METHOD AND APPARATUS FOR EFFICACY IMPROVEMENT IN MANAGEMENT OF CASES WITH EQUIVOCAL SCREENING RESULTS

Automatic recommendation of a colposcopic procedure, further DNA testing and additional clinical procedures based on data from machine based cytological specimen scoring, histological specimen scoring, biomedical specimen scoring or biological specimen scoring. A computerized biological specimen processing system scores a biomedical specimen taken from a patient. A functional measure of risk is computed from the score, data taken about the patient, such as patient age and case history, and clinical information. The clinical information includes co-existence of disease, risk factors, and symptoms. The system automatically determines the risk category, whether low-risk, high-risk, mid-risk or potential-risk based on the functional measure of risk and risk thresholds. The system recommends cytology follow-up, additional clinical procedures, further DNA testing and specimen analysis based on the risk, categories.
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METHOD AND APPARATUS FOR EFFICACY IMPROVEMENT IN
MANAGEMENT OF CASES WITH EQUIVOCAL SCREENING RESULTS

BACKGROUND OF THE INVENTION

This invention relates to a method and apparatus to triage cases with equivocal results from a screening process in the areas of cytology, histology, radiology, and other medical applications, and more particularly to a method and apparatus for the triage of borderline gynecological specimens.

FIELD OF THE INVENTION

Clinical management of patients with borderline Pap smears read as "atypical" has been a matter of considerable controversy. The Bethesda System attempts to reduce diagnostic confusion and unnecessary colposcopic referrals by standardizing cervical cytology terminology. See "The Bethesda System for Reporting Cervical/Vaginal Cytological Diagnosis, Definitions, Criteria, and Explanatory Notes for Terminology and Specimen Adequacy," by Kurman et al., New York, Springer-Verlag, 1993. The Bethesda System defines the categories of Atypical Squamous Cells of Undetermined Significance (ASCUS) and Atypical Glandular Cells of Undetermined Significance (AGUS) to restrict a previously non-specific morphologic criteria of "atypia". The cytologically borderline diagnosis is intrinsically subjective and prone to variability in human interpretation. In addition, the associated condition of human papillomavirus (HPV) infection is variable resulting in variable cytologic symptoms. Thus, many borderline cases may go undetected or underdetected. Therefore, the ASCUS and AGUS diagnosis still present problems of proper patient management. Because of the indication of abnormality, many clinicians use a colposcopic procedure for all women with ASCUS,

To resolve overly aggressive patient management, noncytologic triage testing, for example HPV testing, may be used to classify women with a diagnosis of ASCUS or AGUS into low- and high-risk groups. Women testing positive for cancer-associated HPV types may be regarded as a high-risk group, whereas women testing positive for non-oncogenic HPV types, or negative for HPV, may be regarded as a low-risk group. ASCUS and AGUS patients in the high-risk group require a colposcopic procedure, whereas the low-risk group may be safely followed up by cytology. See "Human Papillomavirus Testing by Hybrid Capture Appears to be Useful in Triaging Women with a Cytological Diagnosis of Atypical Squamous Cells of Undetermined Significance," by Cox et al., Am J Obstet Gynecol, 1995, 172, 3:946-954; and "Utility of HPV DNA Testing and Liquid-based cytology in the triage of Women with equivocal Pap smears," by Manos et al., Abstract, 15th international Papillomavirus Conference, Queensland, Dec. 1-5, 1996. Studies show that infection by certain HPV types is a main cause of cervical neoplasia. See "Epidemiological Evidence Showing that Human Papillomavirus Infection Causes Most Cervical Intraepithelial Neoplasia," by Schiffman et al., J National Cancer Inst., 1993, 85:958-64. However, HPV may be a necessary but not sufficient cause of most cases of cervical cancer. Almost 70% of the younger,
age less than 30, ASCUS and AGUS patients are in the HPV high-risk group, however only 5% are likely to progress to cervical neoplasia. See Manos et al., Ibid. Therefore, up to 65% of these women undergo a high cost colposcopic procedure unnecessarily. In addition, the HPV test does not have perfect sensitivity and therefore some patients with cervical neoplasia but with equivocal cytology outcome may test as HPV low-risk and may be left untreated. See Schiffman et al., Ibid.

**SUMMARY OF THE INVENTION**

The invention provides a method and apparatus that uses additional independent scores determined by computerized screening systems to increase the sensitivity and specificity of a triage procedure thus providing efficacy improvement in management of cases with equivocal screening results. A computerized screening system, such as the AutoPap 300® system available from NeoPath Inc. of Redmond, Washington, provides an analysis score that could be used in triage of patients having equivocal cytology results such as ASCUS (Atypical Squamous Cells of Undetermined Significance), AGUS (Atypical Glandular Cells of Undetermined Significance) or LSIL (Low-grade Squamous Intraepithelial Lesions). In one embodiment, a computerized biological specimen processing system may be used to classify a case into low-risk, mid-risk, and high-risk categories.

A biological specimen, such as a Pap smear or a monolayer cervical smear, for example, a CYTYC® ThinPrep prepared specimen, or a specimen prepared from liquid-based fixation collection, is loaded into a slide processing fixation system. The method of the invention processes the slide automatically or semi-automatically and generates one or multiple analysis
scores based on morphology, photometric, and contextual characteristics of the cellular characteristics in the specimen. For example, an analysis score may be generated by the method disclosed in pending US Patent Application Serial No. 08/571,686, filed 12/13/95, which is a file wrapper continuation of abandoned U.S. Patent Application Serial No. 07/838,064, filed 2/18/92, to Nelson et al., entitled "METHOD FOR IDENTIFYING NORMAL BIOMEDICAL SPECIMENS." This analysis score reflects the likelihood that a slide is abnormal; the higher the evaluation score value, the higher the likelihood that abnormal cells are present.

Abnormal biological morphological change does not normally occur in isolation in Pap smear specimens. Such abnormal change may be found in a number of cellular formations such as free lying cells, and cellular aggregates such as sheets, syncytia, and clusters. See "Diagnostic Cytopathology of the Uterine Cervix, Monographs in Clinical Cytology," by Patten, S.F., S. Karger, 1978. The analysis score may be designed to not rely solely upon the detection of one form of abnormality or another. For example, the NeoPath AutoPap® system is designed to enhance detection of an apparent rare event, for example, a single truly abnormal cell, by integrating the results of three image interpretation modules to detect cellular and cell population evidence of abnormality: a single cell module for free lying cells, a group module for aggregate sheets and syncytia, and a thick group module for aggregate syncytia, and clusters. The analysis score may be developed using a training strategy that incorporates a large number of abnormal slides from different diagnostic categories as well as slides representing subcategories within each group.
The abnormal cells and slides having more severe diagnosis may be weighted more heavily in the training process. This produces an analysis score having a high correlation with the severity of disease.

