



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

P950009/S2

Ms. Mary K. Norton
Director of Regulatory
and Clinical Affairs
NEOPATH, INC.
8271 154th Avenue, N.E.
Redmond, Washington 98052

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY - 5 1998

Re: P950009/S2
AutoPap® Primary Screening System
Filed: June 6, 1996
Amended: July 8, July 23, August 13, August 15, October 21,
November 8, 1996; August 29, October 17, November 7,
December 11, 1997; February 4, February 27, March 30,
March 31, and April 30, 1998

Dear Ms. Norton:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the AutoPap® Primary Screening System. The AutoPap® Primary Screening System is an automated cervical cytology screening device intended for use in initial screening of Papanicolaou (Pap) smear slides. The AutoPap® Primary Screening System identifies up to 25% of successfully processed slides as requiring no further review. The AutoPap® Primary Screening System also identifies at least 15% of all successfully processed slides for a second manual review.

The device is to be used only on conventionally prepared Pap smear slides and is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions; it is not intended to be used on slides designated by the laboratory as "high risk".

Intended users are trained cytology laboratory personnel operating under the direct supervision of a qualified cytology supervisor or laboratory manager/director.

The PMA supplement is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device as modified upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may

use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/pmapage.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Peter E. Maxim, Ph.D. at (301) 594-1293.

Sincerely yours,

Kimber C. Richter

Kimber C. Richter, M.D.
Deputy Director for Clinical and Review Policy
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

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I. General Information

Device Generic Name

Cervical cytology device:
Automated image analysis cytology screening device

Device Trade Name

AutoPap[®] Primary Screening System

Applicant's Name and Address

NeoPath, Inc.
8271 154th Avenue NE
Redmond, WA 98052

PMA Number

P950009/S002

Date of Panel Recommendation

January 28, 1998

Date of Notice of Approval to the Applicant

May 5, 1998

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II. Indications for Use

The AutoPap® Primary Screening System is an automated cervical cytology screening device intended for use in initial screening of Papanicolaou (Pap) smear slides. The AutoPap® Primary Screening System identifies up to 25% of successfully processed slides as requiring no further review. The AutoPap® Primary Screening System also identifies at least 15% of all successfully processed slides for a second manual review.

The device is to be used **only** on conventionally prepared Pap smear slides (glass slides and coverslips) and is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions; it is not intended to be used on slides designated by the laboratory as “high risk.”

Intended users are trained cytology laboratory personnel operating under the direct supervision of a qualified cytology supervisor or laboratory manager/director.

III. Device Description

The AutoPap® Primary Screening System is an automated cytology screening device that classifies slides using a high speed video microscope, image interpretation software, and morphology computers to image and analyze the complex images on a Pap smear. The device is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions. These abnormalities fall within the following diagnostic categories of The Bethesda System (TBS):

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells of undetermined significance (ASCUS)
- Low-grade squamous intraepithelial lesions (LSIL)
- High-grade squamous intraepithelial lesions (HSIL)
- Squamous cell carcinoma

Glandular Cell

- Atypical glandular cells of undetermined significance (AGUS), including Adenocarcinoma in situ (AIS)
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma

A. Device Configuration

The AutoPap® Primary Screening System consists of two main components: the Workstation and the Instrument. The Workstation components (computer, monitor, keyboard, mouse, modem and printer) are mounted on a mobile cart that may be moved to provide access to power and communication connections. The AutoPap® Instrument and Workstation are inter-connected by an Ethernet local area network.

The AutoPap® Workstation is the external interface to the AutoPap® Primary Screening System. The Workstation software continuously monitors the Instrument status and acquires slide-processing data. The

Workstation also stores these data so that reports of Pap smear processing results can be generated and Instrument operation can be validated.

B. *Pap Smear Preparation*

The AutoPap[®] Primary Screening System generally does not require special preparation of conventional Pap smear slides with glass coverslips by the laboratory. Specimens are fixed with an alcohol spray or bath as soon as the sample is taken. Pap smear slides are sent to a cytology laboratory where the specimens are prepared using the standard Papanicolaou staining method and sealed under coverslips.

Each prepared slide is affixed with a slide barcode label and loaded into an AutoPap[®] slide tray, which holds up to eight slides. The trays (up to 36) are placed into the AutoPap[®] Instrument, which then automatically analyzes the slides.

C. *AutoPap[®] Primary Screening System Processing*

After slide trays are loaded into the AutoPap[®] Primary Screening System, they are moved automatically from the input hopper to the microscope stage. For each slide in the tray, the device checks the slide for physical integrity, reads the slide barcode label, scans and analyzes the slide at low power, and then scans and analyses prioritized high-power fields.

During this process, numerous checks are performed to ensure that the microscope slide and specimen are adequate for device analysis. At the conclusion of scanning, various scores and measures are computed for each successfully processed slide. These scores are compared to threshold values to determine the slide processing result. This process continues for each slide in the tray. When the last slide in the tray has completed processing, the tray barcode is read and the slide tray is moved to the output hopper. Each tray has a unique barcode to facilitate the location of individual slides within a group of trays.

Before the first tray and after each tray is processed, a comprehensive system integrity assessment of the Instrument is performed automatically for quality assurance to ensure that all data collection and image analysis mechanisms are operating within specified limits.

The results of all these tests are compared to specific performance limits to validate the processing result for each slide in the tray.

A slide is *completely processed* if the slide is checked for physical integrity, scanned and evaluated, and further qualified by system integrity checking. If slide processing is interrupted (for example, by power failure), partial, non-qualified results for slides will be stored by the device. These slides are termed *incompletely processed* and will not be validated or given slide processing results. The laboratory may print a report indicating the barcodes of these slides, which should be rerun on the Instrument.

Results for completely and incompletely processed slides are validated and summarized into slide processing results. As slide processing results are computed, they may be printed in slide processing reports from the Workstation.

The AutoPap® Primary Screening System algorithms include the AutoPap® 300 QC System algorithms plus additional, or “second opinion,” algorithms to improve the detection of abnormal slides.

The histogram in Figure 1 illustrates how the AutoPap® Primary Screening System classified slides from the clinical study into **No further Review/Review/QC Review** categories. The classification percentages in the figure are averages, representing slides across all study sites.

The slides in zones B and D represent the additional **Review** and **QC Review** slides, respectively, classified by the AutoPap® Primary Screening System’s “second opinion” algorithms.

