
P\big(F^{+PR}(n_1,n_2,m)|T^+(n_1),A^+(n_1),D\leq t_w\big) =& P\big(T^+(n_1),T^+(n_1,m)|T^+(n_1),A^+(n_1),D\leq t_w\big), \\
=& P\big(T^+(n_1,m)|T^+(n_1),A^+(n_1),D\leq t_w\big), \\
\geq& P\big(T^+(n_1,m)|A^+(n_1),D\leq t_w\big), \\
\geq& P\big(T^+(n_1,1)|A^+(n_1),D\leq t_w\big), \\
=& P\big(T^+(n_1)|A^+(n_1),D\leq t_w\big), \\
\geq& (1-Sp^m)P\big(T^+(n_1)|A^+(n_1),D\leq t_w\big).
\end{aligned}$$

As such, since the condition is always satisfied, then $\mathbb{E}[W^{PR}] \leq \mathbb{E}[W^{IR}]$. Finally, for the second part, it can be shown that:

$$\frac{\partial}{\partial m}\mathbb{E}[W^X] \geq 0, \;\; \forall X \in \{PR, IR, AR\},$$

which leads to the results shown in the lemma. Taking the limit as $m \to \infty$ reduces the expected waste to that of the no re-testing case, completing the proof. □

Appendix B

Appendix for Chapter 3

B.1 Mathematical Proofs

Throughout, we denote the optimal Tier 1 (Tier 2) assignment by $\boldsymbol{x^{1*}}$ ($\boldsymbol{x^{2*}}$)

Proof of Lemma 3.1. By Remark 3.1, when $m = 1$, $\mathbb{E}[FN^1(\boldsymbol{x^1})|\boldsymbol{p}]$ becomes independent of the assignment. For $m \geq 2$, suppose that the optimal assignment for the $m \times n$ testing matrix does not follow Assignment **RH**. Then by Corollary 3.2, there exists a $2 \times n$ sub-matrix, with rows i_1 and i_2, such that its assignment does not follow **RH**. Since $\mathbb{E}[FN^1(\boldsymbol{x^{1*}})|\boldsymbol{p}]$ is additive across rows, we can write:

$$\begin{aligned}\mathbb{E}[FN^1(\boldsymbol{x^{1*}})|\boldsymbol{p}] &= \sum_{i=1}^{m} \mathbb{E}[FN_i^1(\boldsymbol{x^{1*}})|\boldsymbol{p}] \\ &= \sum_{\substack{i=1 \\ i\neq i_1,i_2}}^{m} \mathbb{E}[FN_i^1(\boldsymbol{x^{1*}})|\boldsymbol{p}] + \mathbb{E}[FN_{i_1}^1(\boldsymbol{x^{1*}})|\boldsymbol{p}] + \mathbb{E}[FN_{i_2}^1(\boldsymbol{x^{1*}})|\boldsymbol{p}],\end{aligned}$$

where $\mathbb{E}[FN_i^1(\boldsymbol{x^{1*}})]$ is the Tier 1 expected number of false negatives of row i. Consider an

assignment, denoted by $\hat{\boldsymbol{x}}^{\mathbf{1}}$, where the subjects in the $2 \times n$ matrix, comprised of rows i_1 and i_2, are reassigned such that they follow Assignment **RH**, while the original assignment of all other rows is maintained. Observe that, for all $i \neq i_1, i_2$, $\mathbb{E}[FN_i^1(\boldsymbol{x}^{\mathbf{1}*})] = \mathbb{E}[FN_i^1(\hat{\boldsymbol{x}}^{\mathbf{1}})]$. Moreover, since Assignment **RH** is optimal for a $2 \times n$ matrix, $\forall \boldsymbol{p}$, we have:

$$\mathbb{E}[FN_{i_1}^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|\boldsymbol{p}] + \mathbb{E}[FN_{i_2}^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|\boldsymbol{p}] \leq \mathbb{E}[FN_{i_1}^1(\boldsymbol{x}^{\mathbf{1}*})|\boldsymbol{p}] + \mathbb{E}[FN_{i_2}^1(\boldsymbol{x}^{\mathbf{1}*})|\boldsymbol{p}],$$

that is, $\mathbb{E}[FN^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|\boldsymbol{p}] \leq \mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|\boldsymbol{p}]$, implying that there exists an optimal assignment that follows **RH**. □

Proof of Lemma 3.2. For all sensitivity functions that satisfy Eq. (3.4), it follows, by definition, that:

$$k\frac{\partial^2 Se(n,k)}{\partial k^2} + 2\frac{\partial Se(n,k)}{\partial k} \geq 0 \Rightarrow \frac{\partial}{\partial k}\left[Se(n,k) + k\frac{\partial Se(n,k)}{\partial k}\right] \geq 0.$$

Thus, we get:

$$\begin{aligned} & Se(n,k+1) + (k+1)\frac{\partial Se(n,k+1)}{\partial k} - Se(n,k) - k\frac{\partial Se(n,k)}{\partial k} \geq 0 \\ \Rightarrow & \frac{\partial}{\partial k}\left[(k+1)Se(n,k+1) - kSe(n,k)\right] \geq 0. \end{aligned}$$

For a given realization n_d of N_d, let $i = 1, \cdots, I(n, n_d)$. As such, $i \leq n_d/2 \Rightarrow i \leq n_d - i \Rightarrow i - 1 \leq n_d - i$, which gives:

$$i\ (1 - Se(n,i)) + (n_d - i)(1 - Se(n, n_d - i)) \geq (i-1)(1 - Se(n, i-1)) + (n_d - i + 1)(1 - Se(n, n_d - i + 1)). \tag{B.1}$$

Multiplying both sides of Eq. (B.1) by $P(N_d = n_d)$ and noting that:

$$\mathbb{E}\left[FN^1(\boldsymbol{x^1})|\big(Y_i(\boldsymbol{x^1})|N_d = n_d\big) = 1\right] = i\ (1 - Se(n,i)) + (n_d - i)(1 - Se(n, n_d - i)),$$

we obtain $a(i, n_d) \geq a(i-1, n_d)$ for all realizations n_d of N_d and for all $i = 1, \cdots, I(n, n_d)$. $\square$

Proof of Theorem 3.1. By Lemma 3.1, it is sufficient to show that Theorem 3.1 holds for a $2 \times n$ matrix. Suppose that the optimal assignment, denoted by $\boldsymbol{x^{1*}}$, does not follow **RH**.

Case 1: $N_d = n$

From Corollary 3.3, we have that:

$$\mathbb{E}[FN^1(\boldsymbol{x^{1*}})|N_d = n]P(N_d = n) = \sum_{i=0}^{\lfloor n/2 \rfloor} a(i,n)\mathbb{E}\big[Y_i(\boldsymbol{x^{1*}})|N_d = n\big]. \tag{B.2}$$

By Corollary 3.2, there exists a subject k, $k < n$, such that $p_{1j} < p_{2j}$ for all $j = 1, \cdots, k$, and $p_{1j} \geq p_{2j}$ for all $j = k+1, \cdots, n$. For a given Tier 1 assignment, $\boldsymbol{x^1}$, let $P_k^{\boldsymbol{x^1}}(n^1_{d,r}, n^2_{d,r})$ $\big(P_{n-k}^{\boldsymbol{x^1}}(n^1_{d,r}, n^2_{d,r})\big)$ denote the probability that the $2 \times k$ $\big(2 \times (n-k)\big)$ sub-matrix has $n^1_{d,r}$ and $n^2_{d,r}$ positive subjects in rows 1 and 2, respectively. By conditioning on the outcome of the $2 \times k$ sub-matrix, we get:

$$\mathbb{E}\big[Y_i(\boldsymbol{x^{1*}})|N_d = n\big] = \sum_{n^1_{d,r}, n^2_{d,r}} P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) \left[P_{n-k}^{\boldsymbol{x^{1*}}}(i - n^1_{d,r}, n - n^2_{d,r} - i) + P_{n-k}^{\boldsymbol{x^{1*}}}(n - n^1_{d,r} - i, i - n^2_{d,r})\right]. \tag{B.3}$$

Substituting Eq. (B.3) into Eq. (B.2) gives:

$$\mathbb{E}[FN^1(\boldsymbol{x^{1*}})|N_d = n]P(N_d = n) = \sum_{n^1_{d,r}, n^2_{d,r}} P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})\Big[\sum_{i=0}^{\lfloor n/2 \rfloor} a(i,n)\big(P_{n-k}^{\boldsymbol{x^{1*}}}(i - n^1_{d,r}, n - n^2_{d,r} - i) + P_{n-k}^{\boldsymbol{x^{1*}}}(n - n^1_{d,r} - i, i - n^2_{d,r})\big)\Big].$$

Observe that for any $n^1_{d,r}, n^2_{d,r}$ pair with $n^1_{d,r} > n^2_{d,r}$, there exists a symmetric pair. By

combining these symmetric terms we get:

$$\mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|N_d = n]P(N_d = n) = \sum_{\substack{n^1_{d,r},n^2_{d,r} \\ n^1_{d,r}=n^2_{d,r}}} C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r})$$
$$+ \sum_{\substack{n^1_{d,r},n^2_{d,r} \\ n^1_{d,r}>n^2_{d,r}}} \left[C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) + C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) \right],$$

$$\text{where} \quad C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) = \sum_{i=0}^{\lfloor n/2 \rfloor} a(i,n) \left[P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^1_{d,r}, n - n^2_{d,r} - i) + P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \right].$$

In what follows, we show that, for $n^1_{d,r} > n^2_{d,r}$, $C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) \geq C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r})$. Starting with $C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r})$ and performing a change of variable $j = i - n^1_{d,r} + n^2_{d,r}$ for the first term, we can write:

$$C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) = \sum_{j=n^2_{d,r}-n^1_{d,r}}^{\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r}} a(j + n^1_{d,r} - n^2_{d,r}, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j)$$
$$+ \sum_{i=0}^{\lfloor n/2 \rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}).$$

Since $n^1_{d,r} > n^2_{d,r}$, one can split the sums as follows:

$$\begin{aligned}
C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) = &\sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i) \\
&+ \sum_{i=0}^{\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}} a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i) \\
&+ \sum_{i=0}^{\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}) \\
&+ \sum_{i=\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}+1}^{\lfloor n/2\rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}).
\end{aligned}$$

Combining terms gives:

$$\begin{aligned}
C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) = &\sum_{i=0}^{\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}} \Big[a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}) \\
&\qquad + a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i)\Big] \\
&+ \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i) \\
&+ \sum_{i=\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}+1}^{\lfloor n/2\rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}).
\end{aligned}$$

Let

$$I_{21} \equiv \sum_{i=0}^{\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}} \Big[a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}) + a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i)\Big],$$

$$I_{22} \equiv \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i+n^1_{d,r}-n^2_{d,r},n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i), \quad \text{and}$$

$$I_{23} \equiv \sum_{i=\lfloor n/2\rfloor+n^2_{d,r}-n^1_{d,r}+1}^{\lfloor n/2\rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}).$$

As such, $C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r}, n^2_{d,r}) = I_{21} + I_{22} + I_{23}$. Similarly, performing a change of variable $j = i - n^1_{d,r} + n^2_{d,r}$ for the second term of $C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r})$ gives:

$$\begin{aligned} C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) = &\sum_{i=0}^{\lfloor n/2 \rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ &+ \sum_{j=n^2_{d,r}-n^1_{d,r}}^{\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r}} a(j + n^1_{d,r} - n^2_{d,r}, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}). \end{aligned}$$

Noting that $n^1_{d,r} > n^2_{d,r}$ and splitting the sums gives:

$$\begin{aligned} C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) = &\sum_{i=0}^{\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r}} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ &+ \sum_{i=\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1}^{\lfloor n/2 \rfloor} a(i,n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ &+ \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i + n^1_{d,r} - n^2_{d,r}, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \\ &+ \sum_{i=0}^{\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r}} a(i + n^1_{d,r} - n^2_{d,r}, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}). \end{aligned}$$

Collecting terms gives:

$$\begin{aligned}C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) = &\sum_{i=0}^{\lfloor n/2\rfloor + n^2_{d,r} - n^1_{d,r}} \Big[a(i,n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ &\qquad + a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r})\Big] \\ &+ \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \\ &+ \sum_{i=\lfloor n/2\rfloor + n^2_{d,r} - n^1_{d,r}+1}^{\lfloor n/2\rfloor} a(i,n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i).\end{aligned}$$

Let

$$I_{31} = \sum_{i=0}^{\lfloor n/2\rfloor + n^2_{d,r} - n^1_{d,r}} \left[a(i,n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) + a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r})\right],$$

$$I_{32} = \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}), \quad \text{and}$$

$$I_{33} = \sum_{i=\lfloor n/2\rfloor + n^2_{d,r} - n^1_{d,r}+1}^{\lfloor n/2\rfloor} a(i,n)P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i).$$

As such, $C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r}, n^1_{d,r}) = I_{31} + I_{32} + I_{33}$. In what follows, we show that $I_{31} \geq I_{21}$, $I_{32} \geq I_{22}$, and $I_{33} \geq I_{23}$.

(i) To show $I_{31} \geq I_{21}$

We have:

$$\begin{aligned} i &\leq \lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} \\ &\leq n/2 + n^2_{d,r} - n^1_{d,r} \\ &< n/2 + (n^2_{d,r} - n^1_{d,r})/2 \quad (\text{since } n^1_{d,r} > n^2_{d,r}). \end{aligned}$$

This gives $i - n^2_{d,r} < n - n^1_{d,r} - i$. Now, since $p_{1i} \geq p_{2i}$ for all $i = k+1, \cdots, n$ we get:

$$P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \geq P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i). \tag{B.4}$$

Also, since $n^1_{d,r} > n^2_{d,r}$, then, by Lemma 3.2, we have that $a(i + n^1_{d,r} - n^2_{d,r}, n) - a(i, n) \geq 0$. Multiplying both sides of Eq. (B.4) by the latter and rearranging gives:

$$\begin{aligned} &a(i,n)P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) + a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \\ &\geq a(i,n)P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) + a(i + n^1_{d,r} - n^2_{d,r}, n)P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i). \end{aligned}$$

Since this is true for all $i \leq \lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r}$ then summing over all of these terms directly implies that $I_{31} \geq I_{21}$.

