Automated Rescreening in Cervical Cytology

Mathematical Models for Evaluating Overall Process Sensitivity, Specificity and Cost

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OBJECTIVE: To develop mathematical models to assist decision makers with the difficult task of evaluating the use of automated rescreening in the process of screening cervical smears.

STUDY DESIGN: Using assumptions about incidence, per smear screening costs, and the sensitivity and specificity of cytotechnologists, pathologists and the rescreening device, basic probability models were developed to describe the overall sensitivity, specificity and cost of the screening process.

RESULTS: The optimal screening policy is highly dependent on assumptions, and an automated system can significantly affect the overall system cost and accuracy.

CONCLUSION: Mathematical planning models are valuable tools to assist decision makers in the design of a screening process for cervical smears. (Acta Cytol 1997; 41:209–223)

Keywords: cervix neoplasms; cervix diseases; mass screening; cervical smears; quality assurance, health care.

At a recent public hearing of the Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration (FDA), the premarket approval applications for two automated rescreening systems were examined. Both these systems, developed by Neuromedical Systems, Inc., and NeoPath, Inc., were subsequently accepted by the FDA and have been described in a number of publications. In each case, an automated system is designed to operate in conjunction within an existing human screening process by rescreening all standard cervical smears that are determined to be normal by cytotechnologists. Two other companies, Cytyc Corporation and Roche Image Analysis Systems, Inc., have taken a different approach and have developed alternative processes to improve the method by which cervical smears are prepared for interpretation. These systems also have been described in the literature. In essence, these companies believe that the overall effectiveness of the
total screening system can be improved more significantly and at a lower cost by increasing the sensitivity and specificity of human interpretation. From the numerous publications and from the discussion at the recent FDA hearings, it is clear that the overall effectiveness of an automated cervical smears rescreening process has yet to be determined. For any automated system that is intended to function as one component within a larger screening process, it is important to examine the effect that the automated system has on the overall process sensitivity, the overall process specificity and the overall process economics. This paper provides mathematical models for determining and comparing the overall process sensitivity, process specificity and process cost of automated rescreening to those of a standard system that uses human screening of cervical smears by one or more cytotecnologists, one pathologist and the random rescreening of any specified fraction of the negative smears. For this standard process, the mathematical models that are used in the comparisons in the current paper are taken from previous work by the authors. The use of automated rescreening also is compared to the optimal standard human process that minimizes the expected total cost per smear, as discussed in these earlier papers.

**Intended Use of Analytic Models**

All of these models were developed as part of a continuing effort to apply the teachings of W. Edwards Deming to understand and improve the process of screening cervical smears. In this improvement effort, the underlying philosophy is based on the value of developing an understanding of the physical and statistical performance of a process and the subsequent overall optimization of that process. The analytic models introduced in this paper are intended to assist risk managers, laboratory personnel and regulators with the difficult task of understanding the advantages and disadvantages of automated redirected screening of cervical smears. The ultimate objectives are to improve the screening process and to reduce the total medical costs and the total number of deaths that result from cervical cancer.

It is very important to emphasize that the intent of this paper is not to advocate any particular approach to laboratory screening but to illustrate the value of using an analytic approach to exploring any relative benefits and consequences of alternative screening policies. Accordingly, the use of the analytic models presented in this paper should be considered with reference to a larger analysis and planning philosophy, such as the one illustrated in Figure 1. In this context, a decision maker must estimate values for a number of parameters that de-
fine the laboratory situation under study. In the present analysis, these “inputs” include the sensitivity and specificity of each cytotechnologist, pathologist and the rescreening device, the incidence of cervical cancer or its precursors; the per screening cost of the cytotechnologist, pathologist and rescreening device; and the costs of a false negative and a false positive. Based on these estimates, the models presented below then determine the overall screening process sensitivity, process specificity and process cost.