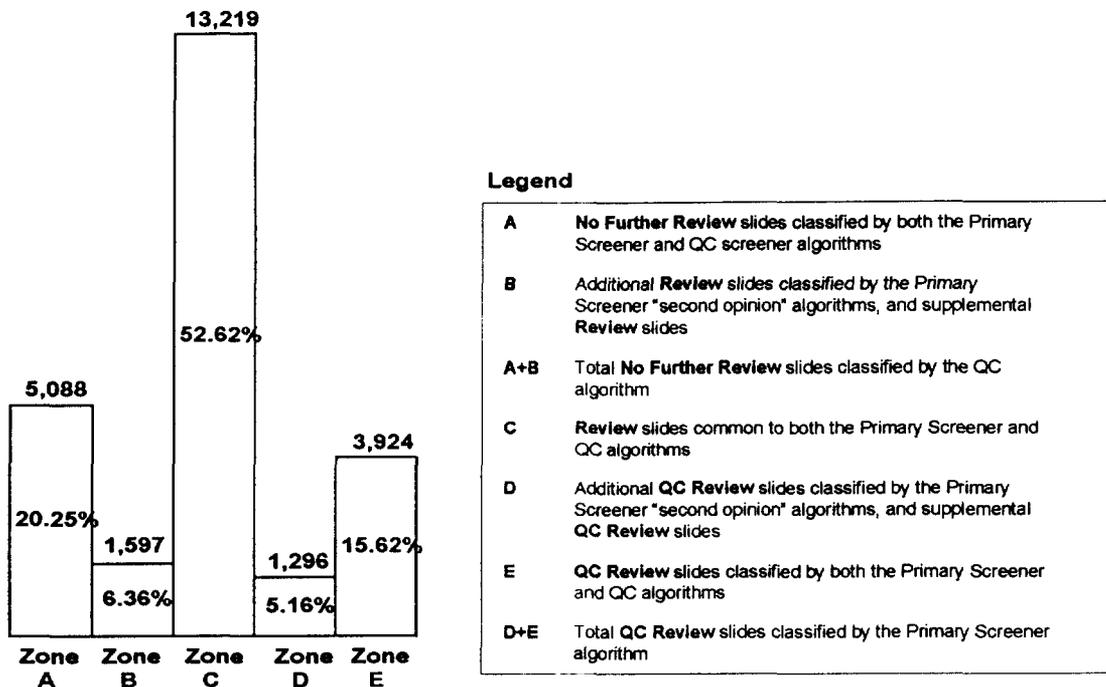


Figure 1 AutoPap® Primary Screening System classification of slides across all study sites.

D. AutoPap® Slide Classification

The AutoPap® Primary Screening System algorithms are trained to detect evidence of morphologic changes associated with epithelial abnormalities, specimen adequacy, and benign cellular changes and infections. For each processed slide, the AutoPap® Primary Screening System uses this morphological information to classify slides as No Further Review, Review, or QC Review.

Each slide is processed only once on the AutoPap® Primary Screening System. Each successfully processed slide is assigned a score, which the device uses to rank slides according to the likelihood that a slide contains abnormalities, unsatisfactory conditions, or benign cellular changes. Some slides may not be suitable for processing on the device due to problems with the slide, the coverslip, or the preparation of the specimen; these slides require manual screening.

Classification of No Further Review Slides

The AutoPap® Primary Screening System classifies up to, but no more than, 25% of all successfully processed slides as **No Further Review**. The **No Further Review** slides have the highest probability of being normal, and may be archived by the laboratory as within normal limits (WNL).

Classification of Review Slides

The remaining slide population, at least 75%, is likely to contain the abnormal or unsatisfactory slides. These slides are classified as **Review** by the AutoPap® Primary Screening System and require manual review. All **Review** slides that are classified as WNL by the cytotechnologist are eligible for rescreening.

Classification of QC Review (Rescreen) Slides

The AutoPap® Primary Screening System also classifies at least 15% of *all* successfully processed slides as eligible for rescreening. The slides in this enriched group have the highest likelihood of being abnormal. This enriched group of slides may be used as a substitute for the 10% random selection of slides that constitutes laboratory quality control review.

E. AutoPap® Primary Screening System Lab Workflow

The workflow of the AutoPap® Primary Screening System in a laboratory is shown in Figure 2.

Manual Screening

After the slides are processed by the AutoPap® Primary Screening System, a variety of reports may be printed that contain the slide classification results. The main report used during primary screening is the Ranked Review Report, which lists slides classified as **Review**, ranks slides according to probable abnormality, and provides slide adequacy information (see **AutoPap Reports** section in this document).

The cytotechnologist screens the **Review** slides and typically passes the abnormal slides to a senior cytotechnologist or a cytopathologist for manual review. Slides determined to be WNL by the

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cytotechnologist are passed on to a laboratory technician for sorting for quality control rescreening.

Quality Control Rescreen

After the cytotechnologists have completed the initial manual screening of the **Review** slides, a QC Ranked Review Report is printed. This report identifies the slides selected by the device for quality control rescreening and provides the barcode numbers of **QC Review** and **Review** slides in ranked order. **QC Review** slides screened originally by a cytotechnologist as WNL are required to be selected a second time. Additional **Review** slides may be selected by rank to supplement the quantity of **QC Review** slides to satisfy the laboratory's QC Review rate requirements. This enriched population of slides can be used as a substitute for the 10% random selection of slides that constitutes laboratory quality control review.