(ii) To show $I_{32} \geq I_{22}$

We have that $n^1_{d,r} - n^2_{d,r} \leq k < n$ which implies that $(n + n^2_{d,r} - n^1_{d,r})/2 > 0$, but in these cases we have that $i \leq -1 < (n - n^1_{d,r} + n^2_{d,r})/2$. As such, we get that $i - n^2_{d,r} < n - n^1_{d,r} - i$. Also, since $p_{1i} \geq p_{2i}$ for all $i = k+1, \cdots, n$ we get $P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r}) \geq P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i)$. Multiplying both sides by $a(i + n^1_{d,r} - n^2_{d,r}, n) \geq 0$ and adding over all cases we get:

$$\sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i+n^1_{d,r}-n^2_{d,r}, n)P^{\boldsymbol{x}^{1*}}_{n-k}(n-n^1_{d,r}-i, i-n^2_{d,r}) \geq \sum_{i=n^2_{d,r}-n^1_{d,r}}^{-1} a(i+n^1_{d,r}-n^2_{d,r}, n)P^{\boldsymbol{x}^{1*}}_{n-k}(i-n^2_{d,r}, n-n^1_{d,r}-i),$$

which directly gives $I_{32} \geq I_{22}$.

(iii) To show $I_{33} \geq I_{23}$

Sub-case 1: $n^1_{d,r} - n^2_{d,r} \leq 2\lfloor n/2 \rfloor - n + 2$

In this case we get that (from the imposed condition)

$$\Big[\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1\Big] - n^2_{d,r} \geq n - n^1_{d,r} - \Big[\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1\Big].$$

As such, for all $i \geq \lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1$ we have $i - n^2_{d,r} \geq n - n^1_{d,r} - i$, and since $p_{1i} \geq p_{2i}$ for all $i = k+1, \cdots, n$ we get $P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \geq P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - i, i - n^2_{d,r})$. Multiplying both sides by $a(i,n) \geq 0$ and summing over all cases gives $I_{33} \geq I_{23}$.

Sub-case 2: $n^1_{d,r} - n^2_{d,r} > 2\lfloor n/2 \rfloor - n + 2$ and n is odd

Under the imposed condition we get:

$$\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1 < n/2 + (n^2_{d,r} - n^1_{d,r})/2 \leq \lfloor n/2 \rfloor.$$

Separating the sum in I_{33} as follows

$$\begin{aligned} I_{33} = & \sum_{i=\lfloor n/2 \rfloor + n^2_{d,r} - n^1_{d,r} + 1}^{n/2 + (n^2_{d,r} - n^1_{d,r})/2 - 1} a(i,n) P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ & + \sum_{i=n/2 + (n^2_{d,r} - n^1_{d,r})/2 + 1}^{\lfloor n/2 \rfloor} a(i,n) P^{\boldsymbol{x}^{1*}}_{n-k}(i - n^2_{d,r}, n - n^1_{d,r} - i) \\ & + a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 - (n^1_{d,r} + n^2_{d,r})/2), \end{aligned}$$

and performing a change of index $j = n + n^2_{d,r} - n^1_{d,r} - i$ for the first term gives:

$$I_{33} = \sum_{j=n/2+(n^2_{d,r}-n^1_{d,r})/2+1}^{\lfloor n/2 \rfloor} \Big[a(n + n^2_{d,r} - n^1_{d,r} - j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}) \\ + a(j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j)^{v_1} \Big] \\ + a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 - (n^1_{d,r} + n^2_{d,r})/2).$$

Note that upon change of index the upper bound of the sum is equal to $n - \lfloor n/2 \rfloor - 1$, which is equal to $\lfloor n/2 \rfloor$ (since n is odd). Upon similar algebraic manipulations, we get:

$$I_{23} = \sum_{j=n/2+(n^2_{d,r}-n^1_{d,r})/2+1}^{\lfloor n/2 \rfloor} \Big[a(n + n^2_{d,r} - n^1_{d,r} - j) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) \\ + a(j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}) \Big] \\ + a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 - (n^1_{d,r} + n^2_{d,r})/2).$$

Comparing the first terms of I_{33} and I_{23} (their second terms are equal) we have:

$$j \geq n/2 + (n^2_{d,r} - n^1_{d,r})/2 + 1 > n/2 + (n^2_{d,r} - n^1_{d,r})/2,$$

which implies both $j > n + n^2_{d,r} - n^1_{d,r} - j$ and $j - n^2_{d,r} > n - n^1_{d,r} - j$. As such, by Lemma 3.2, we get that $a(j, n) - a(n + n^2_{d,r} - n^1_{d,r} - j, n) \geq 0$ and $P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) \geq P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r})$. Multiplying both sides of the latter with the former and reorganizing gives:

$$a(n + n^2_{d,r} - n^1_{d,r} - j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}) + a(j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) \\ \geq a(n + n^2_{d,r} - n^1_{d,r} - j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) + a(j, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}).$$

Summing over all cases and adding $a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{\mathbf{1}*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 -$

$(n^1_{d,r} + n^2_{d,r})/2)$, on both sides directly gives $I_{33} \geq I_{23}$.

Sub-case 3: $n^1_{d,r} - n^2_{d,r} > 2\lfloor n/2 \rfloor - n + 2$ and n is even

Following a similar procedure to that of Sub-case 2 we get:

$$\begin{aligned} I_{33} = \sum_{j=n/2+(n^2_{d,r}-n^1_{d,r})/2+1}^{n/2-1} \Big[& a(n + n^2_{d,r} - n^1_{d,r} - j) P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}) \\ & + a(j, n) P^{\boldsymbol{x}^{1*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) \Big] \\ & + a(n/2, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - n^2_{d,r}, n/2 - n^1_{d,r}) \\ & + a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 - (n^1_{d,r} + n^2_{d,r})/2) \end{aligned}$$

$$\begin{aligned} I_{23} = \sum_{j=n/2+(n^2_{d,r}-n^1_{d,r})/2+1}^{n/2-1} \Big[& a(n + n^2_{d,r} - n^1_{d,r} - j, n) P^{\boldsymbol{x}^{1*}}_{n-k}(j - n^2_{d,r}, n - n^1_{d,r} - j) \\ & + a(j, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n - n^1_{d,r} - j, j - n^2_{d,r}) \Big] \\ & + a(n/2, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - n^1_{d,r}, n/2 - n^2_{d,r}) \\ & + a(n/2 + (n^2_{d,r} - n^1_{d,r})/2, n) P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - (n^1_{d,r} + n^2_{d,r})/2, n/2 - (n^1_{d,r} + n^2_{d,r})/2). \end{aligned}$$

The first term of I_{33} was shown to be greater than the first term of I_{23} in Sub-case 2. For the second term, we note that $n^1_{d,r} > n^2_{d,r}$ which gives $n/2 - n^1_{d,r} < n/2 - n^2_{d,r}$ implying that $P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - n^2_{d,r}, n/2 - n^1_{d,r}) \geq P^{\boldsymbol{x}^{1*}}_{n-k}(n/2 - n^1_{d,r}, n/2 - n^2_{d,r})$. Multiplying both sides of the latter equation by $a(n/2, n) \geq 0$ shows the second term of I_{33} is greater than I_{32}. Since the last term is equal among the two, we thus get that $I_{33} \geq I_{23}$.

Thus, we have shown that $C^{\boldsymbol{x}^{1*}}(n^2_{d,r}, n^1_{d,r}) - C^{\boldsymbol{x}^{1*}}(n^1_{d,r}, n^2_{d,r}) \geq 0$. Also, since $n^1_{d,r} > n^2_{d,r}$ and $p_{1j} < p_{2j}$ for all $j = 1, \cdots, k$ we get that $P^{\boldsymbol{x}^{1*}}_k(n^1_{d,r}, n^2_{d,r}) \leq P^{\boldsymbol{x}^{1*}}_k(n^2_{d,r}, n^1_{d,r})$. Multiplying the

last two equations and expanding gives:

$$\begin{aligned}
&C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r}) + C^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) \\
&\leq C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) + C^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r}).
\end{aligned}$$

As such, we get that:

$$\begin{aligned}
&\sum_{\substack{n^1_{d,r}, n^2_{d,r} \\ n^1_{d,r} = n^2_{d,r}}} C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) \\
+ &\sum_{\substack{n^1_{d,r}, n^2_{d,r} \\ n^1_{d,r} > n^2_{d,r}}} \left[C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r}) + C^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})\right] \\
&\leq \sum_{\substack{n^1_{d,r}, n^2_{d,r} \\ n^1_{d,r} = n^2_{d,r}}} C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) \\
+ &\sum_{\substack{n^1_{d,r}, n^2_{d,r} \\ n^1_{d,r} > n^2_{d,r}}} \left[C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) + C^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r})P_k^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r})\right].
\end{aligned}$$

Consider the assignment, denoted by $\hat{\boldsymbol{x}}^{\mathbf{1}}$, where the first k subjects of row 1 are interchanged with the first k subjects of row 2. Observe that $\hat{x}^1$ follows Assignment **RH**,

$$\begin{aligned}
&P_k^{\boldsymbol{x^{1*}}}(n^2_{d,r}, n^1_{d,r}) = P_k^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r}, n^2_{d,r}), \quad \text{and} \\
&P_{n-k}^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) = P_{n-k}^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r}, n^2_{d,r}) \Rightarrow C^{\boldsymbol{x^{1*}}}(n^1_{d,r}, n^2_{d,r}) = C^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r}, n^2_{d,r}).
\end{aligned}$$

As such, by substituting back gives:

$$\begin{aligned}
&\sum_{\substack{n^1_{d,r},n^2_{d,r}\\ n^1_{d,r}=n^2_{d,r}}} C^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r},n^2_{d,r})P_k^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^2_{d,r},n^1_{d,r})\\
&+\sum_{\substack{n^1_{d,r},n^2_{d,r}\\ n^1_{d,r}>n^2_{d,r}}} \left[C^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r},n^2_{d,r})P_k^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^1_{d,r},n^2_{d,r})+C^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^2_{d,r},n^1_{d,r})P_k^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(n^2_{d,r},n^1_{d,r})\right]\\
&\leq \sum_{\substack{n^1_{d,r},n^2_{d,r}\\ n^1_{d,r}=n^2_{d,r}}} C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r},n^2_{d,r})P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r},n^2_{d,r})\\
&+\sum_{\substack{n^1_{d,r},n^2_{d,r}\\ n^1_{d,r}>n^2_{d,r}}} \left[C^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r},n^2_{d,r})P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^1_{d,r},n^2_{d,r})+C^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r},n^1_{d,r})P_k^{\boldsymbol{x}^{\mathbf{1}*}}(n^2_{d,r},n^1_{d,r})\right],
\end{aligned}$$

which directly implies $\mathbb{E}[FN^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|N_d=n]\leq\mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|N_d=n]$. Since $\boldsymbol{x}^{\mathbf{1}*}$ is the optimal assignment, then it must be true that $\mathbb{E}[FN^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|N_d=n]=\mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|N_d=n]$. As such, there exists an optimal assignment which follows **RH**.

Case 2: $N_d<n$

We note that under any realization, $n-N_d$ columns would have zero positive subjects. Letting Φ denote the set of all possible $n-N_d$ columns, by conditioning on the columns having zero positive subjects we get:

$$\mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|N_d=n_d]P(N_d=n_d)=\sum_{\phi\in\Phi}\left[\sum_{i=0}^{\lfloor n_d/2\rfloor}a(i,n_d)\mathbb{E}\big[Y_i(\boldsymbol{x}^{\mathbf{1}*})|N_d=n_d\big]\right]P^{\boldsymbol{x}^{\mathbf{1}*}}(\phi|N_d=n_d).$$

By Corollary 3.2, there exists a subject k such that $p_{1j}<p_{2j}$ for all $j=1,\cdots,k$ and $p_{1j}\geq p_{2j}$ for all $j=k+1,\cdots,n$. For a given Tier 1 assignment, $\boldsymbol{x}^{\mathbf{1}}$, let $P_k^{\boldsymbol{x}^{\mathbf{1}}}(n^1_{d,r},n^2_{d,r})$ $\big(P^{\boldsymbol{x}^{\mathbf{1}}}_{n-k}(n^1_{d,r},n^2_{d,r})\big)$ be the probability that the $2\times k$ $\big(2\times(n-k)\big)$ sub-matrix has $n^1_{d,r}$ and $n^2_{d,r}$ positive subjects in rows 1 and 2, respectively. Consider the assignment, denoted by

$\hat{\boldsymbol{x}}^{\mathbf{1}}$, where the first k subjects of row 1 are interchanged with the first k subjects of row 2. Observe that $\hat{x}^1$ follows Assignment **RH**. From our previous result (i.e., Case 1) we have

$$\sum_{i=0}^{\lfloor n_d/2 \rfloor} a(i,n_d)\mathbb{E}\big[Y_i(\boldsymbol{x}^{\mathbf{1}*})|N_d=n_d\big] = \sum_{i=0}^{\lfloor n_d/2 \rfloor} a(i,n_d)\mathbb{E}\big[Y_i(\hat{\boldsymbol{x}}^{\mathbf{1}})|N_d=n_d\big].$$

Also, since we are conditioning on columns that have no positive subjects in both rows then $P^{\boldsymbol{x}^{\mathbf{1}*}}(\phi|N_d=n_d) = P^{\hat{\boldsymbol{x}}^{\mathbf{1}}}(\phi|N_d=n_d)$ for all $\phi \in \Phi$. Thus, we get that $\mathbb{E}[FN^1(\hat{\boldsymbol{x}}^{\mathbf{1}})|N_d=n_d] = \mathbb{E}[FN^1(\boldsymbol{x}^{\mathbf{1}*})|N_d=n_d]$ implying that there exists an optimal assignment which follows **RH**.