By using these models, decision makers can examine, rapidly, a wide variety of scenarios and can develop a deeper understanding of alternative complex screening processes in cervical cytology. Note that the decision maker could be a laboratory manager, an insurer or a representative of a regulatory body. Ultimately, it is hoped that decision makers will use such information to take some action to improve the design of the screening process. Finally, while the specific examples presented below may suggest benefits of redirected or nonredirected screening for any given scenario, these examples are meant primarily as illustrations of some of the types of comparisons that are possible with the models. It is important to emphasize that alternative scenarios with assumptions that are different from those used in this paper might produce completely different results. Therefore, if the methods provided in this paper are used by future researchers, extreme care should be taken to develop reliable estimates or to perform a wide range of studies to examine the results for alternative values for these estimates.

While the examples in this paper take a global perspective and include all resultant societal costs and consequences incurred throughout the entire system, perhaps not well known presently, the calculations provided below also could be repeated easily to examine the impact of each screening policy on only the portions of these costs that are incurred at the laboratory or insurer level. Of course, if only the laboratory level costs of false diagnoses are considered rather than all societal costs, then considerably different results will be produced. Under the global perspective, the concept of “cost” can be considered to include all medical and psychological consequences of false diagnoses (lost life, reduced health status, expense of subsequent medical treatment, etc.). Although some of these costs and other assumptions may be subject to some debate, the examples in this paper are presented for a range of possible values so that readers can determine the appropriate policy and the corresponding improvement in any given situation. Finally, in all cases examined in this paper, the minimum cost standard (nonredirected) policy uses one cytotechnologist and 0% rescreening of presumed negatives. In many practical cases this may be the optimal policy, but for processes with low sensitivity and high false negative costs, this need not always be the case.25,26 Although a primary objective of the current paper is to introduce these models and to illustrate their use, future papers will explore results and implications for a range of possible scenarios.

**Automated Redirected Rescreening Process**

In order to develop mathematical models for overall process sensitivity, specificity and economics, the automated redirected screening system is assumed to operate in the manner shown in Figure 2. In this process, every smear is examined by a cytotechnologist and is determined to be either negative or positive, with all positive determinations reviewed by a pathologist. If both a cytotechnologist and a pathologist determine the smear to be positive, it is given a final determination of positive. Alternatively, the pathologist may revise a positive determination from the cytotechnologist to a final result of negative. All negative determinations from the cytotechnologist are submitted to the redirected rescreening device. If the redirected rescreening system determines the smear to be suspect, then the smear is routed back to the cytotechnologist for a

![Figure 2](image)
second screening and then, if determined to be positive, to the pathologist. Any smears that the automated device accepts as negative, or redirects but the cytotechnologist still classifies as negative, are given a final determination of negative.

Following the notation that was introduced in earlier papers, the sensitivities of an initial review of a smear by cytotechnologists, pathologists and the redirected screening system are assumed to be $1-\alpha_C$, $1-\alpha_P$, and $1-\alpha_M$, respectively. Similarly, the specificities of the initial review of a smear by cytotechnologists, pathologists and the redirected screening system are assumed to be $1-\beta_C$, $1-\beta_P$, and $1-\beta_M$, respectively. If a smear is redirected to a cytotechnologist by the rescreening system, the sensitivity and specificity of the cytotechnologist are denoted as $1-\alpha_{CR}$ and $1-\beta_{CR}$, respectively. Similarly, a pathologist is assumed to review a redirected smear with a sensitivity and specificity of $1-\alpha_{PR}$ and $1-\beta_{PR}$, respectively.

Note that this notation allows the user to model situations in which sequential reviews of the same smear are not independent. For example, knowledge that a smear has been redirected may influence the review process. In this context, it might be reasonable to assume that, for example due to heightened vigilance, the sensitivities of either or both the cytotechnologist and the pathologist are higher for redirected smears. The directional change in the specificities of the cytotechnologists and the pathologists who are reading a redirected smear is less clear. Similar to the case for sensitivity, heightened vigilance may increase specificities. Conversely, such as if there is a tendency to “believe the machine,” specificities for redirected smears may decrease. Although in the examples presented in this paper the sensitivities and specificities for a redirected smear are assumed to be higher than those of an initial review of a smear, an analyst alternatively could define the values for these parameters differently.