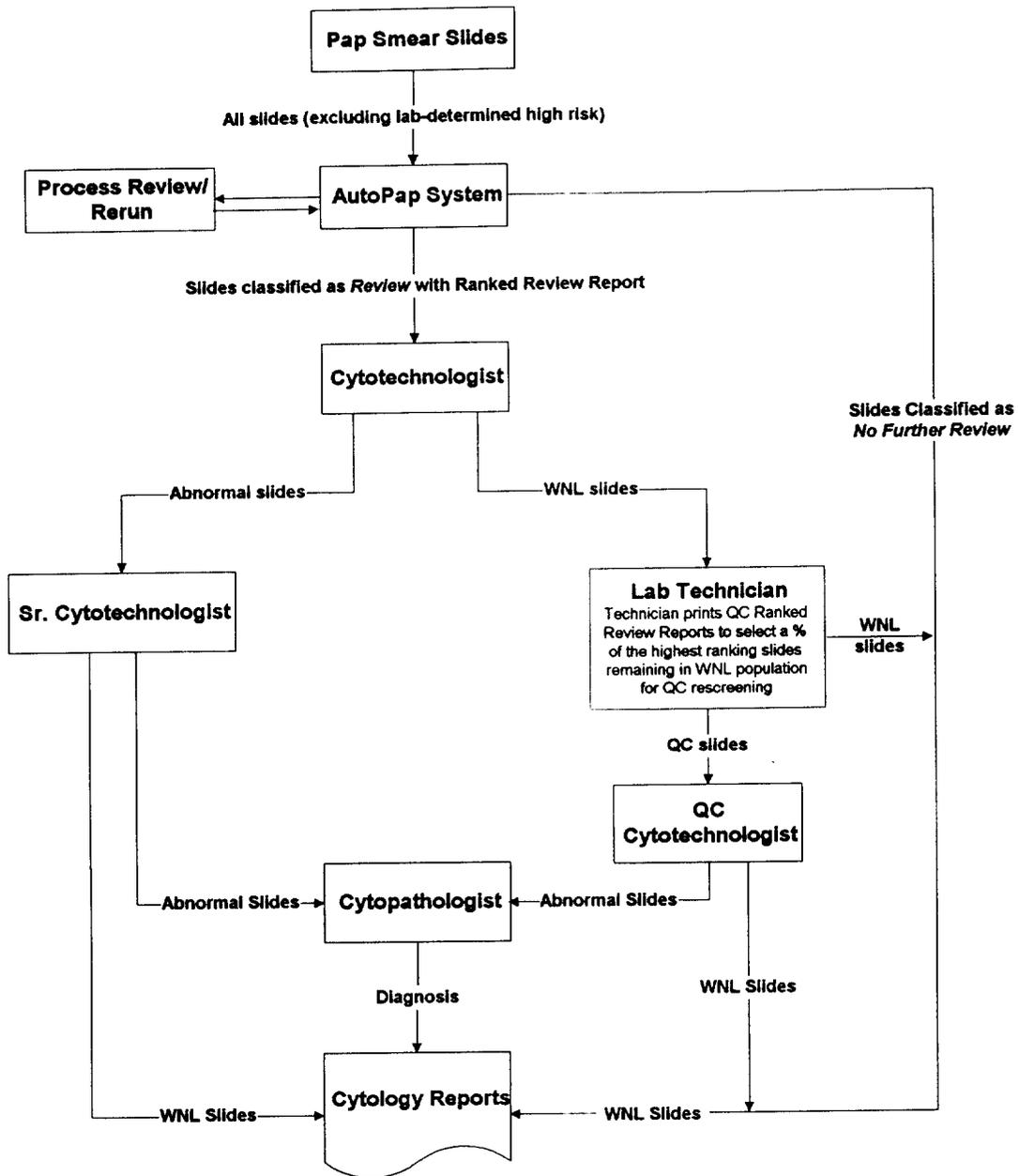


Figure 2 AutoPap® Primary Screening System laboratory workflow.

F. AutoPap[®] Reports

The AutoPap[®] reports, including the Archive Report, Ranked Review Report, and Quality Control (QC) Ranked Review Report, provide the following information.

Ranking Information

To assist the cytotechnologist during manual review, the device ranks the slides for probable abnormality. Each slide is individually ranked from 1 to n , where a rank of 1 indicates a slide most likely to contain abnormality and n is the slide least likely to contain abnormality (n is the number of slides in a print set). Additionally, each slide is assigned a group ranking, ranging from 1 to 5, where a rank of 1 indicates the group most likely to contain abnormalities.

The AutoPap Archive Report for **No Further Review** slides does not provide slide ranks for probable abnormality or a slide adequacy evaluation of unsatisfactory because these slides are classified as WNL and archived.

Evaluation of Slide Adequacy

The device evaluates slide adequacy according to The Bethesda System slide adequacy criteria. The device reports three adequacy parameters: squamous component (detected, not detected), endocervical component (detected, not detected), and inflammation/obscuration (a percentage of the coverslip area). The AutoPap[®] Primary Screening System uses the combination of these parameters to classify the slide as satisfactory, satisfactory but limited by (SBLB), or unsatisfactory.

Processing Information

The device confirms that the slide was completely and successfully processed.

G. Device Limitations

This section describes the limitations on the use of the AutoPap[®] Primary Screening System.

High Risk Slides

The AutoPap® Primary Screening System analysis of Pap smears is not intended to replace laboratory slide review processes for “high-risk” slides. Such “high risk” slides are those where a primary health care provider has requested special handling of a case for a specified concern, or where the clinical laboratory, through its own procedures, has identified a need for a high-level screening of the case.

The Bethesda System Categories

The performance characteristics of the AutoPap® Primary Screening System have not been established for the detection of the following diagnostic categories of The Bethesda System:

Endometrial cells, cytologically benign, in a post-menopausal woman.

Reactive changes associated with radiation and atrophy with inflammation.

Rare malignant neoplasm's, such as extrauterine and metastatic carcinomas, and sarcomas.

Conventional Pap Smears

The AutoPap® Primary Screening System is intended to process only conventionally prepared (not liquid-based) cervical/vaginal Pap smear slides that meet the slide, coverslip, and staining characteristics stated in the Operator's Manual.

Staining

Although the AutoPap® Primary Screening System is compatible with a wide range of staining procedures currently implemented in clinical laboratories, the device is *not* compatible with all staining methods currently in use. NeoPath can assist the laboratory in ensuring that the staining method is compatible with the device.

Training

All personnel who use the AutoPap® Primary Screening System should be trained in the use of the device. NeoPath will train laboratory-designated personnel in the use of the device.

False Negatives

The AutoPap® Primary Screening System classifies up to 25% of the slides as **No Further Review**. This population of slides may contain a small number of abnormal or unsatisfactory slides. In addition, slides with infections present may be classified as **No Further Review**.

IV. Alternative Practices and Procedures

Laboratories currently perform Pap smear screening by a manual microscopic examination of Pap smear slides. Laboratories perform the quality control function by removing a random sample of slides from the population classified as normal for a second manual examination.

There are two devices for which there is an approved PMA for adjunctive and quality control testing of Pap smears.

V. Marketing History

The AutoPap® 300 QC System, for which there is an approved PMA for adjunctive and quality control testing of Pap smears, is in commercial use in laboratories in the United States. The AutoPap® 300QC System has also been marketed in Australia, Japan, Italy, and Korea.

The AutoPap® 300 QC System, as both a primary and quality control screening system, has been marketed in Canada, Australia, the Netherlands, Japan, and Korea.

VI. Adverse Effects of the Device on Health

Clinical testing with the AutoPap® Primary Screening System has shown that a small number of abnormal or unsatisfactory slides may not be detected by the AutoPap® Primary Screening System. As with manual screening, false negative and false positive results may still occur. False negatives may result in the delay of additional diagnostic procedures and possibly treatment for the patient. False positives result in more slides being screened and referred for pathologist review or additional diagnostic tests.

VII. Summary of Studies

A. Reports of Nonclinical Studies

Testing was conducted to determine the requirements for abnormal cell sensitivity, the requirements for the image analysis algorithm, and advanced methods for image collection. Several studies were conducted to characterize the interactions between the algorithms, system software, and optical-mechanical systems. Additional evaluations of the various algorithm modules helped determine the acceptance ranges for focus, prevalence of bubbles and other obscuring matter, and slide thickness.

B. Reports of Preclinical Studies

Early Studies

Several preclinical studies were conducted to gather estimates of the performance of the AutoPap® 300 QC System and to determine the validity of the protocols developed to test intended use.

Several thousand slides were processed and analyzed, providing information regarding the performance of the software technology, the reliability of the hardware, and the ability of the laboratories to follow the protocol design. These tests provided preliminary data regarding estimates of sensitivities to abnormal slides as well as process yield information.

The results of clinical studies, for the AutoPap® 300 QC System were considered by the FDA in support of the current Prospective Intended Use Study for the AutoPap Primary Screening System®.

During the clinical trials, for the QC System, two sensitivity studies - the Historical Sensitivity Study (HSS) and the Current Archive Study (CAS) - evaluated the performance of the device on abnormal slides. This study data was considered in the review of the current submission to provide information about the expected sensitivity of the AutoPap® Primary Screening System to all the Bethesda System categories - particularly to HSIL and above

HSS

Five labs participated in the HSS which used large sample sizes of archived abnormal slides: AGUS, LSIL, HSIL, detected cancer (squamous, glandular, and Extrauterine) and detected false negative slides. The study used the sign-out diagnoses from each laboratory as the study diagnoses. Each abnormal slide also required a normal matched-control slide which gave a total of 3,589 slides used in the analysis.