By employing an additional independent scoring system, the invention provides for reduction of unnecessary colposcopic procedures by triaging low-risk cases for cytology follow-up. The invention may further provide for increasing lesion detection sensitivity on high-risk cases by requiring colposcopic procedures, rather than depending on an HPV test which has imperfect sensitivity, for triage. The invention also increases significant lesion detection sensitivity in the cases incorrectly diagnosed as within normal limits by human screening.

The invention provides a triage method based on a gynecological specimen taken from a patient comprising the steps of: scoring the gynecological specimen with a computerized biomedical specimen processing system to generate a gynecological specimen score; and automatically recommending with a computer that the patient undergo a colposcopic procedure if the gynecological specimen score falls in a predetermined range of biomedical specimen scores.

The invention also provides a triage method based on a cytological specimen taken from a patient, the method comprising the steps of: scoring the cytological specimen with a computerized cytological specimen processing system to generate a cytological specimen score; and automatically recommending with a computer that the cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores.

The invention also provides a triage method based
on a histological specimen taken from a patient, the method comprising the steps of: scoring the histological specimen with a computerized histological specimen processing system to generate a histological specimen score; and automatically recommending with a computer that the histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores.

The invention also provides a triage method based on a cytological specimen taken from a patient, the method comprising the steps of: scoring the cytological specimen with a computerized cytological specimen processing system to generate a cytological specimen score; obtaining an additional cytological specimen from the patient; and automatically recommending with a computer that the additional cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores.

The invention also provides for a triage method based on a histological specimen taken from a patient, the method comprising the steps of: scoring the histological specimen with a computerized histological specimen processing system to generate a histological specimen score; obtaining an additional histological specimen from the patient; and automatically recommending with a computer that the additional histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores.

The invention also provides for a method to manage patients having undetermined significance biological specimens comprising the steps of: scoring a biological specimen from a patient with a
computerized biological specimen processing system to generate a specimen score; automatically recommending with a computer that the patient does not require an additional clinical procedure if the specimen score falls in a first predetermined range of specimen scores; and automatically recommending with a computer that the patient requires an additional clinical procedure if the specimen score falls in a second predetermined range of specimen scores; and automatically recommending with a computer that the patient requires an additional test if the specimen score falls in a third predetermined range of specimen scores.

The invention also provides for a method to manage patients having undetermined significance biological specimens comprising the steps of: scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score; automatically recommending with a computer that the biological specimen requires additional analysis if the specimen score falls in a first predetermined range of specimen scores; and automatically recommending with a computer that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

The invention also provides a method to manage patients having undetermined significance biological specimens comprising the steps of: scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score; automatically recommending with a computer that an additional biological specimen be taken from the patient and that the additional biological specimen requires analysis if the specimen
score falls in a first predetermined range of specimen scores; and automatically recommending with a computer that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

The invention also provides a method of case triage efficacy enhancement for treatment of a patient with equivocal screening test results comprising the steps of: obtaining a cytological specimen from the patient; scoring the cytological specimen with a computerized scoring system to generate an analysis score for the cytological specimen; determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; determining whether the cytological specimen represents a high-risk case and if the cytological specimen represents a high-risk case recommending a colposcopic procedure for the patient; and determining whether the cytological specimen represents a mid-risk case and if the cytological specimen represents a mid-risk case recommending a further test on the cytological specimen.

The invention also provides a method of case triage sensitivity enhancement for treatment of a patient having within normal limits screening test results, the method comprising the steps of: obtaining a cytological specimen from the patient; scoring the cytological specimen with a computerized screening system to generate an analysis score for the cytological specimen; determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; and determining whether the cytological specimen represents a
potential-risk case and if the cytological specimen represents a potential-risk case recommending a further test of the cytological specimen for the patient.

The invention also provides an apparatus for diagnosis and colposcopy treatment recommendation based on a gynecological specimen taken from a patient, the apparatus comprising: means for scoring the gynecological specimen having a gynecological specimen score output; and means for recommending that the patient undergo a colposcopic procedure connected to the gynecological specimen score output.

The invention also provides an apparatus for triage based on a cytological specimen taken from a patient, the apparatus comprising: means for scoring the cytological specimen having a cytological specimen score output; and means for recommending that the cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores, wherein the recommending means is connected to the cytological specimen score output.

The invention also provides an apparatus for triage based on a histological specimen taken from a patient, the apparatus comprising: means for scoring the histological specimen having a histological specimen score output; and means for recommending that the histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores, wherein the recommending means is connected to the histological specimen score output.

The invention also provides an apparatus for triage based on a cytological specimen taken from a patient, the apparatus comprising: means for scoring
the cytological specimen having a cytological specimen score output; and means for recommending that an additional cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores, wherein the scoring means is connected to the cytological specimen score output.

The invention also provides an apparatus for triage based on a histological specimen taken from a patient, the apparatus comprising: means for scoring the histological specimen having a histological specimen score output; and means for recommending that an additional histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores, wherein the recommending means is connected to the histological specimen score output.

The invention also provides an apparatus to manage patients having undetermined significance biological specimens comprising: means for scoring a biological specimen from a patient having a biological specimen score output; means for recommending with a computer that the patient does not require an additional clinical procedure if the specimen score falls in a first predetermined range of specimen scores; and means for recommending with a computer that the patient requires an additional clinical procedure if the specimen score falls in a second predetermined range of specimen scores; and means for recommending with a computer that the patient requires an additional test if the specimen score falls in a third predetermined range of specimen scores.

The invention also provides an apparatus to manage patients having undetermined significance biological specimens comprising: means for scoring a
biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score; means for recommending with a computer that the biological specimen requires additional analysis if the specimen score falls in a first predetermined range of specimen scores; and means for recommending with a computer that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

The invention also provides an apparatus to manage patients having undetermined significance biological specimens comprising: means for scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score; means for recommending that an additional biological specimen be taken from the patient and that the additional biological specimen requires analysis if the specimen score falls in a first predetermined range of specimen scores; and means for recommending that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

The invention also provides an apparatus for case triage efficacy enhancement for treatment of a patient with equivocal screening test results comprising: means for obtaining a cytological specimen from the patient; means for scoring the cytological specimen with a computerized scoring system to generate an analysis score for the cytological specimen; means for determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; means for determining whether the
cytological specimen represents a high-risk case and if the cytological specimen represents a high-risk case recommending a colposcopic procedure for the patient; and means for determining whether the cytological specimen represents a mid-risk case and if the cytological specimen represents a mid-risk case recommending a further test on the cytological specimen.