**Overall Process Sensitivity and Specificity**

In order to determine the overall process sensitivity and specificity, it is convenient to introduce the following notation. Let $C+$ and $C-$ respectively denote the events “a cytotechnologist determines the smear to be positive” and “a cytotechnologist determines the smear to be negative.” Similar events will be denoted as $P+$ and $P-$ and $M+$ and $M-$ for the determinations of the pathologist and the redirected screening system, respectively. Using this notation, the overall screening process can detect a positive smear in the following two mutually exclusive and collectively exhaustive ways:

1. $C+$ and $P+$, and
2. $C-$ and $M+$ and $C+$ and $P+$.

Using the notation defined above for the individual sensitivities of the cytotechnologist, the pathologist and the rescreening device, the probabilities for the above two events are $(1-\alpha_C)(1-\alpha_P)$ and $\alpha_C(1-\alpha_M)(1-\alpha_{CR})(1-\alpha_{PR})$, respectively. By summing these probabilities, the overall process sensitivity, defined as the probability that the entire process ultimately will determine a truly positive smear to be positive, is

$$P\{\text{System says positive | slide is positive}\} = (1-\alpha_C)(1-\alpha_P) + \alpha_C(1-\alpha_M)(1-\alpha_{CR})(1-\alpha_{PR}).$$

Similarly, the overall screening process can determine a truly negative smear to be negative in the following four mutually exclusive and collectively exhaustive ways:

1. $C+$ and $P-$,
2. $C-$ and $M-$,
3. $C-$ and $M+$ and $C-$,

Again, by computing the probability of each of these four events and summing the results, the overall process specificity, defined as the probability that the entire process ultimately determines a truly negative smear to be negative, can be shown to be

$$P\{\text{System says negative | slide is negative}\} = 1 - \beta_C\beta_P - \beta_{PR}\beta_M\beta_{CR}(1-\beta_C).$$

The overall sensitivity and specificity of a redirected screening process now can be compared to those of a standard process using 10% rescreening with a single cytotechnologist, as prescribed by the Clinical Laboratory Improvement Act (CLIA), and of more general policies that use J cytotechnologists and a pathologist rescreening rate of r. For this general (nonredirected) system, the overall sensitivity and overall specificity were derived in previous papers to be:

$$P\{\text{System says positive | slide is positive}\} = (1-\alpha_P)[1-\alpha_C'(1-r)],$$

and

$$P\{\text{System says negative | slide is negative}\} = 1 - \beta_P[1-(1-r)(1-\beta_C')].$$
Note that the CLIA system, with a 10% rescreening rate, can be represented by these general expressions by setting the rescreening rate to \( r = 0.10 \) and the number of cytotechnologists to \( J = 1 \).

**Comparison of Accuracy of Redirected Screening Versus Conventional Screening**

Using the expressions shown above for any particular set of inputs, the performance of redirected rescreening now can be compared, analytically, to alternative human screening policies. For example, by algebraically rearranging the above expressions, it can be shown mathematically that a standard policy with \( J \) cytotechnologists, one pathologist and a rescreening rate of \( r \) will have a higher sensitivity than the overall redirected rescreening process if

\[
\text{Sensitivity of rescreening device} = 1 - \alpha_M \leq \frac{(1-\alpha_p) \left[ 1 - \alpha - \frac{1}{1-r} \right]}{(1-\alpha_{CR})(1-\alpha_{PR})}
\]

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**Figure 3** (A) Effect of sensitivity of a rescreening device on total process sensitivity. (B) Effect of the specificity of a rescreening device on total process specificity.
and a standard policy will have a higher specificity 
than the overall redirected rescreening process if

\[ \text{Specificity of rescreening device} = 1 - \beta_M \leq 1 - \frac{\beta_P [1 - (1 - r) (1 - \beta_C) / \beta_C]}{\beta_{PR} \beta_{CR} (1 - \beta_C)} \]

Note that for the CLIA policy with one cytotechnologist and a rescreening rate of 10%, these conditions 
reduce to:

\[ \text{Sensitivity of rescreening device} = 1 - \alpha_M \leq \frac{0.1 (1 - \alpha_P)}{(1 - \alpha_{CR})(1 - \alpha_{PR})} \]

and

\[ \text{Specificity of rescreening device} = 1 - \beta_M \leq 1 - \frac{0.1 \beta_P}{\beta_{PR} \beta_{CR}} \]

Although all implications of these inequalities have 
yet to be fully explored, one important general 
conclusion is that the sensitivity and specificity of a 
redirected rescreening process must not always be 
better than those of a conventional screening 
process. That is, mathematically, either type of 
screening process can be more accurate than the 
other, and the process that is preferable will depend 
on the specific values of the inputs. This mathematical 
result illustrates the importance of developing 
accurate estimates in order to identify the optimal 
screening policy and associated benefits for any 
particular scenario.