The AutoPap[®] 300 QC System classified as **QC Review** 82% of the HSIL's and 79% of the cancers at a 10% QC Review rate. The sensitivity of the device to various cancers showed 77% of them being identified for QC rescreening. In this study the **No Further Review** rate was up to 30% and the **QC Review** rate was 10%. For the AutoPap[®] Primary Screening System, algorithms were designed to detect more glandular cell abnormalities and unsatisfactory slides. This design change required that the original up to 10% QC Review rate be increased to 15% and that the original 30% No Further Review rate be decreased to 25%. All the slides classified for QC Review by the AutoPap[®] 300 QC System were still classified as such by the AutoPap[®] Primary Screening System.

CAS

Five laboratories participated in the CAS study, which used recent abnormal slides processed by the laboratory during the same time period that the prospective, intended use study for the AutoPap[®] 300 QC System was being conducted. The diagnostic categories included ASCUS, AGUS, LSIL, HSIL, cancer, and detected false negatives. There was a total of 2,584 slides that qualified for use in this analysis. Acceptable sensitivities were demonstrated for all categories of abnormality errors by study sites.

The data results showed that the device had a significant sensitivity to cancer slides and for a subpopulation of biopsy-confirmed HSIL and cancer slides.

A study was conducted to evaluate the performance of the AutoPap[®] 300 QC System on slides with a low prevalence of abnormal cells. A set of 181 difficult slides were re-screened by the NeoPath Cytopathology Department to determine the actual number of abnormal cells on each slide: 109 slides had 20 or more abnormal

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cells; 72 slides had less than 20 abnormal. The 181 slides were classified as Review or No Review at a 30% No Review rate.

The data show that 61.1% (44/72) of the slides containing less than 20 abnormal cells were classified as Review while 38.9% (28/72) were classified as No Review. The data are similar for the slides containing 20 or more abnormal cells; 61.5% (67/109) were classified as Review and 38.5% (42/109) were put in the No Review category.

Feasibility Study

A feasibility study was conducted to compare the effectiveness of the current laboratory screening process with and without the incorporation of AutoPap® ranked review reports in the screening process. Slides classified as Review by the AutoPap® Primary Screening System are ranked according to their evaluation score.

The objective of this study was to compare the effectiveness of the laboratory cytotechnologist screening process with and without the incorporation of AutoPap® ranked review reports in that process.

The analysis confirmed the following:

- The AutoPap® Assisted Practice was similar to Current Practice in the detection of abnormal cases.
- The AutoPap® Assisted Practice was similar to Current Practice in the detection of WNL cases.

The ranked review reports indicated that the slide rank correlated with the likelihood of the slide being abnormal.

C. Reports of Clinical Studies

A Prospective, Intended Use Study was conducted at five cytology laboratories to evaluate the effectiveness of the AutoPap® Primary Screening System in detecting abnormal and normal Pap smears when the device was used as a combined primary screening system and quality control rescreener.

Of the 31,507 Pap smear slides in the study, 25,124 were evaluated in a two-arm study comparing current practice with an AutoPap® Primary Screening System-assisted practice (referred to in this section

and in the data tables as the AutoPap® Assisted Practice). These two study arms were defined as follows:

- Current Practice consisted of 100% manual initial screening and 10% random rescreening (designated as *quality control*)
- AutoPap® Assisted Practice consisted of 100% AutoPap® System initial screening, at least 75% AutoPap®- assisted manual screening, and 15% AutoPap®- assisted manual rescreening

Slides not meeting the inclusion criteria for the study, such as high risk slides, were excluded from the analysis. The AutoPap® Primary Screening System is not intended to replace individual laboratory processes for screening high risk slides.

The goal of the clinical study was to demonstrate that, compared to current laboratory practice, the AutoPap® Primary Screening System detected more abnormal slides in the following diagnostic categories:

ASCUS+ (All abnormal slides <i>combined</i>)	Atypical squamous cells of undetermined significance and above; additionally includes the categories AGUS, LSIL, HSIL, AIS, and cancer
LSIL	Low-grade squamous intraepithelial lesion
LSIL+	In addition to LSIL, includes the categories HSIL, AIS, and cancer

An additional goal was to demonstrate that, compared to current practice, the device detected an equivalent number of satisfactory but limited by (SBLB) and unsatisfactory slides.

Slide Accountability

As shown in Table 1, the study analyzed a total of 25,124 slides.

Table 1 Slide Accountability

Number of slides in study	31,507
Excluded (High risk)	-3,200
Excluded (Device exclusions)*	-1,132
Excluded (Lab exclusions)†	-1,004
Entered in study	26,171
Failed processing on AutoPap	-963
Processed on AutoPap	25,208
Excluded from analysis (no truth determination)‡	-84
Total Slides Analyzed	25,124

* Broken slides, slides with plastic coverslips, non-Pap smear slides

† Multiple slides from one patient, dotted slides, markings, etc.

‡ Slides not available from labs for truth determination

Study Truth (Truth Determination Process)

Study truth was determined by cytological confirmation, not by histologic biopsy. The true diagnosis for the slides analyzed during the clinical trial was determined as follows:

- When the cytotechnologists' screening diagnoses from the AutoPap® Assisted Practice and Current Practice agreed, this diagnosis was considered to be the true cytological diagnosis for the slide, or truth.
- When the cytotechnologists' screening diagnoses from the AutoPap® Assisted Practice and Current Practice disagreed, an external discrepancy panel (EDP) was convened. An external discrepancy panel consisted of a group of three cytopathologists who independently diagnosed a slide. If two out of three agreed, a diagnosis was determined; otherwise, the slide was reviewed at a multi-head microscope until a consensus diagnosis was achieved. A total of 24 cytopathologists, or 8 groups of 3, participated in this process.
- When adequacy determinations between the two study arms agreed, this was also considered to be truth.

- When adequacy determinations between the two study arms disagreed, a single, independent senior cytotechnologist reviewed the slide to determine truth.

Definition of High Risk

During the study, each laboratory applied its own definition of high risk. A high risk definition consisted of one or more of the reasons listed below:

Physician-designated high risk patients; prior abnormal gynecological history; postmenopausal or abnormal vaginal bleeding; DES patients; previous breast cancer or history of malignancy; previous tissue or Pap diagnosis of HPV, dysplasia, or HIV infection; multiple sex partners; visible lesion; early age of sexual intercourse; smoker.

All known high risk slides were excluded from the study. Table 2 shows the percentage of slides excluded for high risk reasons at each site.

Table 2 High Risk Exclusion Rates by Site

Site	High Risk Exclusion %
1	5.70%
2	6.13%
3	7.09%
4	11.80%
5	14.27%

Clinical Study Results

In this clinical study, 25,124 slides were analyzed in a comparison of two study arms: the AutoPap® Assisted Practice and Current Practice. The slides were submitted to the truth determination process described in Section C.1.2 so that each slide had a final cytologic diagnosis (study truth). The cytotechnologist diagnoses from one study arm could be compared to the other study arm as well as to study truth. The distribution of these 25,124 slides is shown in the following tables:

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Table 3 Distribution of Study Slides

Diagnosis	Number of Slides
Unsatisfactory	171
WNL	23,556
All Abnormals	1,397
Total	25,124

Table 4 Distribution of Abnormal Slides

Diagnosis	Number of Slides
ASCUS	998
AGUS	51
LSIL	278
HSIL	67
AIS	1
Cancer	2
Total	1,397

Summary of the Analyses of Diagnostic Categories

In this study, the AutoPap® Primary Screening System was used to detect abnormal and normal Pap smears, whereby up to 25% of the slides could be classified for **No Further Review** and archived by the laboratory.

