IMPROVED LAB TESTING OF PAP SMEARS FOR CERVICAL CANCER: 
SUMMARY AND RESULTS OF SOME STATISTICAL QUALITY MODELS

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SUMMARY

This paper summarizes several recent studies by the authors regarding laboratory inspection procedures that are commonly used in the examination of Pap smears for the detection of cervical cancer. In particular, the policy that is mandated under the Clinical Laboratory Improvement Amendments Act of 1988 (CLIA, 1988) for the quality control of Pap smears is critiqued, and some possible improved inspection policies are suggested and examined. These alternative inspection policies are motivated by a desire to reduce the high costs associated with diagnostic errors and are similar to manufacturing policies that use multiple 100% inspections in order to eliminate nonconforming product in the presence of inspection error. Using mathematical and expected cost models, it is shown that significant improvements in the detection of cervical cancer and in total costs are possible by changing the policies that are currently mandated under CLIA '88.

INTRODUCTION

Recent litigation and several large settlements due to false negative Pap smear results have attracted considerable media attention and public concern. For example, Robb (1993) stated that 15 of every 100 pathologists is currently involved in a malpractice lawsuit, of which 10% directly concern a false negative determination from a Pap smear. In order to minimize future liability and total costs, the re-design of clinical laboratory policies should depend on the ability to detect truly positive and truly negative patients and on all costs that are incurred as a result of these policies.

For example, as an attempt to improve the accuracy of the screening process, the Clinical Laboratory Improvement Amendments of 1988 requires that laboratories randomly sample and rescreen by a pathologist a minimum of ten percent (10%) of all Pap smear slides that are judged to be negative by cytotechnologists. Additionally, all (100%) of the slides judged to be positive by cytotechnologists are re-examined by a pathologist. A recent editorial by Melamed and Flehinger (1992) in the medical journal Acta Cytologica, however, criticized the use of this mandatory 10% random rescreening rule as a means of detecting unacceptable performance in Pap smear screening. Although many other authors also have questioned this policy and proposed alternative quality assurance policies, a study by Ashton (1989) indicated that most laboratories continue to apply the 10% rescreening rule as a method of quality assurance in cervical cytology, with some facilities partially rescreening negative slides at a rate higher than 10% (Koss, 1993).

Mathematical and economic models have been developed by the authors to study the effects of using a rescreening rate other than 10% and/or multiple rescreenings on the overall sensitivity, specificity, and total costs of possible alternative screening policies. The results of these analyses sug-
suggest that significant improvements in the detection of cervical cancer and in total costs are possible via alternative screening policies instead of the usual screening policy currently mandated under CLIA '88, with one to three repeated screenings by cytotechnologists and 0% or 100% of all negative slides being rescreened by a pathologist (Kaminsky and Benneyan, 1995).

PROBABILITY OF DETECTING TRULY POSITIVE AND TRULY NEGATIVE PATIENTS

Kaminsky et al (1995a, 1995b) developed mathematical models which describe the probability of detecting truly positive and truly negative patients, based on the following assumptions:

1. Each cytotechnologist and each pathologist has a sensitivity of \( 1 - \alpha_c \) and \( 1 - \alpha_p \), respectively. Thus, the probability that a pathologist will correctly determine a truly positive slide to be positive is \( 1 - \alpha_p \) and, similarly, the probability that a cytotechnologist will correctly determine a truly positive slide to be positive is \( 1 - \alpha_c \). These sensitivities are assumed to remain constant over time and to be independent of the rescreening rate.

2. Each cytotechnologist and each pathologist has a specificity of \( 1 - \beta_c \) and \( 1 - \beta_p \), respectively. Thus, the probability that the cytotechnologist will correctly determine a truly negative slide to be negative is \( 1 - \beta_c \), and similarly, the probability that the pathologist will determine a truly negative slide to be negative is \( 1 - \beta_p \). Again, it is assumed that these specificities remain constant over time and are independent of the rescreening rate.

3. Each slide may be repeatedly inspected by a number, \( j \), of independent cytotechnologists. A negative reading by any cytotechnologist causes a slide to be read by the next cytotechnologist. If any cytotechnologist determines a slide to be positive, the slide is given to a pathologist for confirmation. If all \( j \) cytotechnologists determine the slide to be negative, it is placed in a pool of size \( n \), where \( n_j \) of these slides are randomly selected for rescreening by a pathologist.