The invention also provides an apparatus for case triage sensitivity enhancement for treatment of a patient having within normal limits screening test results, the apparatus comprising: means for obtaining a cytological specimen from the patient; means for scoring the cytological specimen with a computerized screening system to generate an analysis score for the cytological specimen; means for determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; and means for determining whether the cytological specimen represents a potential-risk case and if the cytological specimen represents a potential-risk case recommending a further test of the cytological specimen for the patient.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art through the description of the preferred embodiment, claims and drawings herein wherein like numerals refer to like elements.

BRIEF DESCRIPTION OF THE DRAWINGS

To illustrate this invention, a preferred embodiment will be described herein with reference to the accompanying drawings.

Figure 1 shows one embodiment of a method for enhancing case triage efficacy of the invention.
Figure 2 shows one embodiment of a method for enhancing case triage sensitivity of the invention.

Figure 3 shows an alternate embodiment of a method of the invention for enhancing triage sensitivity.

Figure 4 shows one embodiment of an interactive based scoring mechanism of the invention.

Figures 5A, 5B and 5C show an automated cytology system as employed by the method and apparatus of the invention.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT**

Refer now to Figure 1 which shows one embodiment of a method for enhancing case triage efficacy 100 of the invention. A computerized screening system 20 receives cytology specimens from cases where screening results were determined to be equivocal 10. The computerized screening system 20 performs an analysis on a cytology specimen 10 providing an analysis score 22. In step 30, the method of the invention performs a low-risk thresholding. If the analysis score 22 falls below a low-risk threshold, for example .386 in an analysis score range from 0.000 to 1.000, then the method of the invention identifies the case as a low-risk case 32. The low-risk threshold is determined from a training result obtained during preparation for a clinical trial. In the training environment, the true condition of the cases is known and consequently the low-risk threshold value is determined by the analysis scores for the training slide population that most likely will contain only low-risk cases. Pending U.S. Application Serial Number 08/309,063 to Lee et al., entitled "METHOD FOR CYTOLOGICAL SYSTEM DYNAMIC NORMALIZATION" provides an example of determining an analysis score. The method of the invention determines low-risk cases 32 as those cases not
requiring immediate medical attention, and recommends a cytology follow-up in step 40. In one embodiment, cytology follow-up may comprise another cytology test within 3-6 months.

For cases not identified as low-risk cases 32, the method of the invention performs high-risk thresholding in step 50. If the analysis score 22 exceeds a high-risk threshold, for example .604 in an analysis score range from 0.000 to 1.000, in step 50, the method of the invention identifies the case as a high-risk case 54. Like the low-risk threshold, the high-risk threshold is determined from a training result obtained during preparation for a clinical trial. In the training environment, the true condition of the cases is known and consequently the high-risk threshold value is determined by the analysis scores for the training slide population that most likely will contain only high-risk cases. Otherwise, the method of the invention identifies the case as a mid-risk case 52. The method of the invention suggests a colposcopic procedure in step 90 for high-risk cases 54 identified in the high-risk thresholding step 50.

In one embodiment, the method of the invention may employ the analysis score 22 to perform the low-risk thresholding step 30 and the high-risk thresholding step 50 as shown below:

IF ( Analysis_score < Low_risk_threshold ) then Low_risk case
ELSE IF ( Analysis_score > High_risk_threshold ) then High_risk case
ELSE Mid-risk case.

In an alternate embodiment, the method of the invention may employ other factors such as patient age, case history, risk factors, symptoms and clinical
information in performing the low-risk thresholding step 30 and the high-risk thresholding step 50. Examples of clinical information include: last menstrual period, collection date, whether the patient is pregnant, postpartum, abnormal gynecologic presentation, cyclic, postmenopausal, postabortion, had a hysterectomy, taking birth control, prescription hormones, has an IUD, the source of the specimen (cervical, endocervical, vaginal, cervical stump) and how the sample was procured (aspiration, Cervex-Brush™, cytobrush, spatula, swab). Case history may include information such as: other concurrent tests (biopsy, colposcopy) an abnormal Pap smear, abnormal bleeding, cancer, chemotherapy, colposcopy and radiation. In this embodiment, the low-risk thresholding step 30 and the high-risk thresholding step 50 comprise the following logic:

IF (Function_1(Analysis_score, age, case history, clinical information) < Low_risk_threshold ) then

Low_risk case

ELSE IF

(Function_2(Analysis_score, age, case history, clinical information) > High_risk_threshold ) then

High_risk case

ELSE Mid-risk case

where

Function_1(Analysis_score, age, case history, clinical information) = Analysis_score * f1(age) * f2(case history) * f3(clinical information)

where

f1(age) = 0.5 if age < 30
    1.0 if 50 > age ≥ 30
    1.5 if age ≥ 50
and

\[ f_2(\text{case history}) = \begin{cases} 
0.5 & \text{if all previous tests are normal} \\
1.0 & \text{if no previous test information is available} \\
3.0 & \text{if all previous tests are abnormal} \\
2.0 & \text{otherwise}
\end{cases} \]

and

\[ f_3(\text{clinical information}) = \begin{cases} 
0.5 & \text{if no co-existing disease, no high risk factors, and no symptoms} \\
1.0 & \text{if no clinical information is available} \\
3.0 & \text{if having co-existing disease and high risk factor and with symptoms} \\
2.0 & \text{otherwise}
\end{cases} \]

and where

\[ \text{Function}_2(\text{Analysis score, age, case history, clinical information}) = \text{Analysis score} \times f_1'(\text{age}) \times f_2'(\text{case history}) \times f_3'(\text{clinical information}) \]

where

\[ f_1'(\text{age}) = \begin{cases} 
0.8 & \text{if age < 40} \\
1.2 & \text{if age \geq 50}
\end{cases} \]

and
\[ f_2' \text{(case history)} = 0.8 \text{ if all previous tests are normal} \\
1.0 \text{ if no previous test information is available} \\
2.0 \text{ if all previous tests are abnormal} \\
1.5 \text{ otherwise} \]

\[ f_3' \text{(clinical information)} = 0.8 \text{ if no co-existing disease, no high risk factors, and no symptoms} \\
1.0 \text{ if no clinical information is available} \\
2.0 \text{ if having co-existing disease and high risk factor and with symptoms} \\
1.5 \text{ otherwise.} \]

The high-risk and low-risk thresholds are developed in the training procedure described above. The coefficient functions described above are selected to preserve the significance of the thresholds derived by this training procedure. For example, a patient with an analysis score of 0.2 whose age is less than 30, where all her previous tests are abnormal, and who has no coexisting disease will have a Function_1 value of 0.15. This value is considered low-risk because it is less than 0.386. Further, a patient with an analysis score of 0.2 whose age is greater than 50, where all her previous tests were abnormal, and who has co-existing disease, will have a Function_1 value
of 2.7 and a Function_2 value of 0.96. This patient is considered high-risk because 0.96 is greater than 0.604.