The results of this study showed that the AutoPap® Assisted Practice improved the laboratories' ability to detect abnormal cervical cells and precursors, while also effectively assessing specimen adequacy. The AutoPap® Primary Screening System improved sensitivity by increasing the detection of abnormalities in the **Review** population and by enhancing the recovery of abnormalities that may have been missed during initial manual screening in the rescreen population (termed **QC Review**), without decreasing specificity.

Table 5 compares the AutoPap® Assisted Practice to Current Practice for all diagnostic categories. The diagonal values (shaded) in the table show where the two study arms agreed on the diagnosis. The off-diagonals show where the study arms disagreed. These discordance's were used to compare the diagnostic performance between the two study arms.

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The *Total* columns in the table show the number of abnormal slides for each diagnostic category that were correctly classified by each study arm. The values shown in parenthesis are the total number of slides in each diagnostic category as determined by truth.

Table 5 AutoPap Assisted Practice Diagnosis vs. Current Practice Diagnosis
(N) = Total Number of Slides in the Diagnostic Category as Determined by Truth

		Current Practice Diagnosis							Total	
		Unsat (171)	WNL (23,566)	ASCUS (998)	AGUS (51)	LSIL (278)	HSIL (67)	AIS (1)	Cancer (2)	
AutoPap- Assisted Practice Diagnosis	Unsat (171)	99	38	0	0	0	0	0	0	137
	WNL (23,566)	34	23,566	163	8	25	1	1	0	23,788
	ASCUS (998)	0	232	603	0	0	0	0	0	835
	AGUS (51)	0	9	0	34	0	0	0	0	43
	LSIL (278)	0	45	0	0	208	0	0	0	253
	HSIL (67)	0	3	0	0	0	63	0	0	66
	AIS (1)	0	0	0	0	0	0	0	0	0
	Cancer (2)	0	2	0	0	0	0	0	0	2
	Total	133	23,885	766	42	233	64	1	0	25,124

Epithelial Abnormalities

This section provides the results for the epithelial abnormality categories of ASCUS+ (includes ASCUS, AGUS, LSIL, HSIL, AIS, and cancer) ASCUS/AGUS, LSIL, LSIL+ (includes LSIL, HSIL, AIS, and cancer), and HSIL+ (includes HSIL, AIS, and cancer). To determine whether a statistically significant greater number of slides in these categories were detected by the cytotechnologists in the AutoPap® Assisted Practice arm, a one-sided exact conditional binomial test was used.

Note that the lower right cells in the following 2x2 tables are blank because only abnormal slides are considered for the analysis of performance.

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ASCUS+

Table 6 shows the results for slides identified by the truth determination process to be ASCUS+. The laboratories detected a statistically significant greater number of ASCUS+ slides in the AutoPap® Assisted Practice compared to Current Practice.

Table 6 Classification of ASCUS+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	908	291	1,199
	WNL (-)	198	291	198
		1,106	291	1,397

ASCUS/AGUS

The following two tables show the results for slides identified by the truth determination process to be ASCUS and AGUS, respectively. When ASCUS and AGUS are combined for analysis, the laboratories detected a statistically significant greater number of ASCUS/AGUS slides in the AutoPap® Assisted Practice arm compared to the Current Practice arm.

Table 7 Classification of ASCUS Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	603	232	835
	WNL (-)	163		163
		766	232	998

Table 8 Classification of AGUS Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	34	9	43
	WNL (-)	8		8
		42	9	51

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LSIL

Table 9 shows the results for slides identified by the truth determination process to be LSIL. The laboratories detected a statistically significant greater number of LSIL slides in the AutoPap® Assisted Practice compared to Current Practice.

Table 9 Classification of LSIL Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	208	45	253
	WNL (-)	25		25
		233	45	278

LSIL+

Table 10 shows the results for slides identified by the truth determination process to be LSIL+, which includes the categories LSIL, HSIL, AIS, and cancer. The laboratories detected a statistically significant greater number of LSIL+ slides in the AutoPap® Assisted Practice compared to Current Practice.

Table 10 Classification of LSIL+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	271	50	321
	WNL (-)	27		27
		298	50	348

HSIL+

In the prospective study of over 25,100 slides, only 70 HSIL+ slides were available for analysis. HSIL+ includes the categories HSIL, AIS, and cancer. **Table 11** shows that the laboratories detected more HSIL+ slides in the AutoPap® Assisted Practice as compared to Current Practice. There were an insufficient number of smears to determine whether this increased detection was statistically significant.

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Table 11 Classification of HSIL+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	63	5	68
	WNL (-)	2	2	2
		65	5	70

Specimen Adequacy

This section provides the results for the specimen adequacy categories of satisfactory but limited by (SBLB) and unsatisfactory. The AutoPap® Primary Screening System evaluates slide adequacy according to The Bethesda System criteria. The device reports three adequacy parameters: squamous component (detected, not detected), endocervical component (detected, not detected), and inflammation/obscuration (a percentage of the coverslip area).

Satisfactory But Limited By (SBLB)

Out of 5,873 slides identified by the truth determination process to be SBLB, the laboratories detected 5,059 slides in the AutoPap® Assisted Practice compared to 4,728 slides detected by Current Practice. The AutoPap® Assisted Practice is equivalent to Current Practice in identifying SBLB slides.

Unsatisfactory (Unsat)

Out of 171 slides identified by the truth determination process to be unsatisfactory, the laboratories detected 137 slides in the AutoPap® Assisted Practice compared to 133 detected by Current Practice. The AutoPap® Assisted Practice is equivalent to Current Practice in identifying unsatisfactory slides.

Benign Cellular Changes (BCC)

The cytotechnologists on each arm of the study assessed the slides for evidence of epithelial abnormality and the presence or absence of Practice. There were an insufficient number of smears to determine whether this increased detection was statistically significant.

The results were compared to study truth for the slides and showed that the detection of BCC, reactive changes, and infection was equivalent in the AutoPap® Assisted Practice and Current Practice arms of the study.

Out of 5,156 slides identified by the truth determination process to be BCC, the AutoPap® Assisted Practice detected 3,276 compared to 3,431 detected by Current Practice.

Reactive Changes

The WNL slide population was evaluated for the presence of reactive changes. Of the 23,556 WNL slides, 3,037 were noted for reactive changes by the cytotechnologists on either arm of the study. Of the 3,037 slides with reactive changes, 2,978 were noted for inflammation (without atrophy).

Infections

In the study, cytotechnologists on both study arms examined slides for the presence of infections, including actinomyces, herpes, coccobacilli, trichomonas, and candida. If a cytotechnologist on either or both study arms detected the presence of infection on a Pap smear, this was considered truth for the slide.

The following table provides a breakdown by infection subcategories of the 2,925 slides noted for infections.