Case 3: $N_d > n$

We note that under any realization, $N_d - n$ columns would have two positive subjects (one in each row). By conditioning on these columns, the proof follows similarly to that of Case 2. □

Proof of Theorem 3.2 . Similar to the proof of Theorem 3.1, we start with the perfect information setting for a $2 \times n$ matrix. Let $n^1_{d,r}$ and $n^2_{d,r}$ respectively denote the number of positive subjects in rows 1 and 2, and assume, without loss of generality, that $n^1_{d,r} \geq n^2_{d,r}$. Suppose an optimal Tier 1 assignment, which we denote by assignment $v1$, does not follow **RH**. Then, it must be true that $0 < n^2_{d,r} \leq n^1_{d,r} < n$ (note that if $n^1_{d,r} = n$ or $n^2_{d,r} = 0$, the assignment must follow **RH**). We have $\mathbb{E}[N_r^{v1}] = Se(n, n^1_{d,r}) + Se(n, n^2_{d,r})$. Next consider another assignment, denoted by $v2$, in which one positive subject is moved from row 2 to row 1, leading to $\mathbb{E}[N_r^{v2}] = Se(n, n^1_{d,r}+1) + Se(n, n^2_{d,r}-1)$. By concavity of $Se(n,k)$, we have that:

$$\frac{\partial}{\partial k}\left[Se(n,k+1) - Se(n,k)\right] \leq 0,$$

hence the difference, $Se(n,k+1) - Se(n,k)$ is decreasing in k. Then, since $n^1_{d,r} > n^2_{d,r} - 1$, we have that $Se(n, n^1_{d,r}+1) - Se(n, n^1_{d,r}) \leq Se(n, n^2_{d,r}) - Se(n, n^2_{d,r}-1) \Rightarrow Se(n, n^1_{d,r}+1) +$

$Se(n, n^2_{d,r} - 1) \geq Se(n, n^1_{d,r}) + Se(n, n^2_{d,r}) \Rightarrow \mathbb{E}[N^{v2}_r] \leq \mathbb{E}[N^{v1}_r]$. However, since assignment $v1$ is optimal, then it must be true that $\mathbb{E}[N^{v2}_r] = \mathbb{E}[N^{v1}_r]$. As such, there exists an optimal assignment which follows **RH**. The remainder of the proof is exactly the same as that of Theorem 3.1. □

Proof of Theorem 3.3. Since the set of subjects resulting from a Tier 1 outcome of $\boldsymbol{r} = (1, \cdots, 1)$ is ROI (the condition imposed by the theorem), then by Corollary 3.4 the set of subjects is also ROI for all $\boldsymbol{r}$. As such, the ordering of the risk is preserved for any possible outcome, and due to the symmetry between Assignment **RH** in Tier 1 and Assignment **CH** in Tier 2, the result directly follows from Theorem 3.1. □

Details on Example 3.2. Starting with an arbitrary row $i = 1, \cdots, m$, Eq. (3.8) implies the following:

$$
\begin{aligned}
& P(D_{i1} = 1 | R_i = 1, D_{i2} = 1) \leq P(D_{i1} = 1 | R_i = 1) \\
\Leftrightarrow & P(R_i = 1 | D_{i1} = 1, D_{i2} = 1) \leq \frac{P(R_i = 1 | D_{i1} = 1) P(R_i = 1 | D_{i2} = 1)}{P(R_i = 1)} \\
\Leftrightarrow & \quad Se(2,2) \leq \frac{\big[p_{i2} Se(2,2) + (1 - p_{i2}) Se(2,1)\big] \big[p_{i1} Se(2,2) + (1 - p_{i1}) Se(2,1)\big]}{p_{i1} p_{i2} Se(2,2) + \big[p_{i1}(1 - p_{i2}) + p_{i2}(1 - p_{i1})\big] Se(2,1) + (1 - p_{i1})(1 - p_{i2})(1 - Sp)} \\
\Leftrightarrow & \quad Se(2,2) \leq \frac{p_{i1} p_{i2} Se(2,2)^2 + \big[p_{i1}(1 - p_{i2}) + p_{i2}(1 - p_{i1})\big] Se(2,2) Se(2,1) + (1 - p_{i1})(1 - p_{i2}) Se(2,1)^2}{p_{i1} p_{i2} Se(2,2) + \big[p_{i1}(1 - p_{i2}) + p_{i2}(1 - p_{i1})\big] Se(2,1) + (1 - p_{i1})(1 - p_{i2})(1 - Sp)} \\
\Leftrightarrow & \quad (1 - Sp) Se(2,2) \leq Se(2,1)^2 \, .
\end{aligned}
$$

As such,

$$P(D_{i1} = 1 | R_i = 1, D_{i2} = 1) \leq P(D_{i1} = 1 | R_i = 1) \Leftrightarrow Se(2,1)^2 \geq (1 - Sp) Se(2,2).$$

Similarly, it can be shown that:

$$P(D_{i1} = 1 | R_i = 1, D_{i2} = 0) \geq P(D_{i1} = 1 | R_i = 1) \Leftrightarrow Se(2,1)^2 \geq (1 - Sp) Se(2,2),$$

providing the result. □

Remark B.1. For any 2×2 testing matrix and sensitivity function satisfying Eq. (3.4),

$$\min_{\boldsymbol{x^2}} \mathbb{E}\big[FN^2(\boldsymbol{x^2})|\boldsymbol{R}(\boldsymbol{x^1}) = \boldsymbol{r}\big] \equiv \max_{\boldsymbol{x^2}} \sum_{j=1}^{2} P(N_{d,r}^{j}(\boldsymbol{x^2}) = 2|N_d = 2, \boldsymbol{R}(\boldsymbol{x^1}) = \boldsymbol{r}), \quad \forall\, \boldsymbol{r} \in \boldsymbol{R}.$$

Proof of Remark B.1. Notice that for $N_r \neq 2$ or $N_d \neq 2$, the expression $\mathbb{E}[FN^2(\boldsymbol{x^2})|\boldsymbol{R}(\boldsymbol{x^1}) = r]$ becomes independent of the second tier assignment, $\boldsymbol{x^2}$. This follows because for $N_r = 1$, there is only one possible assignment; and for $N_r = 2$ and $N_d = 0, 1, 3, 4$, all possible assignment lead to the same realization of number of positive subjects in each column (e.g., when $N_d = 3$, all possible assignments lead to 2 positive subjects in one column and 1 positive subject in the other). On the other hand, for $N_r = 2$ and $N_d = 2$, two outcomes are possible: the two positive subjects occur either in the same column or in different columns. By Lemma 3.2, the first case has a lower expected number of false negatives, and the result follows. □

B.2 Derivations of the Performance Measures

Adaptive array pooling scheme under the homogeneous population assumption

In the following, we derive expressions for each performance measure for the proposed adaptive array pooling scheme under the homogeneous population assumption.

$$
\begin{aligned}
\mathbb{E}[FN(m,n)] =& \sum_{l=1}^{3} \mathbb{E}\big[FN^l(m,n)\big] \\
=& m \sum_{k=1}^{n} k\big[1 - Se(n,k)\big] P(N_{d,r} = k) + n \sum_{n_r=1}^{m} \sum_{k=1}^{n_r} k\big[1 - Se(n_r,k)\big] P(N_r = n_r) P(N_{d,c} = k | N_r = n_r) + 0 \\
=& m \sum_{k=1}^{n} k\big[1 - Se(n,k)\big] \binom{n}{k} \big(\mu_p\big)^k (1-\mu_p)^{n-k} \\
&+ n \sum_{n_r=1}^{m} \sum_{k=1}^{n_r} k\big[1 - Se(n_r,k)\big] \binom{m}{n_r} \big(P(R=1)\big)^{n_r} \big(1 - P(R=1)\big)^{m-n_r} \binom{n_r}{k} (\mu_p')^k (1-\mu_p')^{n_r-k},
\end{aligned}
$$

$$
\begin{aligned}
\mathbb{E}[FP(m,n)] =& \sum_{l=1}^{3} \mathbb{E}\big[FP^l(m,n)\big] \\
=& 0 + 0 + n(1-Sp) \sum_{n_r=1}^{m} \sum_{k=0}^{n_r} (n_r - k) Se(n_r,k) P(N_r = n_r) P(N_{d,c} = k | N_r = n_r) \\
=& n(1-Sp) \sum_{n_r=1}^{m} \sum_{k=0}^{n_r} (n_r - k) Se(n_r,k) \binom{m}{n_r} P(R=1)^{n_r} \big(1 - P(R=1)\big)^{m-n_r} \binom{n_r}{k} (\mu_p')^k (1-\mu_p')^{n_r-k},
\end{aligned}
$$

and

$$
\begin{aligned}
\mathbb{E}[T(m,n)] =& \sum_{n_r=0}^{m} \mathbb{E}[T(m,n) | N_r = n_r] P(N_r = n_r) \\
=& m P(N_r = 0) + \sum_{n_r=1}^{m} \left[m + n + n \; n_r \sum_{k=0}^{n_r} Se(n_r,k) P(N_{d,c} = k | N_r = n_r) \right] P(N_r = n_r) \\
=& m\big(1 - P(R=1)\big)^m \\
&+ \sum_{n_r=1}^{m} \left[m + n + n \; n_r \sum_{k=0}^{n_r} Se(n_r,k) \binom{n_r}{k} (\mu_p')^k (1-\mu_p')^{n_r-k} \right] \binom{m}{n_r} P(R=1)^{n_r} \big(1 - P(R=1)\big)^{m-n_r},
\end{aligned}
$$

where $P(R=1)$, i.e., the probability of a row testing positive, is given by

$$
P(R=1) = \sum_{k=0}^{n} Se(n,k) \binom{n}{k} (\mu_p)^k (1-\mu_p)^{n-k},
$$

and μ_p', the updated prevalence rate (i.e., the probability that a subject is positive given

that its corresponding row pool tests positive in Tier 1), is given by

$$\mu_p' = \frac{\sum_{k=0}^{n-1} Se(n,k+1)\binom{n-1}{k}(\mu_p)^k(1-\mu_p)^{n-1-k}}{\sum_{k=0}^{n} Se(n,k)\binom{n}{k}(\mu_p)^k(1-\mu_p)^{n-k}}\ \mu_p.$$

Non-adaptive Non-risk based Array Pooling

Since the **NNP** scheme is non-risk based, all subjects are considered to have the same risk. Let FN_{ij} (FP_{ij}) $i \in \{1,\cdots,M\}$, $j \in \{1,\cdots,N\}$, denote the probability that the subject, located at the intersection of row i and column j, is classified as a false negative (positive). Also, let R_i (C_j) denote the random variable representing the test outcome status for row i (column j), with $R_i = 1$ ($C_j = 1$) representing a positive test outcome of row i (column j). Lastly, let A_{ij} denote the random variable corresponding to the true status of the subject located at the intersection of row i and column j, with $A_{ij} = 1$ if the subject is truly infected, and 0 otherwise. Then, for arbitrary i and j, we can write:

$$\begin{aligned}
\mathbb{E}[FN] =& mn\mathbb{E}[FN_{ij}] \\
=& mn\mathbb{E}[FN_{ij}|A_{ij}=1]P(A_{ij}) \\
=& mn\mu_p\mathbb{E}[FN_{ij}|A_{ij}=1] \\
=& mn\mu_p\big(1-P(R_i=1,C_j=1|A_{ij}=1)\big).
\end{aligned}$$

We note that, conditioned on the true status of the subject at the intersection, the test outcomes of row i and column j are independent. Thus, we can write:

$$\mathbb{E}[FN] = mn\mu_p\big(1-P(R_i=1|A_{ij}=1)P(C_j=1|A_{ij}=1)\big),$$

where

$$P(R_i = 1|A_{ij} = 1) = \sum_{k=0}^{n-1} Se(n, k+1)\binom{n-1}{k}(\mu_p)^k(1-\mu_p)^{n-1-k}, \text{ and}$$
$$P(C_j = 1|A_{ij} = 1) = \sum_{k=0}^{m-1} Se(m, k+1)\binom{m-1}{k}(\mu_p)^k(1-\mu_p)^{m-1-k}.$$

Similarly, we have that:

$$\mathbb{E}[FP] = mn(1-\mu_p)(1-Sp)P(R_i = 1|A_{ij} = 0)P(C_j = 1|A_{ij} = 0), \tag{B.5}$$

where

$$P(R_i = 1|A_{ij} = 0) = \sum_{k=0}^{n-1} Se(n, k)\binom{n-1}{k}(\mu_p)^k(1-\mu_p)^{n-1-k}, \text{ and}$$
$$P(C_j = 1|A_{ij} = 0) = \sum_{k=0}^{m-1} Se(m, k)\binom{m-1}{k}(\mu_p)^k(1-\mu_p)^{m-1-k}.$$

Lastly, the expected number of tests is given by:

$$\begin{aligned}
\mathbb{E}[T] =& m + n + mnP(R_i = 1, C_j = 1) \\
=& m + n + mn\Big[\mu_p P(R_i = 1, C_j = 1|A_{ij} = 1) + (1-\mu_p)P(R_i = 1, C_j = 1|A_{ij} = 0)\Big] \\
=& m + n + mn\Big[\mu_p P(R_i = 1|A_{ij} = 1)P(C_j = 1|A_{ij} = 1) + (1-\mu_p)P(R_i = 1|A_{ij} = 0)P(C_j = 1|A_{ij} = 0)\Big].
\end{aligned}$$

B.3 Case Study: Model Validation and Calibration of the Sensitivity Function Parameter

To validate our model, we evaluate the probability of releasing an HIV-infected blood donation into the blood supply (referred to as the *residual risk* in the transfusion literature) in the United States considering the current practice, i.e., the two-tier Dorfman testing scheme in pools of size 16 using the HIV nucleic acid test (NAT) [40]. We use the sensitivity function utilized in the case study of Section 3.4, given by $Se(n,k) = 1-Sp+(Se(1,1)+Sp-1)(k/n)^{\alpha}$, $\forall k \leq n; k, n \in \mathbb{Z}^{+}$, and calibrate it using published data [33, 106, 119, 138, 139], with individual test sensitivity and specificity values of 0.992 and 0.988 [22], respectively, leading to a calibration parameter of $\alpha = 0.00263$ (see [6] for details). For the mean prevalence rate, we consider 0.00278%, which is representative of the HIV prevalence rate in the United States among the donor population [143].