These coefficients are determined based on patient statistics known during the training process. The coefficients are estimated to improve the accuracy of the triage decision process.

For mid-risk cases 52, the method of the invention advises HPV triage in step 60. The HPV test further categorizes the mid-risk cases 52 into HPV low-risk cases 62 and HPV high-risk cases 64. The method of the invention designates cases testing positive for cancer-associated HPV types to be HPV high-risk cases 64. The method of the invention designates cases positive for non-oncogenic HPV types, or negative HPV DNA to be HPV low-risk cases 62. For HPV low-risk cases 62, the method of the invention recommends a cytology follow-up 70. For HPV high-risk cases 64, the method of the invention recommends a colposcopic procedure in step 80. The method of the invention may recommend other treatment strategies if other standards of care emerge for high-risk cases.

The invention applies to both cytological and histological specimens used to identify cancerous and pre-cancerous conditions based on either image cytometry and DNA testing methods. The DNA testing for cytology includes HPV tests for cervical specimen or fluorescence in-situ hybridization tests for bladder cancer based on the assessment of chromosomes (number, structure) or gene (number, rearrangements), or gene structures. Various polymerase chain reaction (PCR) techniques can be used to determine the presence of circulating tumor cells (CTC) and minimal residual neoplastic disease (MRD). Examples of the clinical utility of this technique include tracking of
hematologic neoplasms with specific genetic alterations, an identification of MRD in epithelial malignancies such as breast and prostate adenocarcinomas or malignant melanoma.

The case triage procedure shown in Figure 1 is applied mainly to cytologically determined borderline (ASCUS, AGUS) cases. However, the ASCUS and AGUS diagnoses are intrinsically subjective and prone to human interpretation variability. Thus, many borderline cases may not be detected cytologically during initial screening. The method and apparatus of the invention therefore further provides for enhancing case triage sensitivity.

Figure 2 shows one embodiment of a method for enhancing triage sensitivity of the invention. The method of the invention 200 begins with a cytology specimen initial screening determined as within normal limits (WNL) cytology specimen 110. A computerized screening system such as the AutoPap 300® receives the WNL cytology specimen 110 in step 120 to generate an analysis score 122. The method performs a potential-risk thresholding test in step 130 to separate the WNL cytology specimens 110 into low-risk cases 132 and potential-risk cases 134. In one embodiment, the potential-risk thresholding test 130 may employ the analysis score 122 to determine a risk category as follows:

IF (Analysis_score < Potential_risk_threshold) then
Low_risk case
ELSE potential-risk case.

In an alternate embodiment, the potential-risk thresholding test 130 may include other factors such as patient age, case history and clinical information. The clinical information may further include such information as co-existing disease, risk factors,
symptoms, etc. In one embodiment, the potential-risk thresholding test 130 comprises the following logic:

IF (Function_3(Analysis_score, age, previous abnormal history, clinical information) < Potential_risk_threshold) then Low_risk case
ELSE potential-risk case
where

Function_3(Analysis_score, age, case history, clinical information) = Analysis_score * f1"(age) * f2"(case history) * f3"(clinical information)

where

f1"(age) = 1.0 if age < 45
0.0 if age ≥ 45

and

f2"(case history) = 0.8 if all previous tests are normal
1.0 if no previous test information is available
2.0 if all previous tests are abnormal
1.5 otherwise

f3"(clinical information) = 0.8 if no co-existing disease, no high risk factors, and no symptoms
1.0 if no clinical information is available
2.0 if having co-existing
disease and high risk factor and with symptoms

1.5 otherwise

In this case, all patients with age greater or equal to 45 will be triaged as low risk cases because clinical data from the AutoPap 300 QC® system suggests that the analysis score is not effective for cases with atrophic cell patterns that occurs in older age individuals.

Those skilled in the art will recognize that other methods such as expert system, Bayes Belief Networks, or artificial neural networks can be used to implement Function_1, Function_2 and Function_3.

The method of the invention automatically recommends a cytology test follow up on a regular time interval, for low-risk cases 132. For potential-risk cases 134, the method of the invention recommends a HPV triage in step 150. The method of the invention categorizes WNL cytology specimens testing positive for cancer-associated HPV types to be HPV high-risk cases 154. WNL cytology specimens 110 testing positive for non-oncogenic HPV types or negative for HPV DNA prompt a cytology follow up recommendation in step 160. HPV high-risk cases 154 prompt a colposcopic procedure recommendation in step 170.

In an alternate embodiment of the invention, the potential-risk cases 134 from the potential-risk thresholding step 130 may be re-screened by another human reader as shown in Figure 3. The potential-risk cases 134 are sent for human rescreening in step 180. The machine may indicate significant locations on the slide for human review.
Lee et al., entitled "INTERACTIVE METHOD AND APPARATUS FOR SORTING BIOLOGICAL SPECIMENS;" provides an example of indicating significant locations on the slide for human review. Either machine-directed rescreening or independent rescreening may be performed in step 180 to categorize the potential-risk cases 134 into non-koilocytic cases 182 and koilocytic cases 184. A non-koilocytic categorization 182 prompts a recommendation for a cytology follow up on a regular time interval in step 190. A koilocytic categorization 184 prompts a recommendation for HPV triage or a colposcopic procedure in step 192.

In one embodiment of the invention, a computerized biomedical specimen processing system provides the analysis score. As disclosed herein the computerized biomedical specimen processing system is used in combination with a host computer to triage cases having equivocal cytology results. One such computerized biomedical specimen processing system is shown and disclosed in the following: pending U.S. Patent Application Serial No. 08/571,686, filed 12/13/95, which is a file wrapper continuation of abandoned U.S. Patent Application Serial No. 07/838,064, entitled "METHOD FOR IDENTIFYING NORMAL BIOMEDICAL SPECIMENS", by Nelson et al., filed February 18, 1992; U.S. Patent No. 5,528,703 which is a continuation in part of abandoned U.S. Patent Application Serial No. 07/838,395, entitled "METHOD FOR IDENTIFYING OBJECTS USING DATA PROCESSING TECHNIQUES", by Lee et al., filed February 18, 1992; U.S. Patent Application Serial No. 07/838,070, now U.S. Pat. No. 5,315,700, entitled "METHOD AND APPARATUS FOR RAPIDLY PROCESSING DATA SEQUENCES", by Johnston et al., filed February 18, 1992; U.S. Patent Application Serial No. 07/838,065, now U.S. Patent No.
5,361,140, filed 02/18/92, entitled "METHOD AND APPARATUS FOR DYNAMIC CORRECTION OF MICROSCOPIC IMAGE SIGNALS" by Hayenga et al.; and allowed U.S. Patent Application Serial No. 08/302,355, for which the issue fee has been paid, filed September 7, 1994 entitled "METHOD AND APPARATUS FOR RAPID CAPTURE OF FOCUSED MICROSCOPIC IMAGES" to Hayenga et al., which is a continuation-in-part of abandoned Application Serial No. 07/838,063 filed on February 18, 1992 the disclosures of which are incorporated herein, in their entirety, by the foregoing references thereto.