Table 12 Detection of Infections

(N) = Total number of slides noted for each infection category

Infections	AutoPap® Assisted Practice	Current Practice
All infections (2,925)	1,985	2,141
Actinomyces (17)	12	8
Candida (1,282)	865	983
Coccobacilli (1,375)	869	897
Herpes (14)	11	9
Trichomonas (343)	275	293

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Site-Specific Comparison of Sensitivity Performance

This section compares the sensitivity results by diagnostic category for each arm of the study. These results are provided for each site. The sensitivity is calculated as:

$$\frac{\text{All slides called abnormal or unsat by the cytotechnologist}}{\text{All true abnormal slides}}$$

In this study, the sensitivity for all abnormalities, ASCUS+, (which includes the categories of ASCUS, AGUS, LSIL, HSIL, AIS, and cancer) for each study arm is:

$$\text{AutoPap}^{\circledR} \text{ Assisted Practice: } \frac{1,199}{1,397} = 85.8\%$$

$$\text{Current Practice: } \frac{1,106}{1,397} = 79.2\%$$

The following table shows the site-specific sensitivity results for the categories of ASCUS+, ASCUS/AGUS, LSIL, LSIL+, and HSIL+. The AutoPap[®] Assisted Practice sensitivities are greater than Current Practice at all sites for all diagnostic categories except for HSIL+ at site 5.

Table 13 Site-Specific Sensitivity Results
Sensitivity %, (N)

		Site 1	Site 2	Site 3	Site 4	Site 5	Total
ASCUS+ (all abnormal)	AutoPap® Assisted Practice	90.6% (163/180)	81.3% (169/208)	90.3% (93/103)	83.5% (406/486)	87.6% (368/420)	85.8% (1,199/1,397)
	Current Practice	80.0% (144/180)	76.4 (159/208)	66.1% (69/103)	80.7% (392/486)	81.4% (342/420)	79.2% (1,106/1,397)
ASCUS/AGUS	AutoPap® Assisted Practice	88.4% (114/129)	78.1% (114/146)	85.1% (57/67)	81.9% (307/375)	86.1% (286/332)	83.7% (878/1,049)
	Current Practice	77.5% (100/129)	76.7% (112/146)	58.2% (39/67)	78.7% (295/375)	78.9% (262/332)	77.0% (808/1,049)
LSIL	AutoPap® Assisted Practice	95.7% (45/47)	87.0% (47/54)	100% (30/30)	86.5% (77/89)	93.1% (54/58)	91.0% (253/278)
	Current Practice	85.1% (40/47)	75.9% (41/54)	86.7% (26/30)	85.4% (76/89)	86.2% (50/58)	83.8% (233/278)
LSIL+	AutoPap® Assisted Practice	96.1% (49/51)	88.7% (55/62)	100% (36/36)	89.2% (99/111)	93.2% (82/88)	92.2% (321/348)
	Current Practice	86.3% (44/51)	75.8% (47/62)	83.3% (30/36)	87.4% (97/111)	90.9% (80/88)	85.6% (298/348)
HSIL+	AutoPap® Assisted Practice	100% (4/4)	100% (8/8)	100% (6/6)	100% (22/22)	93.3% (28/30)	97.1% (68/70)
	Current Practice	100% (4/4)	75% (6/8)	66.7% (4/6)	95.5% (21/22)	100% (30/30)	92.8% (65/70)
LSIL	AutoPap® Assisted Practice	95.7% (45/47)	87.0% (47/54)	100% (30/30)	86.5% (77/89)	93.1% (54/58)	91.0% (253/278)
	Current Practice	85.1% (40/47)	75.9% (41/54)	86.7% (26/30)	85.4% (76/89)	86.2% (50/58)	83.8% (233/278)
LSIL+	AutoPap® Assisted Practice	96.1% (49/51)	88.7% (55/62)	100% (36/36)	89.2% (99/111)	93.2% (82/88)	92.2% (321/348)
	Current Practice	86.3% (44/51)	75.8% (47/62)	83.3% (30/36)	87.4% (97/111)	90.9% (80/88)	85.6% (298/348)
HSIL+	AutoPap® Assisted Practice	100% (4/4)	100% (8/8)	100% (6/6)	100% (22/22)	93.3% (28/30)	97.1% (68/70)
	Current Practice	100% (4/4)	75% (6/8)	66.7% (4/6)	95.5% (21/22)	100% (30/30)	92.8% (65/70)

Site-Specific Comparison of Specificity Performance

In this study, specificity was defined as the percentage of WNL slides determined to be normal and adequate according to the truth determination process, defined as:

All slides called abnormal by cytotech & confirmed as WNL by truth

All true WNL slides

Therefore, the specificity change is defined as:

$$\frac{(\% \text{Specificity of the AutoPap Assisted Practice}) - (\% \text{Specificity of Current Practice})}{\% \text{Specificity of the Current Practice}}$$

In the clinical study, 23,556 slides were diagnosed as WNL according to study truth. Table Table 14 compares the specificity results for each arm of the study. A positive percent change in specificity indicates improved specificity for the AutoPap® Assisted Practice arm; a negative percent change indicates improved specificity for the Current Practice arm.

Table 14 Site-Specific Specificity Comparison

	AutoPap® Assisted Practice Specificity %	Current Practice Specificity %	% Change in Specificity
Site 1	96.1 (3,544/3,689)	97.1 (3,583/3,689)	-1.1
Site 2	97.8 (3,862/3,950)	98.0 (3,870/3,950)	-0.2
Site 3	96.0 (3,652/3,803)	97.9 (3,725/3,803)	-1.9
Site 4	94.9 (5,459/5,751)	93.7 (5,387/5,751)	+1.3
Site 5	93.1 (5,926/6,363)	89.1 (5,669/6,363)	+4.5
Total	95.3 (22,443/23,556)	94.4 (22,233/23,556)	+1.0

Using the data in Table 14, the combined percent change in specificity for all sites is:

$$\frac{95.3 - 94.4}{94.4} \times 100 = +1.0\%$$

These data indicate that, for all study sites combined, the AutoPap® Assisted Practice improved the specificity by 1.0 %.

Comparison of False Negative Performance

The AutoPap® Primary Screening System classified 5,109 slides as **No Further Review**. Of these, 21 had unresolved diagnostic or adequacy truth (1 and 20 slides, respectively), leaving 5,088 slides. **Table 15** shows the false negatives (FNs) in this population as determined by study truth.

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**Table 15 False Negative Performance in the No Further Review Population
(As Determined by Study Truth)**

Diagnosis	No Further Review FNs
Unsat	9
WNL	5,036
ASCUS	31
AGUS	1
LSIL	11
HSIL	0
AIS	0
Cancer	0
Total	5,088

Within the population of 5,036 WNL slides, 4,800 slides were classified as WNL by the cytotechnologists in the current practice arm and as **No Further Review** by the AutoPap® Primary Screening System. After the study was completed, these slides were subjected to further rescreening by a senior cytotechnologist. If the senior cytotechnologist determined that a slide was not WNL, the slide was sent for pathologist confirmation. The results of this rescreening and confirmation showed that an additional 11 unsatisfactory, 10 ASCUS, 1 AGUS, and 3 LSIL slides were detected in the **No Further Review** population. There were no HSIL, AIS, or cancer slides found by the senior cytotechnologist.

Table 16 compares the false negative performance of the AutoPap® Assisted Practice with Current Practice. The table shows the total number of false negative slides for each study arm. In all diagnostic categories (except AIS), the AutoPap® Assisted Practice had fewer false negatives; that is, the AutoPap® Assisted Practice detected more abnormal slides.