Using these data, our Monte Carlo simulation provides an estimate of the residual risk per 1,000,000 donations, with a point estimate and a 95% confidence interval given by 0.66 (0.61-0.72) per million, which is in line with published work that reports the residual risk for HIV infection in the United States, e.g., [143]. In summary, the predictions of our model, with our calibrated sensitivity function, are consistent with published data.

To obtain the calibration parameter for the Ligase Chain Reaction test for chlamydia, we use data from [82], which specifies that the test has perfect sensitivity for a pool of size 4. Thus, we assume that individual testing also has perfect sensitivity (i.e., $Se(1,1) = 1.0$). Also, we assume that the test's specificity, Sp, remains constant with pool size, and we set it to the specificity of the test with a pool of size 4 provided in [82], i.e., $Sp = 0.98$. Finally, to determine parameter α, we use the results of [82], which reports the sensitivity for a pool

of size 10 and the mean prevalence rate of chlamydia, μ_p. We calculate α by conditioning on the number of infected subjects in the pool and matching our results to those in [82], that is, α is chosen such that the following identity holds:

$$Se(n) = \frac{1}{1-(1-\mu_p)^n} \sum_{k=1}^{n} Se(n,k) \binom{n}{k} (\mu_p)^k (1-\mu_p)^{n-k}.$$

Appendix C

Appendix for Chapter 4

C.1 Mathematical Proofs

Proof of Theorem 4.1 (a). We prove the result by showing that for any unordered partition, one can reduce or maintain the values of all three performance measures (i.e., $\mathbb{E}[FN]$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$) by converting the partition into an ordered one. Towards this end, suppose, to the contrary, that the optimal partition, $\mathbf{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$[1], does not follow an ordered partition of S. Then, there must exist two groups, Ω_i^* and Ω_j^*, $i, j \in \{1, \cdots, g\} : i \neq j$, such that:

(i) $\min_{m \in \Omega_i^*} p^m < \max_{m \in \Omega_j^*} p^m$, and **(ii)** $\max_{m \in \Omega_i^*} p^m > \min_{m \in \Omega_j^*} p^m$.

Assume, without loss of generality, that $n_i \leq n_j$.

Case I: $n_i = 1$: Since $n_i = 1$, then it must be true that $n_j > 1$[2]. Due to conditions **(i)** and **(ii)** the single subject in group Ω_i^*, denoted with index k_i, has a lower risk than the subject

[1] If $g = 1$, then all subjects are in one group, and hence it is an ordered partition.

[2] If both groups are of size 1, then they will follow an ordered partition.

with the maximum risk in group Ω_j^*, denoted with index k_j (i.e., $p^{k_i} < p^{k_j}$). Let $\Psi_i = \{k_i\}$ and let $\Psi_j = \{k_j\}$, and define a new partition, $\hat{\mathbf{\Omega}} = \{\hat{\Omega}_1, \cdots, \hat{\Omega}_g\}$, where subjects in Ψ_i are interchanged with subjects in Ψ_j, that is, $\hat{\Omega}_i = (\Omega_i^* \setminus \Psi_i) \cup \Psi_j$, $\hat{\Omega}_j = (\Omega_j^* \setminus \Psi_j) \cup \Psi_i$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l \in \{1, \cdots, g\} : l \neq i, j$. As such, we have that:

$$\prod_{m \in \Omega_j^*} (1 - p^m) < \prod_{m \in \hat{\Omega}_j} (1 - p^m) \Rightarrow n_j \prod_{m \in \Omega_j^*} (1 - p^m) < n_j \prod_{m \in \hat{\Omega}_j} (1 - p^m).$$

In what follows, we will show that $\hat{\mathbf{\Omega}}$ reduces or maintains the value of all performance measures.

(a) **Expected number of false negatives ($\mathbb{E}[FN]$):**

We have that:

$$\begin{aligned}
\mathbb{E}[FN(\mathbf{\Omega}^*)] &= \sum_{l: l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)p^{k_i} + (1 - Se^2) \sum_{m \in \Omega_j^*} p^m, \text{ and} \\
\mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= \sum_{l: l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)p^{k_j} + (1 - Se^2) \sum_{m \in \hat{\Omega}_j} p^m. \\
\Rightarrow \mathbb{E}[FN(\mathbf{\Omega}^*)] - \mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= -(1 - Se)(p^{k_j} - p^{k_i}) + (1 - Se^2)(p^{k_j} - p^{k_i}) \\
&= Se(1 - Se)(p^{k_j} - p^{k_i}) \geq 0.
\end{aligned}$$

As such, $\mathbb{E}[FN(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FN(\mathbf{\Omega}^*)]$.

(b) **Expected number of false positives ($\mathbb{E}[FP]$):**

We have that:

$$\mathbb{E}[FP(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-p^{k_i}) \\ + (1-Sp)Se \sum_{m\in\Omega_j^*}(1-p^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_j^*}(1-p^m), \text{ and}$$

$$\mathbb{E}[FP(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-p^{k_j}) \\ + (1-Sp)Se \sum_{m\in\hat{\Omega}_j}(1-p^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-p^m).$$

$$\Rightarrow \mathbb{E}[FP(\mathbf{\Omega}^*)] - \mathbb{E}[FP(\hat{\mathbf{\Omega}})] = (1-Sp)(1-Se)(p^{k_j}-p^{k_i}) \\ + n_j(1-Sp)(Se+Sp-1)\left[\prod_{m\in\hat{\Omega}_j}(1-p^m) - \prod_{m\in\Omega_j^*}(1-p^m)\right] > 0.$$

As such, $\mathbb{E}[FP(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$.

(c) **Expected number of tests ($\mathbb{E}[T]$):**

We have that:

$$\mathbb{E}[T(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j}\mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_j^*}(1-p^m)\Big), \text{ and}$$

$$\mathbb{E}[T(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j}\mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-p^m)\Big).$$

$$\Rightarrow \mathbb{E}[T(\mathbf{\Omega}^*)] - \mathbb{E}[T(\hat{\mathbf{\Omega}})] = n_j(Se+Sp-1)\left[\prod_{m\in\hat{\Omega}_j}(1-p^m) - \prod_{m\in\Omega_j^*}(1-p^m)\right] > 0.$$

As such, $\mathbb{E}[T(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[T(\mathbf{\Omega}^*)]$.

Thus, by converting groups i and j into an ordered partition, all measures are either maintained or reduced, implying that there exists an optimal partition, which is ordered.

Case II: $n_i > 1$: By Remark 4.2, when the two group sizes are greater than one, the expected number of false negatives resulting from these groups is constant. As such, one can convert any unordered partition into an ordered one without impacting the expected number of false negatives. Thus, we proceed by showing that the remaining performance measures (i.e., $\mathbb{E}[FP]$ and $\mathbb{E}[T]$) are reduced or maintained. By conditions **(i)** and **(ii)**, there exist $\phi \subset \Psi_i \subseteq \Omega_i^*$ and $\phi \subset \Psi_j \subseteq \Omega_j^*$ such that $|\Psi_i| = |\Psi_j|$ and when Ψ_i and Ψ_j are interchanged the resulting set of groups will follow an ordered partition in which the group with the smaller size contains the lowest risk subjects, while the group with the larger size contains the highest risk subjects. We have that:

$$\prod_{m \in \Psi_j} (1 - p^m) - \prod_{m \in \Psi_i} (1 - p^m) > 0 \tag{C.1}$$

Sub-case I: $n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - p^m) > n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - p^m)$

Define a new partition, $\hat{\mathbf{\Omega}} = \{\hat{\Omega}_1, \cdots, \hat{\Omega}_g\}$, where subjects in Ψ_i are interchanged with subjects in Ψ_j, that is, $\hat{\Omega}_i = (\Omega_i^* \setminus \Psi_i) \cup \Psi_j$, $\hat{\Omega}_j = (\Omega_j^* \setminus \Psi_j) \cup \Psi_i$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l \in \{1, \cdots, g\} : l \neq i, j$. In what follows, we will show that partition $\hat{\mathbf{\Omega}}$ reduces or maintains the value of all performance measures. Multiplying the condition imposed in the sub-case, i.e.,

$$n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - p^m) > n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - p^m),$$

by Eq. (C.1), and expanding and rearranging gives:

$$n_i \prod_{m\in\hat{\Omega}_i}(1-p^m) + n_j \prod_{m\in\hat{\Omega}_j}(1-p^m) > n_i \prod_{m\in\Omega_i^*}(1-p^m) + n_j \prod_{m\in\Omega_j^*}(1-p^m).$$

(a) **Expected number of false positives ($\mathbb{E}[FP]$):**

We have that:

$$\begin{aligned}\mathbb{E}[FP(\boldsymbol{\Omega}^*)] = &\sum_{l:l\neq i,j}\mathbb{E}[FP_l] + (1-Sp)Se\sum_{m\in\Omega_i^*}(1-p^m) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_i^*}(1-p^m)\\ &+ (1-Sp)Se\sum_{m\in\Omega_j^*}(1-p^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_j^*}(1-p^m), \text{ and}\\ \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] = &\sum_{l:l\neq i,j}\mathbb{E}[FP_l] + (1-Sp)Se\sum_{m\in\hat{\Omega}_i}(1-p^m) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-p^m)\\ &+ (1-Sp)Se\sum_{m\in\hat{\Omega}_j}(1-p^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-p^m).\end{aligned}$$

Noting that,

$$\sum_{m\in\Omega_i^*\cup\Omega_j^*}(1-p^m) = \sum_{m\in\hat{\Omega}_i\cup\hat{\Omega}_j}(1-p^m),$$

and subtracting the two gives:

$$\frac{\mathbb{E}[FP(\boldsymbol{\Omega}^*)] - \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})]}{(1-Sp)(Se+Sp-1)} = n_i\prod_{m\in\hat{\Omega}_i}(1-p^m) + n_j\prod_{m\in\hat{\Omega}_j}(1-p^m) - n_i\prod_{m\in\Omega_i^*}(1-p^m) - n_j\prod_{m\in\Omega_j^*}(1-p^m) > 0.$$

As such, $\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[FP(\boldsymbol{\Omega}^*)]$.

(b) **Expected number of tests ($\mathbb{E}[T]$):**

We have that:

$$\mathbb{E}[T(\boldsymbol{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_i\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_i^*}(1-p^m)\Big) + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_j^*}(1-p^m)\Big), \text{ and}$$

$$\mathbb{E}[T(\hat{\boldsymbol{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_i\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-p^m)\Big) + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-p^m)\Big).$$

Subtracting the two gives:

$$\frac{\mathbb{E}[T(\boldsymbol{\Omega}^*)] - \mathbb{E}[T(\hat{\boldsymbol{\Omega}})]}{(Se+Sp-1)} = n_i\prod_{m\in\hat{\Omega}_i}(1-p^m) + n_j\prod_{m\in\hat{\Omega}_j}(1-p^m) - n_i\prod_{m\in\Omega_i^*}(1-p^m) - n_j\prod_{m\in\Omega_j^*}(1-p^m) > 0.$$

As such, $\mathbb{E}[T(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[T(\boldsymbol{\Omega}^*)]$.

Thus, by converting groups i and j into an ordered partition, all measures are either maintained or reduced, implying that there exists an optimal partition, which is ordered.