As one example of the use of these mathematical 
models, Figure 3 examines the effect of the sensitivity 
and specificity of the redirected rescreening device 
on the overall process sensitivity and specificity 
for the following conditions:

- Cytotechnologist sensitivity = 1 - \alpha_C = 0.85
- Cytotechnologist specificity = 1 - \beta_C = 0.90
- Pathologist sensitivity = 1 - \alpha_P = 0.90
- Pathologist specificity = 1 - \beta_P = 0.95
- Cytotechnologist rescreening sensitivity = 1 - \alpha_{CR} = 0.95
- Cytotechnologist rescreening specificity = 1 - \beta_{CR} = 0.95
- Pathologist rescreening sensitivity = 1 - \alpha_{PR} = 0.95
- Pathologist rescreening specificity = 1 - \beta_{PR} = 0.98

In this particular situation, and from the results 
of previous papers, \(^{25,26}\) 0% rescreening with one 
cytotechnologist was found to be the minimum cost 
nonredirected policy, and by rearranging the 
above inequalities, 75% rescreening by a pathol-
ogist was found to be the rescreening rate that 
would produce the same overall process sensitivity 
for both human rescreening and redirected rescreening 
(assuming the sensitivity of the rescreening 
device is 75%). Figure 3A compares the overall 
sensitivity of a redirected rescreening process to 
those of the standard 10% CLIA policy and to alter-
native human screening processes with one cyto-
tecnologist and rescreening rates of 0%, 75% and 
100%. Similarly, Figure 3B illustrates the overall 
process specificity for each of these alternative 
screening policies.

As shown in Figure 3A, for this example, when 
the sensitivity of the rescreening device exceeds

\[ 1 - \alpha_M > \frac{0.1 (1 - \alpha_P)}{(1 - \alpha_{CR})(1 - \alpha_{PR})} = \frac{0.1 (0.9)}{(0.95) (0.95)} = 0.0997 = 0.10, \]

then the overall process sensitivity of redirected 
screening is higher than that of the standard CLIA 
policy. It also can be shown mathematically that the 
overall automated rescreening process sensitivity 
always must be greater than that of a 0% conven-
tional rescreening policy (the economic optimal 
policy). That is, a redirected rescreening process 
will have higher overall sensitivity when

\[ 1 - \alpha_M > \frac{r (1 - \alpha_P)}{(1 - \alpha_{CR})(1 - \alpha_{PR})} = \frac{0 (1 - \alpha_P)}{(1 - \alpha_{CR})(1 - \alpha_{PR})} = 0 \text{ (i.e., always).} \]

Figure 3A also provides information for determi-
ning the additional number of correct positive deter-
minations that can be obtained by using one policy 
over another. For example, if the sensitivity of the 
redirected screening device is 75%, then redirected 
rescreening will increase the overall process sensi-
tivity by approximately 8.8% over the CLIA policy 
and, consequently, will provide an additional 88 
correct positive determinations per 1,000 truly pos-
tive cases.

For this example, Figure 3B shows that the over-
all process specificity for redirected screening is 
always higher than that of the standard CLIA policy. 
Although in general this result does not have to be 
true, similar to above, it can be shown mathemati-
cally that the specificity of the overall automated re-
screening process must be less than that of the optimal 0% rescreening policy. That is, a redirected rescreening process will have higher overall specificity when

\[ 1 - \beta_M > 1 - \frac{r \beta_p}{\beta_{PR} \beta_{CR}} = 1 - \frac{0 \beta_p}{\beta_{PR} \beta_{CR}} = 1 - 0 = 1 \text{ (i.e., never).} \]

By examining Figure 3B, redirected rescreening can be seen to increase the overall process specificity by approximately 0.4%, or by an additional four correct negative determinations per 1,000 truly negative cases. Note that while this is a positive benefit, in all cases examined by the authors redirected rescreening did not appear to increase the overall process sensitivity and specificity much more dramatically than this. This result is not consistent with the potential improvements that have been suggested by some manufacturers. Finally, in general, due to tradeoffs between overall sensitivity, specificity, workload, and operating costs, the overall economically optimum policy will not be the one with the highest overall sensitivity and specificity.