The present invention is also related to biological and cytological specimen processing systems as described in the following patent applications which are assigned to the same assignee as the present invention, and which are all hereby incorporated by reference including pending U.S. Patent Application Serial No. 671,984 to Lee entitled "METHOD FOR IDENTIFYING OBJECTS USING DATA PROCESSING TECHNIQUES;" pending U.S. Patent Application Serial No. 08/526,138, filed 9/5/95, which is a file wrapper continuation of abandoned U.S. Patent Application Serial No. 08/153,293, filed 11/16/93, to Nelson et al., entitled "METHOD AND APPARATUS FOR TESTING PROFICIENCY IN SCREENING IMAGES OF BIOLOGICAL SLIDES;" pending U.S. Patent Application Serial No. 08/485,182, filed 06/07/95, to Lee et al., entitled "INTERACTIVE METHOD AND APPARATUS FOR SORTING BIOLOGICAL SPECIMENS;" pending U.S. Patent Application Serial No. 08/309,405, filed 09/20/94, to Frost et al., entitled "AUTOMATIC FOCUSING OF BIOMEDICAL SPECIMENS APPARATUS;" pending U.S. Patent Application Serial No. 08/309,118, filed 9/20/94, to Kuan et al. entitled, "FIELD PRIORITIZATION APPARATUS AND METHOD;" pending U.S. Patent Application Serial No. 08/309,061, filed
Application Serial No. 08/309,117, filed 9/20/94, to Wilhelm et al., entitled "METHOD AND APPARATUS FOR DETECTION OF UNSUITABLE CONDITIONS FOR AUTOMATED CYTOLOGY SCORING;" pending U.S. Patent Application Serial No. 08/309,148, filed 9/20/94, to Lee et al. entitled "METHOD AND APPARATUS FOR IMAGE PLANE MODULATION PATTERN RECOGNITION;" pending U.S. Patent Application Serial No. 08/315,719, filed 9/30/94, to Lee et al., entitled "METHOD AND APPARATUS FOR HIGHLY EFFICIENT COMPUTER AIDED SCREENING;" pending U.S. Patent Application Serial No. 08/472,389, filed 6/7/95, to Oh et al., entitled "IMAGE ENHANCEMENT METHOD AND APPARATUS;" pending U.S. Patent Application Serial No. 08/547,653, filed 10/24/95, to Riley et al., entitled "ASTIGMATISM MEASUREMENT APPARATUS AND METHOD;" allowed U.S. Patent Application Serial No. 08/455,296, for which the issue fee has been paid, filed 5/31/95, to Lee et al., entitled "METHOD AND APPARATUS FOR CONTINUOUSLY MONITORING AND FORECASTING SLIDE AND SPECIMEN PREPARATION FOR A BIOLOGICAL SPECIMEN POPULATION;" pending U.S. Patent Application Serial No. 08/509,181, filed 7/31/95, to Lee et al., entitled "ROBUSTNESS OF CLASSIFICATION MEASUREMENT APPARATUS AND METHOD;" pending U.S. Patent Application Serial No. 08/455,182, filed 5/31/95, to Wilhelm et al., entitled "METHOD AND APPARATUS FOR ASSESSING SLIDE AND SPECIMEN PREPARATION QUALITY;" allowed U.S. Patent Application Serial No. 08/509,182, for which the issue fee has been paid, filed 7/31/95, to Frost et al., entitled "IMAGING SYSTEM TRANSFER FUNCTION CONTROL METHOD AND APPARATUS;" allowed U.S. Patent Application Serial No. 08/455,388, for which the issue fee has been paid, filed 5/31/95, to Lee et al., entitled "METHOD AND APPARATUS FOR INTEGRATING AN AUTOMATED SYSTEM TO A LABORATORY;" pending U.S. Patent
Application Serial No. 08/509,154, filed 7/31/95, to Schmidt et al., entitled "APPARATUS FOR HIGH SPEED MORPHOLOGICAL PROCESSING;" pending U.S. Patent Application Serial No. 08/509,185, filed 7/31/95, to Lee et al., entitled "METHOD AND APPARATUS FOR IMAGE CONTRAST QUALITY EVALUATION."

An interactive scoring method may provide the analysis scores 22, 122 in Figures 1 and 2. Figure 4 shows one embodiment of an interactive scoring method 300 of the invention. Pending U.S. Patent Application Serial No. 08/485,182, filed 06/07/95, to Lee et al., entitled "INTERACTIVE METHOD AND APPARATUS FOR SORTING BIOLOGICAL SPECIMENS" discloses one example of an interactive scoring method of the invention.

The interactive scoring method 300 begins by providing a cytology specimen 310 to a computerized screening system. The method of the invention focuses and performs image acquisition of the cytology specimen 310 in step 320 to provide object images 322. Allowed U.S. Patent Application Serial No. 08/302,355 entitled "METHOD AND APPARATUS FOR RAPID CAPTURE OF FOCUSED MICROSCOPIC IMAGES" discloses an example of a method for focusing and performing image acquisition.

SPECIMEN" disclose examples of methods for the detection of single cell, group, and thick group objects.

The method 300 then provides for scoring and ranking the objects of interest 332 in step 340. In one embodiment of the invention, the method of the invention performs object scoring and ranking from detected features of the objects of interest 332. The features may include morphological features, photometric features, contextual features, as well as group and thick group features. Pending U.S. Patent Application No. 08/309,250 ibid.; pending U.S. Patent Application No. 08/309,061 ibid.; and pending U.S. Patent Application No.08/309,115 ibid disclose an example of the features used to classify objects of interest. Extracted features provide for classification of the objects of interest. Pending U.S. Patent Application No. 08/309,250 ibid.; pending U.S. Patent Application No. 08/309,061 ibid.; and pending U.S. Patent Application No.08/309,115 ibid provide an example of classification according to extracted features. In one embodiment, classification may include integration of multiple cell patterns. Pending U.S. Patent Application No. 08/678,124, which is a file wrapper continuation of abandoned U.S. Patent Application No. 08/308,992 entitled "Apparatus for Identification and Integration of Multiple Cell Patterns" provides an example of classification including integration of multiple cell patterns. The method 300 assigns each potential abnormal object an object score 342 to show a likelihood of the presence of characteristics of interest. In an alternative embodiment of the invention, secondary neural networks or adaptive, non-algorithmic classifiers may be used for object classification. The method 300 provides
for ranking of objects based on the object score 342.