With these assumptions, the probability of detecting truly positive and truly negative patients are:

\[
\text{Probability of Detecting a Truly Positive Patient} = p_j = (1 - \alpha_p) \left[ 1 - \alpha_c^j \left(1 - \frac{n_1}{n}\right)^j \right], \text{ and}
\]

\[
\text{Probability of Detecting a Truly Negative Patient} = q_j = 1 - \beta_p \left[ 1 - \left(1 - \beta_c^j \left(1 - \frac{n_1}{n}\right)^j\right) \right].
\]

If \( N \) positive patients are screened independently, then the number of correct positive and correct negative identifications can be modelled with binomial distributions with parameters \( N \) and \( p_j \) and parameters \( N \) and \( q_j \), respectively. As shown below, these mathematical models can be used to examine the magnitude of the expected number of correct positive and negative identifications as a function of \( \alpha_c \), \( \alpha_p \), \( \beta_c \), \( \beta_p \), and the rescreening rate. Figure 1 illustrates the effect of the rescreening rate on the overall sensitivity for various scenarios, with Figure 1a considering the use of one cytotechnologist and Figure 1b illustrating the use of two cytotechnologists.

As these examples show, the mandated 10% rescreening policy does not significantly improve the detection of truly positive patients when compared to a 0% rescreening policy. Additionally, significant improvements in the detection of truly positive patients are possible by using more than one cytotechnologist. Finally, it can be shown that the pathologist sensitivity, \( 1 - \alpha_p \), is an upper bound on the overall sensitivity of any sequential screening policy, regardless of the rescreening rate, whereas the overall specificity is bounded above by \( 1 - (\beta_p \times \text{rescreening rate}) \).
Figure 1a: Prescreening with 1 Cytotechnologist

Figure 1b: Prescreening with 2 Cytotechnologists

Figure 1: Number of Correct Diagnoses per 1000 Positive Patients
Pathologist Sensitivity = 0.95

Figure 2 shows similar plots for the number of correct identifications of truly negative patients. Figures 1 and 2 illustrate the inherent tradeoff that confronts risk managers - that repeated screenings and additional cytotechnologists decrease the rate of false negatives, but increase the false positive rate and increase operating and labor costs. These tradeoffs are incorporated into the following cost model in order to determine an optimal minimum total cost laboratory screening policy.

**Total Cost of Laboratory Screening Policy**

Kaminsky et al (1995b) also developed a cost model to determine the total cost of any specific laboratory screening policy, based on the following additional assumptions:
Figure 2a: Prescreening with 1 Cytotechnologist

Figure 2b: Prescreening with 2 Cytotechnologists

Figure 2: Number of Correct Diagnoses per 1000 Negative Patients
Pathologist Specificity = 0.80

4. Slides that are judged to be negative by all \( j \) cytotechnologists are accumulated in a pool until that pool reaches a pre-determined size \( n_j \), at which time a random sample of size \( n_j \) is selected for rescreening by a pathologist. (Note that all of the realities of the true system are captured during this concept of a cycle and, furthermore, the cycle defines a regenerative process.)

5. The following costs may be incurred a random number of times during each cycle:

\[
\begin{align*}
k_1 & = \text{per slide screening cost by a cytotechnologist}, \\
k_2 & = \text{per slide screening cost by a pathologist}, \\
k_3 & = \text{per slide cost of a false positive}, \text{ and} \\
k_4 & = \text{per slide cost of a false negative}.
\end{align*}
\]
Using these costs and the previous notation, the expected value of the cost per cycle, EC, can be shown to be:

\[
EC = k_1 \frac{n}{p} \left\{ \frac{(1 - \alpha_c)^j}{1 - \alpha_c} + (1 - p) \frac{[1 - (1 - \beta_c)^j]}{\beta_c} \right\} + k_2 \left[ \frac{n(1 - p')}{p'} + n_1 \right] + \\
+ k_3 \frac{n(1 - p)}{p'} \beta_p \left[ 1 - (1 - \beta_c)^j \left(1 - \frac{n}{n} \right) \right] + k_4 \frac{n}{p} \frac{n}{p'} \left[ 1 - (1 - \alpha_p)^j \left(1 - \alpha_c \left(1 - \frac{n}{n} \right) \right) \right],
\]

where the incidence rate \( p \) is the unconditional probability of a positive patient and the unconditional probability of declaring any patient to be negative is:

\[
\text{Probability Declare Any Patient is Negative} = p' = p \alpha_c^j + (1 - p) (1 - \beta_c)^j.
\]