**Overall Process Economics**

In order to develop an economic model for the expected total cost per smear, the following costs are defined:

- \( k_1 = \text{cost per screening by a cytotechnologist}, \)
- \( k_2 = \text{cost per review by a pathologist}, \)
- \( k_3 = \text{cost of a false positive}, \)
- \( k_4 = \text{cost of a false negative}, \)
- \( k_5 = \text{cost per rescreening by the automated device}. \)

In many situations, these costs may be unknown and will have to be estimated. In particular, consensus regarding the consequences of a false negative result may be unlikely in the near future. For example, if only laboratory level costs were considered, one might argue that since the laboratory primarily incurs only the expense of insurance premiums, its cost of a false positive result is negligible and that its cost of a false negative result is much smaller than the total cost to society. Clearly, these assumptions will significantly affect any analytic comparison. In addition to the above notation for costs, sensitivities and specificities, the probability of a positive smear is denoted by \( p \). If a user were defining a positive slide only to be one with high grade abnormalities, then presumably the numeric values of these parameters would be higher than in a situation in which a positive slide were defined also to include lower grade abnormalities.

An expression for the expected total cost per smear (EC) now can be derived by considering every possible manner by which truly positive and negative smears can be processed through the entire system. These events and their associated errors and costs are summarized in Tables I and II. By computing the probability of each of these events, multiplying these by their associated costs and then summing these products, the total expected cost per smear for the rescreening system can be shown to be

\[ EC = k_1 \left[ \frac{p \left[ 1 - \alpha_c \left( 1 - \alpha_m \right) \right] + \left( 1 - p \right) \left[ 1 - \alpha_m \left( 1 - \beta_c \right) \right]}{1 - \alpha_C} \right] + k_2 \left[ \frac{1 - \alpha_C + \alpha_c \left( 1 - \alpha_m \right) \left( 1 - \alpha_C \right)}{1 - \alpha_C} \right] + k_3 \left[ \frac{p \left[ 1 - \left( 1 - \beta_c \right) \left( 1 - \alpha_p \right) - \alpha_c \left( 1 - \alpha_m \right) \left( 1 - \alpha_C \right) \left( 1 - \alpha_{PR} \right) \right]}{1 - \alpha_C} \right] + k_4 \left[ \frac{p \left[ 1 - \left( 1 - \alpha_p \right) \left( 1 - \alpha_m \right) \left( 1 - \alpha_C \right) \left( 1 - \alpha_{PR} \right) \right]}{1 - \alpha_C} \right] \]

**Comparison of Total Cost of Redirected Screening Versus Conventional Screening**

The expected cost per smear of the overall redirected screening process now can be compared to the expected cost per smear of a screening process that operates with \( j \) cytotechnologists and a pathologist rescreening rate of \( r \). For this process, previous papers\(^{25,26} \) have shown that the expected total cost per smear is:

\[ EC = k_1 \left[ \frac{p \left( 1 - \alpha_C \right)}{1 - \alpha_C} + \left( 1 - p \right) \frac{1 - \left( 1 - \beta_C \right)}{1 - \alpha_C} \right] + k_2 \left[ 1 - p \alpha_C \right] + k_3 \left[ 1 - p \right] \beta_p \left[ 1 - \left( 1 - \beta_C \right) \left( 1 - \alpha_p \right) \right] + k_4 \left[ 1 - \left( 1 - \alpha_p \right) \left( 1 - \alpha_m \right) \left( 1 - \alpha_C \right) \left( 1 - \alpha_{PR} \right) \right] \]

where \( p_1 = p \alpha_C + \left( 1 - p \right) \left( 1 - \beta_C \right) \).