Sub-case II: $n_i\prod_{m\in\Omega_i\setminus\Psi_i}(1-p^m) \leq n_j\prod_{m\in\Omega_j\setminus\Psi_j}(1-p^m)$

Due to conditions **(i)** and **(ii)**, there exist $\phi \subset Z_i \subseteq \Omega_i$ and $\phi \subset Z_j \subseteq \Omega_j$ such that $|Z_i| = |Z_j|$, and when Z_i and Z_j are interchanged the resulting set of groups will follow an ordered partition in which the group with the smaller size contains the highest risk subjects, while the group with the larger size contains the lowest risk subjects. Define a new partition, $\tilde{\boldsymbol{\Omega}} = \{\tilde{\Omega}_1, \cdots, \tilde{\Omega}_g\}$, where subjects in Z_i are interchanged with subjects in Z_j, that is, $\tilde{\Omega}_i = (\Omega_i^* \setminus Z_i) \cup Z_j$, $\tilde{\Omega}_j = (\Omega_j^* \setminus Z_j) \cup Z_i$, and $\tilde{\Omega}_l = \Omega_l^*$ for all $l \in \{1, \cdots, g\} : l \neq i, j$. In what follows, we will show that partition $\tilde{\boldsymbol{\Omega}}$ reduces or maintains the value of all performance

measures. By the condition imposed in the sub-case, i.e.,

$$n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - p^m) \leq n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - p^m),$$

and Eq. (C.1) we get:

$$n_i \prod_{m \in \Omega_i} (1 - p^m) \leq n_j \prod_{m \in \Omega_j} (1 - p^m). \tag{C.2}$$

By definitions of Z_i and Z_j, we have that:

$$\prod_{m \in Z_i} (1 - p^m) - \prod_{m \in Z_j} (1 - p^m) > 0. \tag{C.3}$$

From Eq. (C.2) we have that:

$$n_i \prod_{m \in \Omega_i \setminus Z_i} (1 - p^m) \prod_{m \in Z_i} (1 - p^m) \leq n_j \prod_{m \in \Omega_j \setminus Z_j} (1 - p^m) \prod_{m \in Z_j} (1 - p^m). \tag{C.4}$$

Then, by Eq.s (C.3) and (C.4), it must be true that:

$$n_i \prod_{m \in \Omega_i \setminus Z_i} (1 - p^m) < n_j \prod_{m \in \Omega_j \setminus Z_j} (1 - p^m). \tag{C.5}$$

Multiplying Eq. (C.5) by Eq. (C.3), expanding and rearranging gives:

$$n_i \prod_{m \in \tilde{\Omega}_i} (1 - p^m) + n_j \prod_{m \in \tilde{\Omega}_j} (1 - p^m) > n_i \prod_{m \in \Omega_i} (1 - p^m) + n_j \prod_{m \in \Omega_j} (1 - p^m).$$

Following a similar methodology to that of Sub-case I, one can show that $\mathbb{E}[FP(\tilde{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$ and $\mathbb{E}[T(\tilde{\mathbf{\Omega}})] \leq \mathbb{E}[T(\mathbf{\Omega}^*)]$. As such, for all possible cases, we are always able to construct an ordered partition that reduces or maintains the values of all performance measures, hence concluding the proof. □

Proof of Theorem 4.1 (b). We prove the result by showing that if, in the optimal ordered partition, subject m, with risk p^m, is individually tested, and there exist a subject, having a risk higher than p^m, that is tested in a group, one can always construct an alternative partition that reduces all three performance measures (i.e., $\mathbb{E}[FN]$, $\mathbb{E}[FP]$, and $\mathbb{E}[T]$). Towards this end, suppose, to the contrary, that the optimal partition, $\mathbf{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$, is to test subject m, in group i, individually and there exists a group, $j : j \neq i$, with $n_j > 1$ and all of its subjects have a risk higher than p^m. Let k denote the index of the subject with the highest risk in group j, then $p^k > p^m$. Define a new partition, $\hat{\mathbf{\Omega}} = \{\hat{\Omega}_1, \cdots, \hat{\Omega}_g\}$, where subject m and k are interchanged, i.e., $\hat{\Omega}_i = \{k\}$, $\hat{\Omega}_j = (\Omega_j^* \setminus \{k\}) \cup \{m\}$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l \in \{1, \cdots, g\} : l \neq i, j$. We have that:

$$\prod_{l \in \Omega_j^*} (1 - p^l) < \prod_{l \in \hat{\Omega}_j} (1 - p^l).$$

In what follows, we will show that partition $\hat{\mathbf{\Omega}}$ reduces or maintains the value of all performance measures.

(a) **Expected number of false negatives ($\mathbb{E}[FN]$):**

We have that:

$$\begin{aligned}
\mathbb{E}[FN(\mathbf{\Omega}^*)] &= \sum_{l: l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)p^m + (1 - Se^2) \sum_{l \in \Omega_j^*} p^l, \text{ and} \\
\mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= \sum_{l: l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)p^k + (1 - Se^2) \sum_{l \in \hat{\Omega}_j} p^l. \\
\Rightarrow \mathbb{E}[FN(\mathbf{\Omega}^*)] - \mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= -(1 - Se)(p^k - p^m) + (1 - Se^2)(p^k - p^m), \\
&= Se(1 - Se)(p^k - p^m) \geq 0.
\end{aligned}$$

As such, $\mathbb{E}[FN(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FN(\mathbf{\Omega}^*)]$.

(b) **Expected number of false positives ($\mathbb{E}[FP]$):**

We have that:

$$\begin{aligned}
\mathbb{E}[FP(\boldsymbol{\Omega}^*)] &= \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-p^m) \\
&\quad + (1-Sp)Se\sum_{l\in\Omega_j^*}(1-p^l) - n_j(1-Sp)(Se+Sp-1)\prod_{l\in\Omega_j^*}(1-p^l), \text{ and} \\
\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] &= \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-p^k) \\
&\quad + (1-Sp)Se\sum_{l\in\hat{\Omega}_j}(1-p^l) - n_j(1-Sp)(Se+Sp-1)\prod_{l\in\hat{\Omega}_j}(1-p^l).
\end{aligned}$$

$$\begin{aligned}
\Rightarrow \mathbb{E}[FP(\boldsymbol{\Omega}^*)] - \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] =& (1-Sp)(1-Se)(p^k-p^m) \\
&+ n_j(1-Sp)(Se+Sp-1)\left[\prod_{l\in\hat{\Omega}_j}(1-p^l) - \prod_{l\in\Omega_j^*}(1-p^l)\right] \geq 0.
\end{aligned}$$

As such, $\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[FP(\boldsymbol{\Omega}^*)]$.

(c) **Expected number of tests ($\mathbb{E}[T]$):**

We have that:

$$\begin{aligned}
\mathbb{E}[T(\boldsymbol{\Omega}^*)] &= \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{l\in\Omega_j^*}(1-p^l)\Big), \text{ and} \\
\mathbb{E}[T(\hat{\boldsymbol{\Omega}})] &= \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{l\in\hat{\Omega}_j}(1-p^l)\Big).
\end{aligned}$$

$$\begin{aligned}
\Rightarrow \mathbb{E}[T(\boldsymbol{\Omega}^*)] - \mathbb{E}[T(\hat{\boldsymbol{\Omega}})] =& n_j(Se+Sp-1)\left[\prod_{l\in\hat{\Omega}_j}(1-p^l) - \prod_{l\in\Omega_j^*}(1-p^l)\right] \geq 0.
\end{aligned}$$

As such, $\mathbb{E}[T(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[T(\boldsymbol{\Omega}^*)]$.

As a result, we are always able to construct an ordered partition that reduces or maintains the values of all performance measures whenever the statement given in the theorem does not hold, hence concluding the proof. □

Proof of Theorem 4.2 (1a). We prove the result by showing that if a group of size greater or equal to four exists, then one can always reduce the objective function by placing the two highest risk subjects in a separate group. Towards this end, suppose, to the contrary, that the optimal partition, $\mathbf{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$, has a group, Ω_i^*, with $n_i \geq 4$, and let m and k denote the indices of the two highest risk subjects within the group. Consider a new partition, $\hat{\mathbf{\Omega}}$, that is identical to $\mathbf{\Omega}^*$ except for placing subjects m and k into a separate group. Note that, due to Remark 4.2, the expected number of false negatives under both partitions is equal, thus we proceed by showing that partition $\hat{\mathbf{\Omega}}$ reduces the expected number of false positives over $\mathbf{\Omega}^*$. We have that:

$$\begin{aligned}
\mathbb{E}[FP(\mathbf{\Omega}^*)] &= \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se\sum_{l\in\Omega_i^*}(1-p^l) - n_i(1-Sp)(Se+Sp-1)\prod_{l\in\Omega_i^*}(1-p^l), \text{ and} \\
\mathbb{E}[FP(\hat{\mathbf{\Omega}})] &= \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se\sum_{l\in\hat{\Omega}_i}(1-p^l) - (n_i-2)(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-p^l) \\
&\quad + (1-Sp)Se(2-p^m-p^k) - 2(1-Sp)(Se+Sp-1)(1-p^m)(1-p^k).
\end{aligned}$$

Subtracting the two gives:

$$\begin{aligned}
\frac{\mathbb{E}[FP(\mathbf{\Omega}^*)] - \mathbb{E}[FP(\hat{\mathbf{\Omega}})]}{(1-Sp)(Se+Sp-1)} &= \Big[n_i - 2 - n_i(1-p^m)(1-p^k)\Big]\prod_{m\in\hat{\Omega}_i}(1-p^l) + 2(1-p^m)(1-p^k) \\
&= \Big[n_i - 2 - (n_i-2+2)(1-p^m)(1-p^k)\Big]\prod_{m\in\hat{\Omega}_i}(1-p^l) + 2(1-p^m)(1-p^k) \\
&= \Big[(n_i-2)\big(1-(1-p^m)(1-p^k)\big)\Big]\prod_{m\in\hat{\Omega}_i}(1-p^l) - 2\prod_{l\in\Omega_i^*}(1-p^l) + 2(1-p^m)(1-p^k).
\end{aligned}$$

Since $n_i \geq 4$, then $\Big[(n_i-2)\big(1-(1-p^m)(1-p^k)\big)\Big]\prod_{m\in\hat{\Omega}_i}(1-p^l) \geq 0$. As such, we have that:

$$\begin{aligned}\frac{\mathbb{E}[FP(\boldsymbol{\Omega}^*)]-\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})]}{(1-Sp)(Se+Sp-1)} \geq & -2\prod_{l\in\Omega_i^*}(1-p^l)+2(1-p^m)(1-p^k)\\ =&2(1-p^m)(1-p^k)\left(1-\prod_{m\in\hat{\Omega}_i}(1-p^l)\right)\geq 0.\end{aligned}$$

As such, $\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[FP(\boldsymbol{\Omega}^*)]$. □

Proof of Theorem 4.2 (1b). By Theorem 4.2 (3a), the optimal partition can only have group sizes of either one, two, or three. Also, by Theorem 4.1 (b) one cannot have an individual test on a subject whose risk is lower than the risk of all subjects in a group. As such, to prove the result of the theorem, it is sufficient to show that a group of size two cannot contain subjects whose risk are all lower than the risk of subjects within a group of size three. We prove this by showing that if the statement is not true, one can always construct an alternative partition, by removing the lowest risk subject in the group of size three and placing it in the group of size two, that reduces all performance measures. Towards this end, suppose, by contradiction, that the optimal partition, $\boldsymbol{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$, has groups of size two and three, respectively denoted by Ω_i^* and Ω_j^*, where $\max_{m\in\Omega_i^*}\{p^m\} \leq \min_{m\in\Omega_j^*}\{p^m\}$. Let m_1 and m_2 denote the risk of the two subjects in Ω_i^*, and k_1, k_2, and k_3 denote the risk of the three subjects in Ω_k^*, with $p^{m_1} \leq p^{m_2} \leq p^{k_1} \leq p^{k_2} \leq p^{k_3}$. Consider a new partition, $\hat{\boldsymbol{\Omega}} = \{\hat{\Omega}_1, \cdots, \hat{\Omega}_g\}$, with $\hat{\Omega}_i = \Omega_i^* \cup p^{k_1}$, $\hat{\Omega}_j = \Omega_j^* \setminus \{p^{k_1}\}$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l \in \{1, \cdots, g\} : l \neq i, j$. Note that, by Remark 4.2, this change to the partition will not impact the expected number of false negatives. As such, in what follows, we will show that partition $\hat{\boldsymbol{\Omega}}$ reduces the value of the expected number of false positives.

We have that:

$$\mathbb{E}[FP(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se \sum_{l\in\Omega_i^*\cup\Omega_j^*} (1-p^l) - 2(1-Sp)(Se+Sp-1)(1-p^{m_1})(1-p^{m_2})$$
$$- 3(1-Sp)(Se+Sp-1)(1-p^{k_1})(1-p^{k_2})(1-p^{k_3}), \text{ and}$$
$$\mathbb{E}[FP(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se \sum_{l\in\hat{\Omega}_i\cup\hat{\Omega}_j} (1-p^l) - 2(1-Sp)(Se+Sp-1)(1-p^{k_2})(1-p^{k_3})$$
$$- 3(1-Sp)(Se+Sp-1)(1-p^{m_1})(1-p^{m_2})(1-p^{k_1}).$$

Subtracting the two gives:

$$\frac{\mathbb{E}[FP(\mathbf{\Omega}^*)] - \mathbb{E}[FP(\hat{\mathbf{\Omega}})]}{(1-Sp)(Se+Sp-1)} = \left[(1-p^{m_1})(1-p^{m_2}) - (1-p^{k_2})(1-p^{k_3})\right](1-3p^{k_1}).$$

Noting that $(1-p^{m_1})(1-p^{m_2})-(1-p^{k_2})(1-p^{k_3}) \geq 0$, and $1-3p^{k_1} \geq 0$ (since, by the condition imposed in the theorem, we have $p^{k_1} \leq p^N \leq 1/3$), we get that $\mathbb{E}[FP(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$, concluding the proof. □

Proof of Theorem 4.2 (2). The result trivially follows by noting that individually testing subjects leads to a smaller expected number of false negatives. □

Proof of Theorem 4.2 (3). We prove the result by showing that if more than one subject is individually tested, then one can always reduce the objective function by combining the two subjects into a single group. Towards this end, suppose, to the contrary, that the optimal partition, $\mathbf{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$, has two individual tests, and let m and k denote the indices of these two subjects, which are respectively in groups i and j. Consider a new partition, $\hat{\mathbf{\Omega}}$, that is identical to $\mathbf{\Omega}^*$ except for combining the two subjects

m and k into a single group of size two. We have that:

$$\mathbb{E}[FP(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-p^m) + (1-Sp)(1-p^k), \text{ and}$$

$$\mathbb{E}[FP(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se(2-p^m-p^k) - n_j(1-Sp)(Se+Sp-1)(1-p^m)(1-p^k).$$

$$\Rightarrow \mathbb{E}[FP(\mathbf{\Omega}^*)] - \mathbb{E}[FP(\hat{\mathbf{\Omega}})] = (1-Sp)(1-Se)(2-p^m-p^k) + n_j(1-Sp)(Se+Sp-1)(1-p^m)(1-p^k) \geq 0.$$