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Table 16 Comparison of False Negative Performance for the 25,124 Study Slides

Diagnosis	AP-assisted practice FNs*	Current Practice FNs
Unsat	34	38
ASCUS	163	232
AGUS	8	9
LSIL	25	45
HSIL	1	3
AIS	1	0
Cancer	0	2
Total	232	329

*Includes the No Further Review false negatives shown in Table **Table 15**

Comparison of False Positive Performance

In this study, a false positive was defined as a WNL slide that the cytotechnologist incorrectly classified as abnormal and referred to a cytopathologist, defined as:

$$\frac{\text{All slides called abnormal by cytotech \& confirmed as WNL by truth}}{\text{All true WNL slides}}$$

Therefore, the false positive value change is defined as:

$$\frac{(\text{False Positive Value for Current Practice}) - (\text{False Positive Value for AutoPap Assisted Practice})}{\text{False Positive Value for Current Practice}}$$

A total of 23,556 slides were diagnosed as WNL according to study truth.

Table 17 compares the false positive results for each arm of the study. A positive percent change in the false positive value indicates a reduction of false positives in the AutoPap® Assisted Practice arm; a negative percent change indicates a reduction of false positives in the Current Practice arm.

Table 17 Site-Specific False Positive Value Comparison

	AutoPap® Assisted Practice False Positive Value %	Current Practice False Positive Value %	% False Positive Value Change
Site 1	3.9 (145/3,689)	2.9 (106/3,689)	-36.9
Site 2	2.2 (88/3,950)	2.0 (80/3,950)	-9.8
Site 3	4.0 (151/3,803)	2.1 (78/3,803)	-91.8
Site 4	5.1 (292/5,751)	6.3 (364/5,751)	+19.7
Site 5	6.9 (437/6,363)	10.9 (694/6,363)	+37.0
Total	4.7 (1,113/23,556)	5.6 (1,323/23,556)	+16.0

Using the data in Table 17, the combined false positive value change for all sites is:

$$= \frac{5.62 - 4.72}{5.62} \times 100 = 16\%$$

These data indicate that, for all study sites combined, the AutoPap® Assisted Practice reduced the false positive slides by 16%.

Ranked Review Report Analysis

shows the distribution of the study truth abnormal slides with their associated group ranks. As shown in the table, the AutoPap® Primary Screening System placed the highest proportion of slides in the top ranks for all diagnostic categories. For example, 54 of the 70 HSIL+ slides were placed in the top rank.

Table 18 EDP Confirmed and Concordant Abnormal Slides by Rank

Group Rank	ASCUS	AGUS	LSIL	HSIL+
1	465	20	153	54
2	169	8	48	8
3	139	8	31	3
4	88	5	16	3
5	106	9	19	2
Total	967	50	267	70

These data demonstrate that the AutoPap[®] Primary Screening System was effective in ranking slides according to the potential for abnormality. It is important to note that all slides designated as **Review** by the device require screening since the potential for abnormality exists across all group ranks.

Correlation between Sensitivity and Rank

The clinical study analyzed the diagnostic and adequacy differences, between the two study arms. For example, a discrepancy existed if a cytotechnologist from one arm of the study classified a slide as abnormal while a cytotechnologist from the other arm classified the same slide as WNL. If the cytotechnologists classification of the slide as abnormal was confirmed by truth adjudication, then this correct classification was considered a gain for that study arm. Therefore, the gains for each study arm are defined as:

AutoPap[®] Assisted Practice Gain (AP Gain)

Slides classified by the AutoPap[®] Assisted Practice as abnormal and classified by Current Practice as WNL

Current Practice Gain (CP Gain)

Slides classified by Current Practice as abnormal and classified by the AutoPap[®] Assisted Practice as WNL

Table 19 demonstrates the AutoPap[®] Assisted Practice and Current Practice gains for each diagnostic category by rank. A trend test can be applied to the ratio of AP Gain to CP Gain at each rank to determine whether the difference in gain is correlated to the rank. If the p-value of the test is less than 0.05, then the difference in gain is correlated to the rank.

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Table 19 AutoPap® Assisted Practice gain and Current Practice gain by Rank and Disease Category

Rank (order)	ASCUS+		LSIL		LSIL+	
	AutoPap® Assisted Practice Gain	Current Practice Gain	AutoPap® Assisted Practice Gain	Current Practice Gain	AutoPap® Assisted Practice Gain	Current Practice Gain
0-20 (1)	119	36	21	1	22	1
20-40 (2)	47	35	7	6	9	6
40-60 (3)	41	33	4	2	4	3
60-80 (4)	42	28	7	3	8	3
80-100 (5)	42	23	6	2	7	3
AutoPap Archive	0	43	0	11	0	11
Total	291	198	45	25	50	27

The p-values of this test for ASCUS+, LSIL and LSIL+ were 0.0000, 0.0237, and 0.0219 respectively. These p-values are all less than 0.05, which means that the ratio of AutoPap® Assisted Practice gain to Current Practice gain is correlated with the rank. The lower the rank, the higher the ratio between AutoPap® Assisted Practice gain and Current Practice gain, which demonstrates that the Ranked Review Report helped the cytotechnologists improve their sensitivity.

The AutoPap® Primary Screening System’s additional information improves human manual screening in every rank quintile (group) and in every studied disease category (ASCUS+, LSIL, and LSIL+).

Study Sites and Investigators

Following are the names and addresses of the sites that provided data for the evaluation of the AutoPap® Primary Screening System. They are listed in random order.

SmithKline Beecham Clinical Laboratories, St. Louis

2040 Concourse
 St. Louis, MO 63146
 Primary Investigator: Marianne Prey, MD

SmithKline Beecham Clinical Laboratories, Atlanta

1777 Montreal Circle
 Tucker, GA 30084

Primary Investigator: William M. Miller, MD

Kaiser Permanente, Berkeley

1725 East Shore Hwy.

Berkeley, CA 94710

Primary Investigator: Gene K. Pawlick, MD

Quest Diagnostics, Inc.

1355 Mittel Blvd.

Wood Dale, IL 60191

Primary Investigator: D. Dax Taylor, MD

MDS, Inc., Etobicoke

100 International Boulevard

Etobicoke, Ontario

Canada M9W 6J6

Primary Investigator: Terence J. Colgan, MD

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VIII. Conclusions Drawn from Studies

The AutoPap® Primary Screening System is intended to be used as a cervical cytology combined primary screener and rescreener device. Up to 25 percent of successfully processed slides in each run are designated as **No Further Review** and at least 15 percent of screened slides in each run are designated for a second manual review by trained cytology laboratory personnel under appropriate supervision. The device “is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions.” The device is limited for use with only conventionally prepared Pap smears and is not intended to be used on slides designated by the laboratory as “high risk”. The device is further limited in that performance for some diagnostic categories of the Bethesda System has not been established and that the population of slides designated as **No Further Review** may contain a small number of abnormal or unsatisfactory slides.

The results of the clinical studies presented in the PMA supplement support the safety and effectiveness of the AutoPap® Primary Screening System for the stated intended use.

IX. Panel Recommendations

A public hearing of the FDA Hematology and Pathology Devices Advisory Panel was conducted on September 29, 1996 to review A PMA supplement for the AutoPap® 300 QC System that requested a new indication as a primary screening system based upon evidence derived from an expanded analysis of the original clinical study. The panel's recommendation was that the device was not approvable, and that additional studies to characterize the performance of the device in a prospective, intended use mode be conducted.