These cost expressions can be used to show mathematically that, in all cases, no specific policy will result in the lowest expected total cost. Again, direct comparison of redirected rescreening and conventional human screening policies (with 10% re-

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**Table I**  Errors and Costs for Each Possible Way of Processing a Truly Positive Smear

<table>
<thead>
<tr>
<th>Route</th>
<th>Errors</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>C+ P+</td>
<td>(None)</td>
<td>( k_1 + k_2 )</td>
</tr>
<tr>
<td>C+ P-</td>
<td>FN</td>
<td>( k_1 + k_2 + k_4 )</td>
</tr>
<tr>
<td>C- M-</td>
<td>FN</td>
<td>( k_1 + k_2 + k_4 )</td>
</tr>
<tr>
<td>C- M+ C-</td>
<td>FN</td>
<td>( 2k_1 + k_2 + k_4 )</td>
</tr>
<tr>
<td>C- M+ C+ P+</td>
<td>(None)</td>
<td>( 2k_1 + k_2 + k_5 )</td>
</tr>
<tr>
<td>C- M+ C+ P-</td>
<td>FN</td>
<td>( 2k_1 + k_2 + k_5 )</td>
</tr>
</tbody>
</table>
screening or otherwise) for any particular scenario therefore is critical. As one example, consider the following scenario:

Per screening cost by a cytotechnologist \( = k_1 \) \( = \$3 \)
Per review cost by a pathologist \( = k_2 \) \( = \$9 \)
Cost of false positive test \( = k_3 \) \( = \$750 \)
Cost of a false negative \( = k_4 \) \( = \$1500 \)
Per rescreening cost by automated device \( = k_5 \) \( = \$10 \)
Cytotechnologist sensitivity \( = 1 - \alpha_C \) \( = 0.85 \)
Cytotechnologist specificity \( = 1 - \beta_C \) \( = 0.90 \)
Pathologist sensitivity \( = 1 - \alpha_P \) \( = 0.90 \)
Pathologist specificity \( = 1 - \beta_P \) \( = 0.95 \)
Redirected rescreening sensitivity \( = 1 - \alpha_M \) \( = 0.75 \)
Redirected rescreening specificity \( = 1 - \beta_M \) \( = 0.85 \)
Cytotechnologist rescreening sensitivity \( = 1 - \alpha_{CR} \) \( = 0.95 \)
Cytotechnologist rescreening specificity \( = 1 - \beta_{CR} \) \( = 0.95 \)
Pathologist rescreening sensitivity \( = 1 - \alpha_{PR} \) \( = 0.95 \)
Pathologist rescreening specificity \( = 1 - \beta_{PR} \) \( = 0.95 \)
Incidence \( = p \) \( = 0.015 \).

The costs assumed in this scenario were developed from a number of discussions with personnel from clinical laboratories who are active in cervical cancer screening. In addition, the values assumed for the sensitivities and specificities were chosen to represent a laboratory that is operating with relatively high quality. Because the sensitivity and cost of automated rescreening, as well as other critical estimates, presently may not be known with certainty, the following comparisons examine a range of possibilities. Although these estimates are based on the literature and discussions with several clinicians and laboratory personnel, alternative estimates for cost and accuracy are possible. Specific conclusions, therefore, should be interpreted with caution and should not be extrapolated to other scenarios.

### Total System Cost Versus Sensitivity of Automated Rescreening Device

Figure 4A compares the total expected costs per smear for each alternative screening policy for a range of redirected screening sensitivities. Note that in this particular example, redirected rescreening always will have a higher total cost than both the CLIA policy and the optimal nonredirected policy. It is important, however, that alternative cases can exist for which the total cost of a redirected rescreening process will be lower than that of the CLIA 10% policy and, in some cases, lower than even the optimal nonredirected policy. For example, in Figure 4B the cost of a false negative was raised to $3,500, and the cost of redirected rescreening was lowered to $5 per screening. In this case, redirected rescreening becomes more cost effective than the CLIA policy when the redirected sensitivity \( = 1 - \alpha_M \geq 0.22 \). A conventional process using one cytotechnologist and 0% rescreening is the optimal nonredirected policy in this case and remains more economical than redirected rescreening until \( 1 - \alpha_M \geq 0.71 \).