The method 300 selects high ranked objects for human review in step 350. In one embodiment, a cytologist may review the images 322 of the objects or the object fields of view under a microscope. The cytologist may assign a human object score 352 to each reviewed object 322. The human object score 352 reflects the cytologist's confidence of the presence of characteristics of interest. In one embodiment more than one human may score objects.

The method 300 re-classifies the objects 322 in step 360 based on a combination of the human object score 352, computer object score 342 and objects of interest 332. Pending U.S. Patent Application No. 08/485,182 *ibid* provides an example of integration of human and computer scores. Integration of human and computer scores in step 360 provides an object result with confidence values 362.

The method 300 accumulates object results with confidence values 362 in step 370. The method of the invention uses the accumulated results to create a slide score 372 for the specimen 310. US pending Patent Application Serial No. 08/309,931 entitled "Cytological Slide Scoring Apparatus", and pending U.S. Patent Application Serial No. 08/309,209 entitled "A Method and Apparatus for Robust Biological Specimen Classification" provide examples of slide scoring.

The method of the invention then provides the slide score 372 as an analysis score 22, 122 for the methods for enhancing case triage efficacy of the invention and the method for enhancing case triage sensitivity of the invention as disclosed in Figures 1, 2 and 3.

Now refer to Figures 5A and 5B which show a schematic diagram of one embodiment of the apparatus
of the invention for triaging cases having equivocal cytology results. The apparatus of the invention comprises an imaging system 502, a motion control system 504, an image processing system 536, a central processing system 540, and a workstation 542. The imaging system 502 is comprised of an illuminator 508, imaging optics 510, a CCD camera 512, an illumination sensor 514 and an image capture and focus system 516. The image capture and focus system 516 provides video timing data to the CCD cameras 512, the CCD cameras 512 provide images comprising scan lines to the image capture and focus system 516. An illumination sensor intensity is provided to the image capture and focus system 516 where an illumination sensor 514 receives the sample of the image from the optics 510. In one embodiment of the invention, the optics may further comprise an automated microscope. The illuminator 508 provides illumination of a slide. The image capture and focus system 516 provides data to a VME bus 538. The VME bus distributes the data to an image processing system 536. The image processing system 536 is comprised of field-of-view processors 568. The images are sent along the image bus 564 from the image capture and focus system 516. A central processor 540 controls the operation of the invention through the VME bus 538. In one embodiment the central processor 562 comprises a Motorola 68030 CPU. The motion controller 504 is comprised of a tray handler 518, a microscope stage controller 520, a microscope turret controller 522, and a calibration slide 524. The motor drivers 526 position the slide under the optics. A bar code reader 528 reads a barcode located on the slide 1, as shown in Figure 5C. A touch sensor 530 determines whether a slide is under the microscope objective, and a door interlock 532 prevents operation
in case the doors are open. Motion controller 534 controls the motor drivers 526 in response to the central processor 540. An Ethernet (TM) communication system 560 communicates to a workstation 542 to provide control of the system. A hard disk 544 is controlled by workstation processor 550. In one embodiment, workstation 542 may comprise a Sun SPARC Classic (TM) workstation. A tape drive 546 is connected to the workstation processor 550 as well as a modem 548, a monitor 552, a keyboard 554, and a mouse pointing device 556. A printer 558 is connected to the Ethernet (TM) network 560.

During operation the central computer 540, running a real time operating system, controls the automated microscope and the processor to acquire and digitize images from the microscope. The computer 540 also controls the microscope stage to position the specimen under the microscope objective, and from one to 15 field of view (FOV) processors 568 receive images under control of the computer 540.

Referring now to Figure 5C, there shown is placement of a slide 1 in a tray into an optical path of an automated microscope 3 having a turret 22. The stage 21 is movable in the X,Y plane as well as along a Z axis which is perpendicular to the X,Y plane and which is parallel to the optical axis of the automated microscope. The turret 22 may comprise multiple objective lenses as is well known in the art. The microscope turret 522 receives signals from motor drives 526 and positions a selected objective lens into position for viewing a slide, for example.

In operation the workstation processor 550 uses the analysis score determined during slide processing to implement the triage decisions and recommendations disclosed above. These decisions and recommendations
may be implemented in software, in the C programming language in one embodiment, run on workstation processor 550. These decisions and recommendations may be reported on printer 558 as well as displayed on monitor 552 in a well known manner. These decisions and recommendations may also be available remotely via local area networks or remotely via modem 548, also in a well known manner.

The invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use such specialized components as are required. However, it is to be understood that the invention can be carried out by specifically different equipment and devices, and that various modifications, both as to the equipment details and operating procedures, can be accomplished without departing from the scope of the invention itself.

What is claimed is:
CLAIMS

1. A triage method based on a gynecological specimen taken from a patient comprising the steps of:
   (a) scoring the gynecological specimen with a computerized biomedical specimen processing system to generate a gynecological specimen score; and
   (b) automatically recommending with a computer that the patient undergo a colposcopic procedure if the gynecological specimen score falls in a predetermined range of biomedical specimen scores.

2. A triage method based on a cytological specimen taken from a patient, the method comprising the steps of:
   (a) scoring the cytological specimen with a computerized cytological specimen processing system to generate a cytological specimen score; and
   (b) automatically recommending with a computer that the cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores.

3. A triage method based on a histological specimen taken from a patient, the method comprising the steps of:
   (a) scoring the histological specimen with a computerized histological specimen processing system to generate a histological specimen score; and
   (b) automatically recommending with a computer that the histological specimen undergo a DNA
testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores.

4. A triage method based on a cytological specimen taken from a patient, the method comprising the steps of:
   (a) scoring the cytological specimen with a computerized cytological specimen processing system to generate a cytological specimen score;
   (b) recommending that an additional cytological specimen from the patient be obtained; and
   (c) automatically recommending with a computer that the additional cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores.

5. A triage method based on a histological specimen taken from a patient, the method comprising the steps of:
   (a) scoring the histological specimen with a computerized histological specimen processing system to generate a histological specimen score;
   (b) recommending that an additional histological specimen be obtained from the patient; and
   (c) automatically recommending with a computer that the additional histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores.
6. A method to manage undetermined significance biological specimens from a patient comprising the steps of:

(a) scoring the biological specimen with a computerized biological specimen processing system to generate a specimen score;

(b) automatically recommending with a computer that the patient does not require an additional clinical procedure if the specimen score falls in a first predetermined range of specimen scores;

(c) automatically recommending with a computer that the patient requires an additional clinical procedure if the specimen score falls in a second predetermined range of specimen scores; and

(d) automatically recommending with a computer that the patient requires an additional test if the specimen score falls in a third predetermined range of specimen scores.