Thus, $\mathbb{E}[FP(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$, which concludes the proof. □

Proof of Theorem 4.3. We prove the result by showing that if the condition of the theorem is satisfied and more than one subject is individually tested, then one can always reduce the expected number of tests by combining the two subjects into a single group. Towards this end, suppose, to the contrary, that the optimal partition, $\mathbf{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g \in \{2, \cdots, N\}$, has two individual tests, which, by Theorem 4.1 (b), implies that the two highest risk subjects (i.e., subjects $N-1$ and N) must be individually tested. Consider a new partition, $\hat{\mathbf{\Omega}}$, that is identical to $\mathbf{\Omega}^*$ except that subjects $N-1$ and N are combined into a single group of size two. We have that:

$$\mathbb{E}[T(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2, \text{ and}$$

$$\mathbb{E}[T(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 1 + 2\Big(Se - (Se+Sp-1)(1-p^{N-1})(1-p^N)\Big).$$

$$\Rightarrow \mathbb{E}[T(\mathbf{\Omega}^*)] - \mathbb{E}[T(\hat{\mathbf{\Omega}})] = 1 - 2Se + 2(Se+Sp-1)(1-p^{N-1})(1-p^N).$$

By the condition imposted in the theorem, i.e.,

$$p^N \leq 1 - \left(\frac{Se-0.5}{Se+Sp-1}\right)^{1/2},$$

and the fact that $p^{N-1} \leq p^N$, we get that:

$$(1-p^{N-1})(1-p^N) \geq (1-p^N)^2 \geq \frac{Se-0.5}{Se+Sp-1}.$$
$$\Rightarrow 1-2Se+2(Se+Sp-1)(1-p^{N-1})(1-p^N) \geq 0,$$

leading to $\mathbb{E}[T(\mathbf{\Omega}^*)] \geq \mathbb{E}[T(\hat{\mathbf{\Omega}})]$ and concluding the proof. □

Proof of Theorem 4.5. When $\lambda = 1$, the α-fairness objective function is only a function of $\mathbb{E}[FN]$. Then, by Remark 4.2, the objective function depends only on the partition of grouped subjects and individually tested subjects, i.e., sets Ω^G and Ω^I. Let m^*_α denote the index of the lowest risk subject that is individually tested. We next show that for all $\alpha_1, \alpha_2 \geq 0 : \alpha_1 > \alpha_2$, $m^*_{\alpha_1} = m^*_{\alpha_2}$. Suppose, to the contrary, that $m^*_{\alpha_1} \neq m^*_{\alpha_2}$.

Case i: $m^*_{\alpha_1} < m^*_{\alpha_2}$

We know that both partitions are feasible to both cases, as the constraint is independent of α. As such, by using the optimal partition of α_2 for the case of α_1, one will have a feasible solution with a lower objective function value (since individually testing more subjects reduces the objective function value), leading to a contradiction.

Case i: $m^*_{\alpha_1} > m^*_{\alpha_2}$

Follows similarly to that of Case i.

Hence the proof is completed. □

Appendix D

Appendix for Chapter 5

D.1 Mathematical Proofs

Proof of Property 5.1. Consider the **EM** objective function, given by:

$$\sum_{i=1}^{g} \mathbb{E}_{\tilde{\boldsymbol{P}}}\Big[\mathbb{E}_{\boldsymbol{\Xi}}\Big[\lambda_1 \mathbb{E}[FN_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}] + \lambda_2 \mathbb{E}[FP_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}] + (1-\lambda_1-\lambda_2)\mathbb{E}[T_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}]\Big]\Big].$$

Next, we show that each term in the objective function reduces to the case when $\boldsymbol{\Xi} = \mathbf{0}$.

$$\mathbb{E}_{\boldsymbol{\Xi}}\Big[\mathbb{E}[FN_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}]\Big] = \begin{cases} (1-Se)\sum_{m\in\Omega_i} \mathbb{E}_{\Xi^m}\Big[t\big(\tilde{P}^{(m)}, \Xi^m\big)\Big], & \text{if } n_i = 1, \\ (1-Se^2)\sum_{m\in\Omega_i} \mathbb{E}_{\Xi^m}\Big[t\big(\tilde{P}^{(m)}, \Xi^m\big)\Big], & \text{otherwise,} \end{cases}$$

$$= \begin{cases} (1-Se)\sum_{m\in\Omega_i} \tilde{P}^{(m)}, & \text{if } n_i = 1 \ \Big(\text{by assumption that } \mathbb{E}_{\Xi^m}\big[t\big(\tilde{P}^m, \Xi^m\big)\big] = \tilde{P}^m\Big), \\ (1-Se^2)\sum_{m\in\Omega_i} \tilde{P}^{(m)}, & \text{otherwise,} \end{cases}$$

$$= \mathbb{E}[FN_i(\Omega_i)|\boldsymbol{\Xi} = \mathbf{0}, \tilde{\boldsymbol{P}}],$$

$$\mathbb{E}_{\boldsymbol{\Xi}}\Big[\mathbb{E}[FP_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}]\Big] = \begin{cases} (1-Sp)\sum_{m\in\Omega_i}\Big(1 - \mathbb{E}_{\Xi^m}\Big[t\big(\tilde{P}^{(m)}, \Xi^m\big)\Big]\Big), & \text{if } n_i = 1, \\ (1-Sp)Se\sum_{m\in\Omega_i}\Big(1 - \mathbb{E}_{\Xi^m}\Big[t\big(\tilde{P}^{(m)}, \Xi^m\big)\Big]\Big) & \\ -n_i(1-Sp)(Se+Sp-1)\mathbb{E}_{\Xi^m}\Big[\prod_{m\in\Omega_i}\Big(1 - t\big(\tilde{P}^{(m)}, \Xi^m\big)\Big)\Big], & \text{otherwise.} \end{cases}$$

Noting that random variables Ξ^m, $m = 1, \cdots, N$, are iid, and that $\mathbb{E}_{\Xi^m}\big[t\big(\tilde{P}^m, \Xi^m\big)\big] = \tilde{P}^m$, we can write:

$$\mathbb{E}_{\boldsymbol{\Xi}}\Big[\mathbb{E}[FP_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}]\Big] = \begin{cases} (1-Sp)\sum_{m\in\Omega_i}\Big(1 - \tilde{P}^{(m)}\Big), & \text{if } n_i = 1, \\ (1-Sp)Se\sum_{m\in\Omega_i}\big(1 - \tilde{P}^{(m)}\big) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_i}\big(1 - \tilde{P}^{(m)}\big), & \text{otherwise.} \end{cases}$$

$$= \mathbb{E}[FP_i(\Omega_i)|\boldsymbol{\Xi} = \mathbf{0}, \tilde{\boldsymbol{P}}].$$

Following a similar logic, it can be shown that $\mathbb{E}_{\boldsymbol{\Xi}}\Big[\mathbb{E}[T_i(\Omega_i)|\boldsymbol{\Xi}, \tilde{\boldsymbol{P}}]\Big] = \mathbb{E}[T_i(\Omega_i)|\boldsymbol{\Xi} = \mathbf{0}, \tilde{\boldsymbol{P}}]$, thus concluding the proof. □

Proof of Theorem 5.1. Part 1.) Suppose, to the contrary, that in an optimal solution to (5.9), denoted by $\boldsymbol{\xi}^*$, there exists a subject, denoted by m, in group i, such that $-\delta < \xi^{m*} < \delta$. In what follows, we show that one can always improve the objective function value to (5.9) by either increasing ξ^{m*} to δ or decreasing ξ^{m*} to $-\delta$. Towards this end, consider an alternative solution, denoted by $\tilde{\boldsymbol{\xi}}$, which is identical to $\boldsymbol{\xi}^*$, with the only exception that $\tilde{\xi}^m = \xi^{m*} + \varepsilon$, for some $|\varepsilon| > 0$.

Case I: $n_i = 1$

By using the expressions in Section 5.3.2, the contribution of group i to the objective function in (5.9) is given by:

$$\begin{aligned} Q_i(\boldsymbol{\xi}^*) =& t\big(\tilde{P}^{(m)}, \xi^{m*}\big)\big[\lambda_1(1-Se) - \lambda_2(1-Sp)\big] + 1 - \lambda_1 - \lambda_2 + \lambda_2(1-Sp), \\ Q_i(\tilde{\boldsymbol{\xi}}) =& t\big(\tilde{P}^{(m)}, \tilde{\xi}^{m}\big)\big[\lambda_1(1-Se) - \lambda_2(1-Sp)\big] + 1 - \lambda_1 - \lambda_2 + \lambda_2(1-Sp). \end{aligned}$$

$$\Rightarrow Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = \Big[t\big(\tilde{P}^{(m)}, \tilde{\xi}^{m}\big) - t\big(\tilde{P}^{(m)}, \xi^{m*}\big)\Big]\big[\lambda_1(1-Se) - \lambda_2(1-Sp)\big].$$

Sub-case I: $\lambda_1(1-Se) \geq \lambda_2(1-Sp)$

Let $\varepsilon = \delta - \xi^{m*} > 0 \Rightarrow \tilde{\xi}^m = \delta$, and hence we get that:

$$Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = \Big[t\big(\tilde{P}^{(m)}, \delta\big) - t\big(\tilde{P}^{(m)}, \xi^{m*}\big)\Big]\big[\lambda_1(1-Se) - \lambda_2(1-Sp)\big] \geq 0,$$

since $\lambda_1(1-Se) - \lambda_2(1-Sp) \geq 0$, $\xi^{m*} < \delta$, and $t(\tilde{p}, \xi)$ is increasing in ξ by assumption.

Sub-case II: $\lambda_1(1-Se) < \lambda_2(1-Sp)$

Let $\varepsilon = -\delta - \xi^{m*} < 0 \Rightarrow \tilde{\xi}^m = -\delta$, and hence we get that:

$$Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = \Big[t\big(\tilde{P}^{(m)}, -\delta\big) - t\big(\tilde{P}^{(m)}, \xi^{m*}\big)\Big]\big[\lambda_1(1-Se) - \lambda_2(1-Sp)\big] \geq 0,$$

since $\lambda_1(1-Se) - \lambda_2(1-Sp) < 0$, $\xi^{m*} > -\delta$, and $t(\tilde{p}, \xi)$ is increasing in ξ by assumption.

Case II: $n_i > 1$

Similarly, by using the expressions in Section 5.3.2, the contribution of group i to the objective function in (5.9) is given by:

$$\begin{aligned}
Q_i(\boldsymbol{\xi}^*) =& \Big[\lambda_2(1-Sp)Se - \lambda_1\big(1-Se^2\big)\Big] \sum_{l\in\Omega_i} \Big(1 - t\big(\tilde{P}^{(l)}, \xi^{l*}\big)\Big) \\
&- n_i(Se+Sp-1)\big[1-\lambda_1-\lambda_2+\lambda_2(1-Sp)\big] \prod_{l\in\Omega_i} \Big(1 - t\big(\tilde{P}^{(l)}, \xi^{l*}\big)\Big) \\
&+ (1-\lambda_1-\lambda_2)(1+n_iSe) + \lambda_1(1-Se^2)n_i, \\
Q_i(\tilde{\boldsymbol{\xi}}) =& \Big[\lambda_2(1-Sp)Se - \lambda_1\big(1-Se^2\big)\Big] \sum_{l\in\Omega_i} \Big(1 - t\big(\tilde{P}^{(l)}, \tilde{\xi}^{l}\big)\Big) \\
&- n_i(Se+Sp-1)\big[1-\lambda_1-\lambda_2+\lambda_2(1-Sp)\big] \prod_{l\in\Omega_i} \Big(1 - t\big(\tilde{P}^{(l)}, \tilde{\xi}^{l}\big)\Big) \\
&+ (1-\lambda_1-\lambda_2)(1+n_iSe) + \lambda_1(1-Se^2)n_i.
\end{aligned}$$

$$\Rightarrow Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big)\Big[t\big(\tilde{P}^{(m)}, \xi^{m*}\big) - t\big(\tilde{P}^{(m)}, \tilde{\xi}^{m}\big)\Big],$$

where

$$h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) = \lambda_2(1-Sp)Se - \lambda_1\big(1-Se^2\big) - n_i(Se+Sp-1)\big[1-\lambda_1-\lambda_2+\lambda_2(1-Sp)\big] \prod_{\substack{l\in\Omega_i \\ l\neq m}} \Big(1 - t\big(\tilde{P}^{(l)}, \tilde{\xi}^{l}\big)\Big).$$

Note that $h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big)$ is independent of both ξ^{m*} and $\tilde{\xi}^m$.

Sub-case I: $h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) \leq 0$

Let $\varepsilon = \delta - \xi^{m*} > 0 \Rightarrow \tilde{\xi}^m = \delta$, and hence we get that:

$$Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) \Big[t\big(\tilde{P}^{(m)}, \xi^{m*}\big) - t\big(\tilde{P}^{(m)}, \delta\big)\Big] \geq 0,$$

since $h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) \leq 0$, $\xi^{m*} < \delta$, and $t(\tilde{p}, \xi)$ is increasing in ξ by assumption.

Sub-case II: $h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) > 0$

Let $\varepsilon = -\delta - \xi^{m*} < 0 \Rightarrow \tilde{\xi}^m = -\delta$, and hence we get that:

$$Q_i(\tilde{\boldsymbol{\xi}}) - Q_i(\boldsymbol{\xi}^*) = h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) \Big[t\big(\tilde{P}^{(m)}, \xi^{m*}\big) - t\big(\tilde{P}^{(m)}, -\delta\big)\Big] \geq 0,$$

since $h\big(\boldsymbol{\xi}^*, \tilde{\boldsymbol{\xi}}\big) > 0$, $\xi^{m*} > -\delta$, and $t(\tilde{p}, \xi)$ is increasing in ξ by assumption.