### Total System Cost Versus Cost of Automated Rescreening Device

For the same conditions that were used in Figure 4A but now for a range of redirected rescreening costs \( (k_5) \), Figure 5A again compares the total expected cost of a redirected rescreening process to the alternative human screening policies. In this particular example, for \( k_5 \leq $6.21 \), redirected rescreening becomes more expensive than the CLIA policy. Furthermore, if \( k_5 \) could be reduced to less than $192, redirected rescreening would result in a lower total expected cost per smear than a conventional process with 0% rescreening (the optimal nonredirected policy). In Figure 5B, \( k_4 \) again is raised to $3,500, and the effect of a higher false negative cost is illustrated. In this case, redirected rescreening will have a lower total cost than CLIA and the optimal nonredirected policies if \( k_5 \leq $9.19 \) and \( k_5 < $5.35 \), respectively. These examples illustrate that high false negative costs and low rescreening costs can increase the value of a redirected rescreening process. At the current estimates for the cost of redirected rescreening of $10.00 to $20.00 per smear and for the assumptions used above, however, redirected rescreening is not yet to the point where it would be less expensive than a 0% rescreening policy.
Sensitivity to False Negative Costs and Other Estimates

As illustrated in the above examples, the results of the analytic models introduced in this paper and the best screening policy for any given situation can depend significantly on several of the estimated inputs. Perhaps the most difficult of these to estimate is the average total cost that results from a false negative (k_f). Experience to date has suggested that consensus on this cost is unlikely, with suggested values differing by several orders of magnitude. The false negative cost, moreover, will be very different depending upon whether one is examining the total screening costs or only a subset of these costs at either the patient, laboratory or insurer level.

Figure 4  (A) Effect of the sensitivity of redirected device on overall process cost (false negative cost = $1,500, cost per automated rescreen = $10). (B) Effect of the sensitivity of a redirected device on overall process cost (false negative cost = $3,500, cost per automated rescreen = $5).
In order to illustrate the importance of developing reliable estimates, Figure 6 examines the total cost of each screening policy and any relative benefits of automated rescreening for a wide range of false-negative costs. This figure is based on the same values for all other inputs that were used in the previous examples. As shown, if the false-negative cost is lower than $4,000, then the total cost of an automated rescreening process will be higher than that of the standard CLIA 10% policy. Additionally, unless the $k_4$ cost exceeds $6,200 per false negative, an automated rescreening process will remain more expensive than a nonredirected policy with 0% human rescreening. As this example illus-
trates, a high false negative cost can increase the value of a redirected rescreening process.

A Second Example

To illustrate the effect that changes in the parameters have on the optimal screening policy, another example was constructed with the following parameters:

Per screening cost by a cytotechnologist = $k_1 = $3
Per review cost by a pathologist = $k_2 = $9
Cost of a false positive = $k_3 = $350
Cost of a false negative = $k_4 = $750
Per rescreening cost by automated device = $k_5 = $10
Cytotechnologist sensitivity = $1 - \alpha_C = 0.85$
Cytotechnologist specificity = $1 - \beta_C = 0.985$
Pathologist sensitivity = $1 - \alpha_P = 0.90$
Pathologist specificity = $1 - \beta_P = 0.995$
Redirected rescreening sensitivity = $1 - \alpha_M = 0.80$
Redirected rescreening specificity = $1 - \beta_M = 0.60$
Cytotechnologist rescreening sensitivity = $1 - \alpha_{CR} = 0.90$
Cytotechnologist rescreening specificity = $1 - \beta_{CR} = 0.985$
Pathologist rescreening sensitivity = $1 - \alpha_{PR} = 0.95$
Pathologist rescreening specificity = $1 - \beta_{PR} = 0.995$
Incidence = $P = 0.080$.

Since the sensitivities of the cytotechnologist and the pathologist were not changed from the previous example, the behavior of the overall system sensitivity as the sensitivity of the rescreening device is varied is the same as the curve shown in Figure 3A of the previous example. The other important measures of system performance are displayed in Figures 7–10. Direct comparisons between this example and the previous one, however, should not be made. They represent two different laboratory scenarios. For the new example, alternative human screening policies have been included in the analyses to reflect the fact that the economically optimal human screening policy depends on the cost of a false negative.