7. The method of claim 6 wherein the step of automatically recommending with a computer whether the patient requires an additional clinical procedure further comprises the step of automatically recommending with a computer that the patient requires a colposcopic procedure.

8. A method to manage patients having undetermined significance biological specimens comprising the steps of:

(a) scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score;
(b) automatically recommending with a computer that the biological specimen requires additional analysis if the specimen score falls in a first predetermined range of specimen scores; and

c) automatically recommending with a computer that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

9. The method of claim 8 wherein the step of automatically recommending with a computer that the biological specimen requires additional analysis further comprises the step of automatically recommending with a computer that the patient requires triage.

10. A method to manage patients having undetermined significance biological specimens comprising the steps of:

(a) scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score;

(b) automatically recommending with a computer that an additional biological specimen be taken from the patient and that the additional biological specimen requires analysis if the specimen score falls in a first predetermined range of specimen scores; and

(c) automatically recommending with a computer that the patient requires additional clinical procedures if the specimen score
falls in a second predetermined range of specimen scores.

11. The method of claim 10 wherein the step of automatically recommending with a computer that the biological specimen requires additional analysis further comprises the step of automatically recommending with a computer that the patient requires triage.

12. A method of case triage efficacy enhancement for treatment of a patient with equivocal screening test results comprising the steps of:
   (a) obtaining a cytological specimen from the patient;
   (b) scoring the cytological specimen with a computerized scoring system to generate an analysis score for the cytological specimen;
   (c) determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up;
   (d) determining whether the cytological specimen represents a high-risk case and if the cytological specimen represents a high-risk case recommending a colposcopic procedure for the patient; and
   (e) determining whether the cytological specimen represents a mid-risk case and if the cytological specimen represents a mid-risk case recommending a further test on the cytological specimen.

13. The method of claim 12 wherein the step of determining whether the cytological specimen
represents a low-risk case further comprises the step of comparing the analysis score to a low-risk threshold.

14. The method of claim 12 wherein the step of determining whether the cytological specimen represents a high-risk case further comprises the step of comparing the analysis score to a high-risk threshold.

15. The method of claim 12 wherein the step of determining whether the cytological specimen represents a mid-risk case further comprises the step of comparing the analysis score to a mid-risk range.

16. The method of claim 12 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the method further comprising the step of calculating a functional measure of risk based on the analysis score, the age, the case history, and the clinical information, and wherein the step of determining whether the cytological specimen represents a low-risk case further comprises the step of comparing the functional measure of risk to a low-risk threshold.

17. The method of claim 12 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the method further comprising the step of calculating a functional measure of risk based on the analysis score, the age, the case
history, and the clinical information, and wherein the step of determining whether the cytological specimen represents a high-risk case further comprises the step of comparing the functional measure of risk to a high-risk threshold.

18. The method of claim 12 further comprising the steps of:
   (a) recommending a HPV triage as the further test; and
   (b) recommending a cytology follow-up if the HPV triage indicates that the cytological specimen represents a HPV low-risk case and recommending a colposcopic procedure for the patient if the HPV triage indicates that the cytological specimen represents a HPV high-risk case.

19. A method of case triage sensitivity enhancement for treatment of a patient having initial screening determined as within normal limits screening test results, the method comprising the steps of:
   (a) obtaining a cytological specimen from the patient;
   (b) scoring the cytological specimen with a computerized screening system to generate an analysis score for the cytological specimen;
   (c) determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; and
   (d) determining whether the cytological specimen
represents a potential-risk case and if the cytological specimen represents a potential-risk case recommending a further test of the cytological specimen.

20. The method of claim 19 wherein the step of determining whether the cytological specimen represents a low-risk case further comprises the step of comparing the analysis score to a potential-risk threshold.

21. The method of claim 19 wherein the step of determining whether the cytological specimen represents a potential-risk case further comprises the step of comparing the analysis score to a potential-risk threshold.

22. The method of claim 19 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the method further comprising the step of calculating a functional measure of risk based on the analysis score, the age, the case history, and the clinical information, and wherein the step of determining whether the cytological specimen represents a low-risk case further comprises the step of comparing the functional measure of risk to a potential-risk threshold.

23. The method of claim 19 further comprising the steps of:
   (a) recommending a HPV triage as the further test; and
   (b) recommending a cytology follow-up if the HPV
triate indicates that the cytological specimen represents a HPV low-risk case and recommending a colposcopic procedure for the patient if the HPV triage indicates that the cytological specimen represents a HPV high-risk case.

24. The method of claim 19 further comprising the steps of:
   (a) recommending a rescreening of the cytological specimen; and
   (b) recommending a cytology follow-up on a regular time interval if the rescreening indicates that the cytological specimen represents a low-risk case and recommending a colposcopic procedure for the patient if the rescreening indicates that the cytological specimen represents a high-risk case.

25. The method of claim 19 further comprising the steps of:
   (a) recommending a rescreening of the cytological specimen; and
   (b) recommending a cytology follow-up on a regular time interval if the rescreening indicates that the cytological specimen represents a low-risk case and recommending HPV triage for the patient if the rescreening indicates that the cytological specimen represents a high-risk case.

26. An apparatus for diagnosis and colposcopy treatment recommendation based on a gynecological specimen taken from a patient, the apparatus
comprising:
(a) means for scoring the gynecological specimen having a gynecological specimen score output; and
(b) means for recommending that the patient undergo a colposcopic procedure connected to the gynecological specimen score output.

27. An apparatus for triage based on a cytological specimen taken from a patient, the apparatus comprising:
(a) means for scoring the cytological specimen having a cytological specimen score output; and
(b) means for recommending that the cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores, wherein the recommending means is connected to the cytological specimen score output.

28. An apparatus for triage based on a histological specimen taken from a patient, the apparatus comprising:
(a) means for scoring the histological specimen having a histological specimen score output; and
(b) means for recommending that the histological specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores, wherein the recommending means is connected to the histological specimen score output.
29. An apparatus for triage based on a cytological specimen taken from a patient, the apparatus comprising:

(a) means for scoring the cytological specimen having a cytological specimen score output; and

(b) means for recommending that an additional cytological specimen undergo a DNA testing procedure if the cytological specimen score falls in a predetermined range of cytological specimen scores, wherein the scoring means is connected to the cytological specimen score output.

30. An apparatus for triage based on a histological specimen taken from a patient, the apparatus comprising:

(a) means for scoring the histological specimen having a histological specimen score output; and

(b) means for recommending that an additional patient specimen undergo a DNA testing procedure if the histological specimen score falls in a predetermined range of histological specimen scores, wherein the recommending means is connected to the histological specimen score output.