Hence, in all possible cases, the objective function has been maintained or improved, thus concluding the proof. □

Proof of Theorem 5.1. Part 2.) The proof follows similarly to that of part 1.). However, notice that if $\lambda_1(1 - Se) \geq \lambda_2(1 - Sp)$, then, when $n_i = 1$, Sub-case I is satisfied and the optimal solution is attained at δ. On the other hand, if $n_i > 1$, we have that:

$$\begin{aligned}
\lambda_2(1 - Sp)Se - \lambda_1\big(1 - Se^2\big) &= \lambda_2(1 - Sp)Se - \lambda_1(1 - Se)(1 + Se) \\
&\leq \lambda_2(1 - Sp)Se - \lambda_1(1 - Se)Se \\
&= \big[\lambda_2(1 - Sp) - \lambda_1(1 - Se)\big]Se \leq 0,
\end{aligned}$$

and since

$$n_i(Se+Sp-1)\big[1-\lambda_1-\lambda_2+\lambda_2(1-Sp)\big]\prod_{\substack{l\in\Omega_i\\ l\neq m}}\Big(1-t\big(P^{(l)},\tilde{\xi}^l\big)\Big)\geq 0,$$

we get that $h\big(\boldsymbol{\xi}^*,\tilde{\boldsymbol{\xi}}\big)\leq 0$. Hence, Sub-case I is satisfied and the optimal solution is attained at δ, concluding the proof. □

Proof of Theorem 5.2. We prove the result by showing that for any risk vector realization, any unordered testing scheme can be converted into an ordered testing scheme while reducing or maintaining the values of all three performance measures in the objective function. We only prove the result for Problem **EM**, as the proof for Problem **RM** follows similarly, with the only difference being that the entire risk vector is multiplied by $1+\delta$. Towards this end, consider an estimated risk vector realization, $\tilde{\boldsymbol{p}}$, and suppose, to the contrary, that the optimal testing scheme, $\boldsymbol{\Omega}^*=\{\Omega_1^*,\cdots,\Omega_g^*\}$, for some $g=2,\cdots,N$ [1], is not an ordered testing scheme. Then, there must exist two groups, Ω_i^* and Ω_j^*, $i,j=1,\cdots,g:i\neq j$, such that:

(i) $\min\limits_{m\in\Omega_i^*}\tilde{p}^m<\max\limits_{m\in\Omega_j^*}\tilde{p}^m$, and **(ii)** $\max\limits_{m\in\Omega_i^*}\tilde{p}^m>\min\limits_{m\in\Omega_j^*}\tilde{p}^m$.

Assume, without loss of generality, that $n_i\leq n_j$.

Case I: $n_i=1$:

Since $n_i=1$, then it must be true that $n_j>1$[2]. Due to conditions **(i)** and **(ii)** the single subject in group Ω_i^*, denoted with index k_i, has a lower risk than the subject with the maximum risk in group Ω_j^*, denoted with index k_j (i.e., $\tilde{p}^{k_i}<\tilde{p}^{k_j}$). Let $\Psi_i=\{k_i\}$ and let $\Psi_j=\{k_j\}$, and define a new testing scheme, $\hat{\boldsymbol{\Omega}}=\{\hat{\Omega}_1,\cdots,\hat{\Omega}_g\}$, where subjects in Ψ_i are

[1] If $g=1$, then all subjects are in one group, and hence it is an ordered testing scheme.

[2] If both groups are of size 1, then they will follow an ordered testing scheme.

interchanged with subjects in Ψ_j, that is, $\hat{\Omega}_i = (\Omega_i^* \setminus \Psi_i) \cup \Psi_j$, $\hat{\Omega}_j = (\Omega_j^* \setminus \Psi_j) \cup \Psi_i$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l = 1, \cdots, g : l \neq i, j$. As such, we have that:

$$\prod_{m \in \Omega_j^*} (1 - \tilde{p}^m) < \prod_{m \in \hat{\Omega}_j} (1 - \tilde{p}^m) \Rightarrow n_j \prod_{m \in \Omega_j^*} (1 - \tilde{p}^m) < n_j \prod_{m \in \hat{\Omega}_j} (1 - \tilde{p}^m).$$

In what follows, we will show that $\hat{\mathbf{\Omega}}$ reduces or maintains the value of all performance measures.

(a) **Expected number of false negatives**

We have that:

$$\begin{aligned}
\mathbb{E}[FN(\mathbf{\Omega}^*)] &= \sum_{l:l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)\tilde{p}^{k_i} + (1 - Se^2) \sum_{m \in \Omega_j^*} \tilde{p}^m, \text{ and} \\
\mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= \sum_{l:l \neq i,j} \mathbb{E}[FN_l] + (1 - Se)\tilde{p}^{k_j} + (1 - Se^2) \sum_{m \in \hat{\Omega}_j} \tilde{p}^m. \\
\Rightarrow \mathbb{E}[FN(\mathbf{\Omega}^*)] - \mathbb{E}[FN(\hat{\mathbf{\Omega}})] &= -(1 - Se)(\tilde{p}^{k_j} - \tilde{p}^{k_i}) + (1 - Se^2)(\tilde{p}^{k_j} - \tilde{p}^{k_i}) \\
&= Se(1 - Se)(\tilde{p}^{k_j} - \tilde{p}^{k_i}) \geq 0.
\end{aligned}$$

As such, $\mathbb{E}[FN(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FN(\mathbf{\Omega}^*)]$.

(b) **Expected number of false positives**

We have that:

$$\mathbb{E}[FP(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-\tilde{p}^{k_i}) + (1-Sp)Se \sum_{m\in\Omega_j^*}(1-\tilde{p}^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_j^*}(1-\tilde{p}^m), \text{ and}$$

$$\mathbb{E}[FP(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)(1-\tilde{p}^{k_j}) + (1-Sp)Se \sum_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m).$$

$$\Rightarrow \mathbb{E}[FP(\mathbf{\Omega}^*)] - \mathbb{E}[FP(\hat{\mathbf{\Omega}})] = (1-Sp)(1-Se)(\tilde{p}^{k_j}-\tilde{p}^{k_i}) + n_j(1-Sp)(Se+Sp-1)\left[\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - \prod_{m\in\Omega_j^*}(1-\tilde{p}^m)\right] > 0.$$

As such, $\mathbb{E}[FP(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$.

(c) **Expected number of tests**

We have that:

$$\mathbb{E}[T(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_j^*}(1-\tilde{p}^m)\Big), \text{ and}$$

$$\mathbb{E}[T(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m)\Big).$$

$$\Rightarrow \mathbb{E}[T(\mathbf{\Omega}^*)] - \mathbb{E}[T(\hat{\mathbf{\Omega}})] = n_j(Se+Sp-1)\left[\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - \prod_{m\in\Omega_j^*}(1-\tilde{p}^m)\right] > 0.$$

As such, $\mathbb{E}[T(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[T(\mathbf{\Omega}^*)]$.

Thus, by converting groups i and j into an ordered testing scheme, all measures are either maintained or reduced, implying that there exists an optimal partition, which is ordered.

Case II: $n_i > 1$

Note that when the two group sizes are greater than one, the expected number of false negatives resulting from these groups is constant. As such, one can convert any unordered testing scheme into an ordered one without impacting the expected number of false negatives. Thus, we proceed by showing that the remaining performance measures (i.e., $\mathbb{E}[FP]$ and $\mathbb{E}[T]$) are reduced or maintained. By conditions **(i)** and **(ii)**, there exist $\emptyset \subset \Psi_i \subseteq \Omega_i^*$ and $\emptyset \subset \Psi_j \subseteq \Omega_j^*$ such that $|\Psi_i| = |\Psi_j|$ and when Ψ_i and Ψ_j are interchanged the resulting set of groups will follow an ordered testing scheme in which the group with the smaller size contains the lowest risk subjects, while the group with the larger size contains the highest risk subjects. We have that:

$$\prod_{m \in \Psi_j} (1 - \tilde{p}^m) - \prod_{m \in \Psi_i} (1 - \tilde{p}^m) > 0 \tag{D.1}$$

Sub-case I: $n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - \tilde{p}^m) > n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - \tilde{p}^m)$

Define a new testing scheme, $\hat{\mathbf{\Omega}} = \{\hat{\Omega}_1, \cdots, \hat{\Omega}_g\}$, where subjects in Ψ_i are interchanged with subjects in Ψ_j, that is, $\hat{\Omega}_i = (\Omega_i^* \setminus \Psi_i) \cup \Psi_j$, $\hat{\Omega}_j = (\Omega_j^* \setminus \Psi_j) \cup \Psi_i$, and $\hat{\Omega}_l = \Omega_l^*$ for all $l = 1, \cdots, g : l \neq i, j$. In what follows, we will show that partition $\hat{\mathbf{\Omega}}$ reduces or maintains the value of all performance measures. Multiplying the condition imposed in the sub-case, i.e.,

$$n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - \tilde{p}^m) > n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - \tilde{p}^m),$$

by Eq. (D.1), and expanding and rearranging gives:

$$n_i \prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^m) + n_j \prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) > n_i \prod_{m\in\Omega_i^*}(1-\tilde{p}^m) + n_j \prod_{m\in\Omega_j^*}(1-\tilde{p}^m).$$

(a) **Expected number of false positives ($\mathbb{E}[FP]$):**

We have that:

$$\begin{aligned}\mathbb{E}[FP(\boldsymbol{\Omega}^*)] = &\sum_{l:l\neq i,j}\mathbb{E}[FP_l] + (1-Sp)Se\sum_{m\in\Omega_i^*}(1-\tilde{p}^m) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_i^*}(1-\tilde{p}^m)\\ &+ (1-Sp)Se\sum_{m\in\Omega_j^*}(1-\tilde{p}^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\Omega_j^*}(1-\tilde{p}^m), \text{ and}\\ \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] = &\sum_{l:l\neq i,j}\mathbb{E}[FP_l] + (1-Sp)Se\sum_{m\in\hat{\Omega}_i}(1-\tilde{p}^m) - n_i(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^m)\\ &+ (1-Sp)Se\sum_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - n_j(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m).\end{aligned}$$

Noting that,

$$\sum_{m\in\Omega_i^*\cup\Omega_j^*}(1-\tilde{p}^m) = \sum_{m\in\hat{\Omega}_i\cup\hat{\Omega}_j}(1-\tilde{p}^m),$$

and subtracting the two gives:

$$\frac{\mathbb{E}[FP(\boldsymbol{\Omega}^*)] - \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})]}{(1-Sp)(Se+Sp-1)} = n_i\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^m) + n_j\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - n_i\prod_{m\in\Omega_i^*}(1-\tilde{p}^m) - n_j\prod_{m\in\Omega_j^*}(1-\tilde{p}^m) > 0.$$

As such, $\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[FP(\boldsymbol{\Omega}^*)]$.

(b) **Expected number of tests ($\mathbb{E}[T]$):**

We have that:

$$\mathbb{E}[T(\mathbf{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_i\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_i^*}(1-\tilde{p}^m)\Big) + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\Omega_j^*}(1-\tilde{p}^m)\Big), \text{ and}$$

$$\mathbb{E}[T(\hat{\mathbf{\Omega}})] = \sum_{l:l\neq i,j} \mathbb{E}[T_l] + 2 + n_i\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^m)\Big) + n_j\Big(Se - (Se+Sp-1)\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m)\Big).$$

Subtracting the two gives:

$$\frac{\mathbb{E}[T(\mathbf{\Omega}^*)] - \mathbb{E}[T(\hat{\mathbf{\Omega}})]}{(Se+Sp-1)} = n_i\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^m) + n_j\prod_{m\in\hat{\Omega}_j}(1-\tilde{p}^m) - n_i\prod_{m\in\Omega_i^*}(1-\tilde{p}^m) - n_j\prod_{m\in\Omega_j^*}(1-\tilde{p}^m) > 0.$$

As such, $\mathbb{E}[T(\hat{\mathbf{\Omega}})] \leq \mathbb{E}[T(\mathbf{\Omega}^*)]$.

Thus, by converting groups i and j into an ordered testing scheme, all measures are either maintained or reduced, implying that there exists an optimal partition, which is ordered.