From Figure 10, when the cost of a false negative is $< $4,250 and $> $325, screening with two cytotechnologists and a rescreening rate of 0% is the optimal screening policy. This human screening policy is one in which a cytotechnologist is used to rescreen 100% of the normal smears from the first cytotechnologist and, as such, allows a direct comparison of human rescreening to automated rescreening. When the cost of a false negative is $< $325, then human screening with one cytotechnologist and a rescreening rate of 0% is the optimal screening policy. For a false negative cost $> $4,250, one cytotechnologist with a 100% rescreening rate is the optimal screening policy. In this example, for all false nega-
The models presented in this paper can be used as a formal screening policy, and automated rescreening is never the optimal redirected rescreening device that functions within a larger screening process consisting of cytotechnologists and pathologists. With these models, risk managers and laboratory personnel can evaluate the overall process sensitivity, process specificity, and process economic costs.
ics for a variety of assumptions about the sensitivities and specificities of the individual elements of the process, the incidence of cervical cancer or its precursors, the costs of screening and the costs of false diagnoses. Also, the models can be used to evaluate a number of "what if" and other questions.

For example, what if the sensitivities and specificities of cytotechnologists and pathologists could be improved through the introduction of new technology? Above what cost per false negative will automated rescreening result in a lower total societal cost than the standard CLIA policy or than the opti-
mal (nonredirected) policy? Or, conversely, below what point would the cost of automated rescreening need to be reduced in order for it to be advantageous?

Some Caveats and Issues for Future Research

The examples used in this paper were intended to illustrate several possible uses of these models. It is important to reemphasize that many other scenarios and assumptions are possible and that the models have not been explored sufficiently to report a general set of conclusions. It is hoped that further analysis may produce some general conclusions that can be helpful to a wide variety of decision-makers with different interests. For example, several of the examples in this paper clearly illustrate the inescapable fact that the policy with the highest overall process sensitivity is not necessarily (or even likely) the one with the lowest societal cost. This result again reinforces the value of analytic and economic decision making models and the importance of developing accurate cost estimates.

Additionally, the cost assumptions at the laboratory level are different from those for a regulatory agency more interested in societal consequences. Therefore, the effectiveness of automated screening from the specific points of view of clinical laboratories, insurers and society should be examined separately. Presumably, the models will demonstrate significantly different results from those presented in this paper. It also is clear that specific results, and perhaps the best laboratory screening policy to employ, may differ in various settings depending on the accuracy of work by personnel employed by any particular laboratory, on the prevalence of cervical cancer and its precursors in the demographic and risk group being screened, and on the frequency with which women are screened. Sensitivity to these and other issues are discussed by Benneyan et al.26 and will be explored more fully in later papers.

Finally, note that in the examples in this paper, the models are used by defining a positive smear as one with a true state equal to or beyond a particular point along the disease continuum. For example, a low grade abnormality or higher could be used with all corresponding sensitivities, specificities and costs taken as the weighted averages associated with that class or higher. These models also could be applied separately to each individual class of possible abnormality in the Papanicolaou or Bethesda system. Similarly, the current cost models could be expanded to include the different incidences, sensitivities, specificities and costs associated with each class of abnormality. For example, higher false negative costs probably result from higher grade abnormalities. Conversely, if either automated or human screening processes are more sensitive to detecting these more advanced disease states, then the overall impact of false negatives on societal costs will be reduced. These more detailed approaches might be useful for examining such hypotheses and for more explicitly examining the relative benefits of alternative screening systems on particular abnormality classifications.

Alternative Use of Rescreening for Modern Statistical Quality Control

Although this paper and others22,30 have shown analytically that the CLIA 10% rescreening requirement has little value in terms of reducing the number of false negatives or total cost, it can be argued that the real purpose of rescreening is to monitor the performance of the screening process and to identify individual cytotechnologists and pathologists in need of retraining.30 Improving the process by considering the root causes of the problem ultimately may lead to the greatest savings. As an alternative method for this purpose, the use of statistical quality control charts should be considered. In many industries, this approach is the foundation of a modern quality system. In laboratory applications, the use of control charts has been described in earlier papers.33-38 These charts can be applied effectively to control and improve the quality of any screening process.

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