31. An apparatus to manage patients having undetermined significance biological specimens comprising:

(a) means for scoring a biological specimen from a patient having a biological specimen score output;

(b) means for recommending with a computer that
the patient does not require an additional clinical procedure if the specimen score falls in a first predetermined range of specimen scores; and

5 (c) means for recommending with a computer that the patient requires an additional clinical procedure if the specimen score falls in a second predetermined range of specimen scores; and

10 (d) means for recommending with a computer that the patient requires an additional test if the specimen score falls in a third predetermined range of specimen scores.

32. The apparatus of claim 31 further comprising a means for recommending that the patient requires a colposcopic procedure.

33. An apparatus to manage patients having undetermined significance biological specimens comprising:

20 (a) means for scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score;

25 (b) means for recommending with a computer that the biological specimen requires additional analysis if the specimen score falls in a first predetermined range of specimen scores; and

(c) means for recommending with a computer that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.
34. The apparatus of claim 33 further comprising a means for recommending that the patient requires triage.

35. An apparatus to manage patients having undetermined significance biological specimens comprising:
   (a) means for scoring a biological specimen from a patient with a computerized biological specimen processing system to generate a specimen score;
   (b) means for recommending that an additional biological specimen be taken from the patient and that the additional biological specimen requires analysis if the specimen score falls in a first predetermined range of specimen scores; and
   (c) means for recommending that the patient requires additional clinical procedures if the specimen score falls in a second predetermined range of specimen scores.

36. The apparatus of claim 35 further comprising a means for recommending with a computer that the biological specimen requires triage.

37. An apparatus for case triage efficacy enhancement for treatment of a patient with equivocal screening test results comprising:
   (a) means for obtaining a cytological specimen from the patient;
   (b) means for scoring the cytological specimen with a computerized scoring system to generate an analysis score for the cytological specimen;
(c) means for determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up;

(d) means for determining whether the cytological specimen represents a high-risk case and if the cytological specimen represents a high-risk case recommending a colposcopic procedure for the patient; and

(e) means for determining whether the cytological specimen represents a mid-risk case and if the cytological specimen represents a mid-risk case recommending a further test on the cytological specimen.

38. The apparatus of claim 37 further comprising a means for comparing the analysis score to a low-risk threshold.

39. The apparatus of claim 37 further comprising a means for comparing the analysis score to a high-risk threshold.

40. The apparatus of claim 37 further comprising a means for comparing the analysis score to a mid-risk range.

41. The apparatus of claim 37 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the apparatus further comprising a means for calculating a functional measure of risk based on the analysis score, the age, the case history, and the clinical information, and
wherein the apparatus further comprises a means for determining whether the cytological specimen represents a low-risk case further comprises the step of comparing the functional measure of risk to a low-risk threshold.

42. The apparatus of claim 37 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the apparatus further comprising a means for calculating a functional measure of risk based on the analysis score, the age, the case history, and the clinical information, and wherein the means for determining whether the cytological specimen represents a high-risk case further comprises a means for comparing the functional measure of risk to a high-risk threshold.

43. The apparatus of claim 37 further comprising:
   (a) means for recommending a HPV triage as the further test; and
   (b) means for recommending a cytology follow-up if the HPV triage indicates that the cytological specimen represents a HPV low-risk case and recommending a colposcopic procedure for the patient if the HPV triage indicates that the cytological specimen represents a HPV high-risk case.

44. An apparatus for case triage sensitivity enhancement for treatment of a patient having initial within normal limits screening test results, the apparatus comprising:
   (a) means for obtaining a cytological specimen
from the patient;

(b) means for scoring the cytological specimen with a computerized screening system to generate an analysis score for the cytological specimen;

(c) means for determining whether the cytological specimen represents a low-risk case and if the cytological specimen represents a low-risk case recommending a cytology follow-up; and

(d) means for determining whether the cytological specimen represents a potential-risk case and if the cytological specimen represents a potential-risk case recommending a further test of the cytological specimen.

45. The apparatus of claim 44 wherein the means for determining whether the cytological specimen represents a low-risk case further comprises a means for comparing the analysis score to a potential-risk threshold.

46. The apparatus of claim 44 wherein the means for determining whether the cytological specimen represents a potential-risk case further comprises a means for comparing the analysis score to a potential-risk threshold.

47. The apparatus of claim 44 wherein the patient has an age, a case history, and clinical information comprising co-existence of disease, risk factors, and symptoms, the apparatus further comprising a means for calculating a functional measure of risk based on the analysis score, the age, the
case history, and the clinical information, and wherein the means for determining whether the cytological specimen represents a low-risk case further comprises a means for comparing the functional measure of risk to a potential-risk threshold.

48. The apparatus of claim 44 further comprising:
   (a) means for recommending a HPV triage as the further test; and
   (b) means for recommending a cytology follow-up if the HPV triage indicates that the cytological specimen represents a HPV low-risk case and recommending a colposcopic procedure for the patient if the HPV triage indicates that the cytological specimen represents a HPV high-risk case.

49. The apparatus of claim 44 further comprising:
   (a) means for recommending a rescreening of the cytological specimen; and
   (b) means for recommending a cytology follow-up on a regular time interval if the rescreening indicates that the cytological specimen represents a low-risk case and recommending a colposcopic procedure for the patient if the rescreening indicates that the cytological specimen represents a high-risk case.

50. The apparatus of claim 44 further comprising:
   (a) means for recommending a rescreening of the cytological specimen; and
   (b) means for recommending a cytology follow-up on a regular time interval if the
rescreening indicates that the cytological specimen represents a low-risk case and recommending HPV triage for the patient if the rescreening indicates that the cytological specimen represents a high-risk case.

51. The method of claim 18 wherein the step of recommending a HPV triage further comprises the step of obtaining an additional specimen.

52. The method of claim 23 wherein the step of recommending a HPV triage further comprises the step of obtaining an additional specimen.

53. The method of claim 25 wherein the step of recommending a HPV triage further comprises the step of obtaining an additional specimen.

54. The apparatus of claim 43 wherein the means for recommending a HPV triage makes the recommendation based on an additional specimen.

55. The apparatus of claim 48 wherein the means for recommending a HPV triage makes the recommendation based on an additional specimen.

56. The apparatus of claim 50 wherein the means for recommending the HPV triage makes the recommendation based on an additional specimen.
Fig. 2

1. WNL CYTOLOGY SPECIMENS
2. COMPUTERIZED SCREENING SYSTEM
   - ANALYSIS SCORE
3. POTENTIAL-RISK THRESHOLDING
   - LOW-RISK CASES
     - CYTOLOGY FOLLOW-UP ON REGULAR TIME INTERVAL
   - POTENTIAL-RISK CASES
     - HPV TRIAGE
       - HPV LOW-RISK CASES
         - CYTOLOGY FOLLOW-UP
       - HPV HIGH-RISK CASES
         - COLPOSCOPIC PROCEDURE
   - 200