Sub-case II: $n_i\prod_{m\in\Omega_i\setminus\Psi_i}(1-\tilde{p}^m) \leq n_j\prod_{m\in\Omega_j\setminus\Psi_j}(1-\tilde{p}^m)$

Due to conditions **(i)** and **(ii)**, there exist $\emptyset \subset Z_i \subseteq \Omega_i$ and $\emptyset \subset Z_j \subseteq \Omega_j$ such that $|Z_i| = |Z_j|$, and when Z_i and Z_j are interchanged the resulting set of groups will follow an ordered testing scheme in which the group with the smaller size contains the highest risk subjects, while the group with the larger size contains the lowest risk subjects. Define a new testing scheme, $\tilde{\mathbf{\Omega}} = \{\tilde{\Omega}_1, \cdots, \tilde{\Omega}_g\}$, where subjects in Z_i are interchanged with subjects in Z_j, that is, $\tilde{\Omega}_i = (\Omega_i^* \setminus Z_i) \cup Z_j$, $\tilde{\Omega}_j = (\Omega_j^* \setminus Z_j) \cup Z_i$, and $\tilde{\Omega}_l = \Omega_l^*$ for all $l = 1, \cdots, g : l \neq i, j$. In what follows, we will show that partition $\tilde{\mathbf{\Omega}}$ reduces or maintains the value of all performance

measures. By the condition imposed in the sub-case, i.e.,

$$n_i \prod_{m \in \Omega_i \setminus \Psi_i} (1 - \tilde{p}^m) \leq n_j \prod_{m \in \Omega_j \setminus \Psi_j} (1 - \tilde{p}^m),$$

and Eq. (D.1) we get:

$$n_i \prod_{m \in \Omega_i} (1 - \tilde{p}^m) \leq n_j \prod_{m \in \Omega_j} (1 - \tilde{p}^m). \tag{D.2}$$

By definitions of Z_i and Z_j, we have that:

$$\prod_{m \in Z_i} (1 - \tilde{p}^m) - \prod_{m \in Z_j} (1 - \tilde{p}^m) > 0. \tag{D.3}$$

From Eq. (D.2) we have that:

$$n_i \prod_{m \in \Omega_i \setminus Z_i} (1 - \tilde{p}^m) \prod_{m \in Z_i} (1 - \tilde{p}^m) \leq n_j \prod_{m \in \Omega_j \setminus Z_j} (1 - \tilde{p}^m) \prod_{m \in Z_j} (1 - \tilde{p}^m). \tag{D.4}$$

Then, by Eq.s (D.3) and (D.4), it must be true that:

$$n_i \prod_{m \in \Omega_i \setminus Z_i} (1 - \tilde{p}^m) < n_j \prod_{m \in \Omega_j \setminus Z_j} (1 - \tilde{p}^m). \tag{D.5}$$

Multiplying Eq. (D.5) by Eq. (D.3), expanding and rearranging gives:

$$n_i \prod_{m \in \tilde{\Omega}_i} (1 - \tilde{p}^m) + n_j \prod_{m \in \tilde{\Omega}_j} (1 - \tilde{p}^m) > n_i \prod_{m \in \Omega_i} (1 - \tilde{p}^m) + n_j \prod_{m \in \Omega_j} (1 - \tilde{p}^m).$$

Following a similar methodology to that of Sub-case I, one can show that $\mathbb{E}[FP(\tilde{\mathbf{\Omega}})] \leq \mathbb{E}[FP(\mathbf{\Omega}^*)]$ and $\mathbb{E}[T(\tilde{\mathbf{\Omega}})] \leq \mathbb{E}[T(\mathbf{\Omega}^*)]$. As such, for all cases, we are always able to construct an ordered testing scheme that reduces or maintains the values of all performance measures, concluding the proof. □

Proof of Theorem 5.3. We have that:

$$\mathbb{E}\left[\prod_{m=i}^{j} g(X^{(m)})\right] = \int_a^b \int_a^{x^j} \mathbb{E}\big[g(X^{(i)}) \cdots g(X^{(j)}) | X^{(i)} = x^i, X^{(j)} = x^j\big] f_{X^{(i)},X^{(j)}}(x^i, x^j) dx^i dx^j$$
$$= \int_a^b \int_a^{x^j} g(x^i) g(x^j) \mathbb{E}\big[g(X^{(i+1)}) \cdots g(X^{(j-1)}) | X^{(i)} = x^i, X^{(j)} = x^j\big] f_{X^{(i)},X^{(j)}}(x^i, x^j) dx^i dx^j, \tag{D.6}$$

where

$$\mathbb{E}\big[g(X^{(i+1)}) \cdots g(X^{(j-1)}) | X^{(i)} = x^i, X^{(j)} = x^j\big] =$$
$$\int_{x^i}^{x^j} \int_{x^{i+1}}^{x^j} \cdots \int_{x^{j-2}}^{x^j} g(x^{i+1}) \cdots g(x^{j-1}) f_{X^{(i+1)},\cdots,X^{(j-1)}|X^{(i)}=x^i,X^{(j)}=x^j}(x^{i+1}, \cdots, x^{j-1}) dx^{j-1} \cdots dx^{i+2} dx^{i+1}, \tag{D.7}$$

where

$$f_{X^{(i+1)},\cdots,X^{(j-1)}|X^{(i)}=x^i,X^{(j)}=x^j}(x^{i+1}, \cdots, x^{j-1}) = \frac{f_{X^{(i)},\cdots,X^{(j)}}(x^i, \cdots, x^j)}{f_{X^{(i)},X^{(j)}}(x^i, x^j)}.$$

From [101], we have that:

$$f_{X^{(i)},\cdots,X^{(j)}}(x^i, \cdots, x^j) = \frac{N!}{(i-1)!(N-j)!} F_X(x^i)^{i-1} f_X(x^i) \cdots f_X(x^j) \big(1 - F_X(x^j)\big)^{N-j},$$

and

$$f_{X^{(i)},X^{(j)}}(x^i, x^j) = \frac{N!}{(i-1)!(j-i-1)!(N-j)!} f_X(x^i) f_X(x^j) F_X(x^i)^{i-1} \big(F_X(x^j) - F_X(x^i)\big)^{j-i-1} \big(1 - F_X(x^i)\big)^{N-}$$

As such,we have that:

$$f_{X^{(i+1)},\cdots,X^{(j-1)}|X^{(i)}=x^i,X^{(j)}=x^j}(x^{i+1}, \cdots, x^{j-1}) = (j-i-1)! \frac{f_X(x^{i+1}) \cdots f_X(x^{j-1})}{\big(F_X(x^j) - F_X(x^i)\big)^{j-i-1}}. \tag{D.8}$$

Substituting Eq. (D.8) into Eq. (D.7) gives:

$$\mathbb{E}\big[g(X^{(i+1)})\cdots g(X^{(j-1)})|X^{(i)}=x^i,X^{(j)}=x^j\big]=$$
$$\frac{(j-i-1)!}{\big(F_X(x^j)-F_X(x^i)\big)^{j-i-1}}\int_{x^i}^{x^j}\int_{x^{i+1}}^{x^j}\cdots\int_{x^{j-2}}^{x^j}g(x^{i+1})\cdots g(x^{j-1})f_X(x^{i+1})\cdots f_X(x^{j-1})dx^{j-1}\cdots dx^{i+2}dx^{i+1}.$$

Define $h(t)$ by:

$$h(t)\equiv\int_t^{x^j}g(x)f_X(x)dx.$$

Note that $h(t)$ exists since $g(x)$ and $f_X(x)$ are both continuous (imposed in the theorem), and $h(x^j)=0$ and $dh(t)=-g(t)f_X(t)dt$. Then Eq. (D.7) can be written as:

$$\mathbb{E}[g(X^{(i+1)})\cdots g(X^{(j-1)})|X^{(i)}=x^i,X^{(j)}=x^j]=$$
$$\frac{(j-i-1)!}{(F_X(x^j)-F_X(x^i))^{j-i-1}}\int_{x^i}^{x^j}\cdots\int_{x^{j-3}}^{x^j}\left[\int_{x^{j-2}}^{x^j}g(x^{j-1})f_X(x^{j-1})dx^{j-1}\right]g(x^{i+1})\cdots g(x^{j-2})f_X(x^{i+1})\cdots f_X(x^{j-2})dx^{j-2}\cdots dx^{i+1}$$
$$\frac{(j-i-1)!}{(F_X(x^j)-F_X(x^i))^{j-i-1}}\int_{x^i}^{x^j}\cdots\int_{x^{j-3}}^{x^j}h(x^{j-2})g(x^{i+1})\cdots g(x^{j-2})f_X(x^{i+1})\cdots f_X(x^{j-2})dx^{j-2}\cdots dx^{i+1}$$
$$\frac{(j-i-1)!}{(F_X(x^j)-F_X(x^i))^{j-i-1}}\int_{x^i}^{x^j}\cdots\int_{x^{j-4}}^{x^j}\left[\int_{x^{j-3}}^{x^j}g(x^{j-2})f_X(x^{j-2})h(x^{j-2})dx^{j-2}\right]g(x^{i+1})\cdots g(x^{j-3})f_X(x^{i+1})\cdots f_X(x^{j-3})dx^{j-3}\cdots dx^{i+1}$$

For the integral in brackets, we perform a change of variable $u=h(x^{j-2})$ with $du=-g(x^{j-2})f_X(x^{j-2})dx^{j-2}$, this gives:

$$\mathbb{E}[g(X^{(i+1)})\cdots g(X^{(j-1)})|X^{(i)}=x^i,X^{(j)}=x^j]=$$
$$\frac{(j-i-1)!}{(F_X(x^j)-F_X(x^i))^{j-i-1}}\int_{x^i}^{x^j}\cdots\int_{x^{j-5}}^{x^i}\left[\int_{x^{j-4}}^{x^j}g(x^{j-3})f_X(x^{j-3})\frac{h(x^{j-3})^2}{2}dx^{j-3}\right]g(x^{i+1})\cdots g(x^{j-4})f_X(x^{i+1})\cdots f_X(x^{j-4})dx^{j-4}\cdots dx^{i+1}.$$

Continuing in this manner gives:

$$\begin{aligned}\mathbb{E}\big[g(X^{(i+1)})\cdots g(X^{(j-1)})|X^{(i)}=x^i,X^{(j)}=x^j\big]&=\frac{(j-i-1)!}{\big(F_X(x^j)-F_X(x^i)\big)^{j-i-1}}\frac{h(x^i)^{j-i-1}}{(j-i-1)!}\\&=\left[\int_{x^i}^{x^j}\frac{g(x)f_X(x)dx}{F_X(x^j)-F_X(x^i)}\right]^{j-i-1}.\end{aligned}$$

Substituting the latter in Eq.(D.6) provides the result. □

Proof of Lemma 5.1. The result follows by Remark 5.2, which states that for a given vector

$\boldsymbol{y}$, Problem **CM** reduces to an **SP** Problem, for which the constraint set possesses the total unimodularity property. As such, the optimal solution, corresponding to the specific $\boldsymbol{y}$, will be integral, and hence integrality constraints are not required for the $\boldsymbol{x}$ variables. □

Proof of Theorem 5.5. We prove the result by showing that for any estimated risk vector realization, $\tilde{\boldsymbol{p}}$, if a group of size greater or equal to four exists, then one can always reduce the objective function by placing the two highest risk subjects in a separate group. We only prove the result for Problem **EM**, as the proof for Problem **RM** follows similarly, with the only difference being that the entire risk vector is multiplied by $1+\delta$. Suppose, to the contrary, that the optimal testing scheme, $\boldsymbol{\Omega}^* = \{\Omega_1^*, \cdots, \Omega_g^*\}$, for some $g = 2, \cdots, N$, has a group, Ω_i^*, with $n_i \geq 4$, and let m and k denote the indices of the two highest risk subjects within the group. Consider a new testing scheme, $\hat{\boldsymbol{\Omega}}$, that is identical to $\boldsymbol{\Omega}^*$ except for placing subjects m and k into a separate group. Note that the expected number of false negatives under both partitions is equal, thus we proceed by showing that testing scheme $\hat{\boldsymbol{\Omega}}$ reduces the expected number of false positives over $\boldsymbol{\Omega}^*$. We have that:

$$\mathbb{E}[FP(\boldsymbol{\Omega}^*)] = \sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se\sum_{l\in\Omega_i^*}(1-\tilde{p}^l) - n_i(1-Sp)(Se+Sp-1)\prod_{l\in\Omega_i^*}(1-\tilde{p}^l), \text{ and}$$

$$\begin{aligned}\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] = &\sum_{l:l\neq i,j} \mathbb{E}[FP_l] + (1-Sp)Se\sum_{l\in\hat{\Omega}_i}(1-\tilde{p}^l) - (n_i-2)(1-Sp)(Se+Sp-1)\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l)\\ &+ (1-Sp)Se(2-\tilde{p}^m-\tilde{p}^k) - 2(1-Sp)(Se+Sp-1)(1-\tilde{p}^m)(1-\tilde{p}^k).\end{aligned}$$

Subtracting the two gives:

$$\begin{aligned}\frac{\mathbb{E}[FP(\boldsymbol{\Omega}^*)] - \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})]}{(1-Sp)(Se+Sp-1)} =& \Big[n_i - 2 - n_i(1-\tilde{p}^m)(1-\tilde{p}^k)\Big] \prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l) + 2(1-\tilde{p}^m)(1-\tilde{p}^k) \\ =& \Big[n_i - 2 - (n_i-2+2)(1-\tilde{p}^m)(1-\tilde{p}^k)\Big] \prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l) + 2(1-\tilde{p}^m)(1-\tilde{p}^k) \\ =& \Big[(n_i-2)\big(1-(1-\tilde{p}^m)(1-\tilde{p}^k)\big)\Big] \prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l) - 2\prod_{l\in\Omega_i^*}(1-\tilde{p}^l) + 2(1-\tilde{p}^m)(1-\tilde{p}^k).\end{aligned}$$

Since $n_i \geq 4$, then $\Big[(n_i-2)\big(1-(1-\tilde{p}^m)(1-\tilde{p}^k)\big)\Big]\prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l) \geq 0$. As such, we have that:

$$\begin{aligned}\frac{\mathbb{E}[FP(\boldsymbol{\Omega}^*)] - \mathbb{E}[FP(\hat{\boldsymbol{\Omega}})]}{(1-Sp)(Se+Sp-1)} \geq& -2\prod_{l\in\Omega_i^*}(1-\tilde{p}^l) + 2(1-\tilde{p}^m)(1-\tilde{p}^k) \\ =& 2(1-\tilde{p}^m)(1-\tilde{p}^k)\left(1 - \prod_{m\in\hat{\Omega}_i}(1-\tilde{p}^l)\right) \geq 0.\end{aligned}$$

As such, $\mathbb{E}[FP(\hat{\boldsymbol{\Omega}})] \leq \mathbb{E}[FP(\boldsymbol{\Omega}^*)]$. □