This cost model now can be used to evaluate a variety of screening policies for any set of values of \( k_1, k_2, k_3, k_4, \alpha_c, \alpha_p, \beta_c, \beta_p, p \), and \( n \). Moreover, the optimal rescreening rate \( n/n \) and number of cytotechnologists \( j \) which minimize the total expected cost also can be found, such as by a simple half-interval search. For example, Table 1 compares the expected costs for three situations where the following values were assumed, based on discussions with pathology practitioners:

\[
k_1 = $3.00, \quad k_2 = $9.00, \quad k_3 = $750.00, \quad n = 100, \quad \text{and} \quad p = 0.015.
\]

The scenario in column 3 represents a fairly skilled group of professionals where both the cytotechnologists and the pathologist have high sensitivities and high specificities. In this case, the results show that one screening by a single cytotechnologist with a pathologist rescreening rate of 0% is the policy that minimizes the expected total cost per cycle. Under CLIA, however, this policy is not permitted. It also is interesting to note that the policy of single screening with a 10% rescreening rate, which is the minimum permitted under CLIA, has a higher expected cost than two cytotechnologist screenings with a 0% rescreening rate.

Using these same costs and incidence rate, column 4 compares a second example in which the specificities of the cytotechnologists and pathologist remain high but now the sensitivities are low. This represents a scenario where individuals frequently can report false negative determinations. The results for this example show that the optimal policy now is to use two cytotechnologists, again with a rescreening rate of 0%. In this case, the sequential independent screenings by the cytotechnologists counteract the low sensitivity of each individual, although the expected cost of the optimal policy is considerably higher than that of the previous example. The incremental cost of poor individual sensitivity therefore can be quite high.

Finally, column 5 illustrates a case for which, conversely, 100% rescreening always is optimal. This can happen, for example, when the cost of false negatives is extremely high relative to the cost of false positives and to the cost of a pathologist examining a Pap smear, as might be the case when testing for life threatening medical conditions. Note that high false negative costs very dramatically increase the total cost of any laboratory policy, with higher total costs associated with less rescreening.

Furthermore, Benneyan and Kaminsky (1995) show that the optimal screening policy for any combination of sensitivities, specificities, incidence rate, and number of cytotechnologists always
will employ either 0% or 100% rescreening by a pathologist. That is, in no case will partial rescreening ever result in the best possible laboratory policy. This is a very significant result in light of current laboratory practices and requirements to the contrary.

Cytotechnologist Specificity = 1-\(\beta_c = 95\%
Pathologist Specificity = 1-\(\beta_p = 95\%
Incidence Rate of Cervical Cancer = p = 1.5\%

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* = Optimal policy

Table 1: Comparison of Total Expected Costs per Cycle
CONCLUSION

The mathematical and economic models presented in this paper can assist risk managers, clinicians, and regulatory bodies design more effective and minimum cost screening procedures and requirements. For example, in many cases examined by the authors the addition of a second cytotecnologist significantly reduced both false negatives and total costs. Additionally, the optimal 0% or 100% rescreening policy quite often results in significant savings over the 10% partial rescreening currently mandated under CLIA. These results are similar to industrial experiences where multiple inspections significantly improve overall outgoing quality in the presence of inspection error, the economic optimal number of re-inspections often is between one to three in a wide range of applications, and partial inspection never results in minimum costs.

Further investigation by the authors includes exploring the sensitivity under various scenarios and exceptions to assumptions, such as homogenous cytotecnologists and constant sensitivities and specificities. For example, a possible "reinforcement benefit" may exist for pathologists to occasionally review truly negative slides, rather than only suspected positives, as this may help maintain high pathologist sensitivity and specificity levels. Other SPC methods such as statistical control charts also have been shown to have value for controlling current laboratory quality levels, comparing the effectiveness of individual cytotecnologists and pathologists, and identifying retraining needs (Kaminsky et al, 1995c).

Additional information regarding the derivation and results of these clinical laboratory quality models and reprints of the referenced articles are available by contacting the authors.

REFERENCES