A public hearing of the FDA Hematology and Pathology Devices Advisory Panel was conducted on January 28, 1998, to review the results of that prospective intended use study. The panel unanimously recommended that the PMA supplement was approvable with conditions.

The conditions were:

1. Clearly define the definitions for "high risk" cases, as used in your Prospective Intended Use Study for the AutoPap Primary Screening System®, in the Product Insert.
2. Provide a general description to address that some percentage of slides will not be able to be processed by the AutoPap® Primary Screening System.
3. Provide a table in the Product Insert to inform users of the characterization of slides from the clinical trial results that were placed in the "No Further Review" classification.
4. Clarify that the "No Further Review" population consists of no more than 25% of each run and that the "QC Review" population consists of no less than 15% of each run.
5. Identify that a potential exists for slides that are deemed to be "Unsatisfactory" may possibly be selected for the "No Further Review" classification.

X. CDRH Action on the Application

CDRH issued an approval order for the applicant's PMA Supplement for NeoPath's AutoPap® Primary Screening System in May 5, 1998.

The applicant's manufacturing and control facilities were inspected on and the facilities were found to be in compliance with the Good Manufacturing Practice Regulations (GMPs).

XI. Approval Specifications

Directions for Use: See attached labeling (Attachment A)

Conditions of Approval: FDA approval of this PMA Supplement is subject to full compliance with the conditions described in the approval order (Attachment B).

NeoPath, Inc.

Product Insert: Indication for Use,
AutoPap[®] Primary Screening System

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US

1 **Intended Use**

The AutoPap® Primary Screening System is an automated cervical cytology screening device intended for use in initial screening of Papanicolaou (Pap) smear slides. The AutoPap® Primary Screening System identifies up to 25% of successfully processed slides as requiring no further review. The AutoPap® Primary Screening System also identifies at least 15% of all successfully processed slides for a second manual review.

The device is to be used **only** on conventionally prepared Pap smear slides and is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions; it is not intended to be used on slides designated by the laboratory as “high risk.”

Intended users are trained cytology laboratory personnel operating under the direct supervision of a qualified cytology supervisor or laboratory manager/director.

2 **Limitations**

- The AutoPap® Primary Screening System analysis of Pap smears is not intended to replace laboratory slide review processes for “high-risk” slides. Such “high risk” slides are those where a primary health care provider has requested special handling of a case for a specified concern, or where the clinical laboratory, through its own procedures, has identified a need for a high-level screening of the case.
- The performance characteristics of the AutoPap® Primary Screening System have not been established for the detection of the following diagnostic categories of The Bethesda System:
 - Endometrial cells, cytologically benign, in a post-menopausal woman.
 - Reactive changes associated with radiation and atrophy with inflammation.
 - Rare malignant neoplasms, such as extrauterine and metastatic carcinomas, and sarcomas.
- The AutoPap® Primary Screening System is intended to process only conventionally prepared (not liquid-based) cervical/vaginal Pap smear slides that meet the slide, coverslip, and staining characteristics stated in the Operator’s Manual.
- Although the AutoPap® Primary Screening System is compatible with a wide range of staining procedures currently implemented in clinical laboratories, the device is *not* compatible with all staining methods currently in use. NeoPath can assist the laboratory in ensuring that the staining method is compatible with the device.
- All personnel who use the AutoPap® Primary Screening System should be trained in the use of the device. NeoPath will train laboratory-designated personnel in the use of the device.
- The AutoPap® Primary Screening System classifies up to 25% of the slides as **No Further Review**. This population of slides may contain a small number of abnormal or unsatisfactory slides. In addition, slides with infections present may be classified as **No Further Review**.

3 Summary and Explanation of the AutoPap[®] Primary Screening System

The AutoPap[®] Primary Screening System is an automated cytology screening device that classifies slides using a high speed video microscope, image interpretation software, and morphology computers to image and analyze the complex images on a Pap smear. The device is intended to detect slides with evidence of squamous carcinoma and adenocarcinoma and their usual precursor conditions. These abnormalities fall within the following diagnostic categories of The Bethesda System (TBS):

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells of undetermined significance (ASCUS)
- Low-grade squamous intraepithelial lesions (LSIL)
- High-grade squamous intraepithelial lesions (HSIL)
- Squamous cell carcinoma

Glandular Cell

- Atypical glandular cells of undetermined significance (AGUS), including Adenocarcinoma in situ (AIS)
- Endocervical adenocarcinoma
- Endometrial adenocarcinoma

The AutoPap[®] Primary Screening System consists of two main components: the Workstation (user interface) and the Instrument (slide processor). The Workstation components (computer, monitor, keyboard, mouse, modem, and printer) are mounted on a mobile cart. The Instrument is a floor standing unit designed to be placed against a wall. The Instrument and Workstation are inter-connected by an Ethernet local area network.

3.1 **AutoPap[®] System Processing**

Each prepared Pap smear slide is affixed with a slide barcode label and loaded into an AutoPap[®] slide tray, which holds up to eight slides. The trays (up to 36) are placed into the AutoPap[®] Instrument, which then automatically analyzes the slides.

After slide trays are loaded into the AutoPap[®] Instrument, they are moved automatically from the input hopper to the microscope stage. For each slide in the tray, the device checks the slide for physical integrity, reads the slide barcode label, scans and analyzes the slide at low power, and then scans and analyses prioritized high-power fields.

Before the first tray and after each tray is processed, a comprehensive system integrity assessment of the Instrument is performed automatically for quality assurance to ensure that all data collection and image analysis mechanisms are operating within specified limits. The results of all these tests are compared to specific performance limits to validate the processing result for each slide in the tray.

A slide is *completely processed* if the slide is checked for physical integrity, scanned and evaluated, and further qualified by system integrity checking. If slide processing is interrupted (for example, by power failure), partial, non-qualified results for slides will be stored by the device. These slides are termed *incompletely processed* and will not be validated or given slide processing results. The laboratory may print a report indicating the barcodes of these slides, which should be rerun on the Instrument.

Results for completely and incompletely processed slides are validated and summarized into slide processing results. As slide processing results are computed, they may be printed in slide processing reports from the Workstation.

3.2 **AutoPap[®] Slide Classification**

The AutoPap[®] Primary Screening System algorithms are trained to detect evidence of morphologic changes associated with epithelial abnormalities, specimen adequacy, and benign cellular changes and infections. For each processed slide, the AutoPap[®] Primary Screening System uses this morphological information to classify slides as **No Further Review**, **Review**, or **QC Review**.

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Each slide is processed only once on the AutoPap® Primary Screening System. Each successfully processed slide is assigned a score, which the device uses to rank slides according to likelihood that a slide contains abnormalities, unsatisfactory conditions, or benign cellular changes. Some slides may not be suitable for processing on the device due to problems with the slide, the coverslip, or the preparation of the specimen; these slides require manual screening.

Classification of No Further Review Slides

The AutoPap® Primary Screening System classifies up to, but no more than, 25% of all successfully processed slides as **No Further Review**.

The **No Further Review** slides have the highest probability of being normal and may be archived by the laboratory as within normal limits (WNL).

Classification of Review Slides

The remaining slide population, at least 75%, is likely to contain the abnormal or unsatisfactory slides. These slides are classified as **Review** by the AutoPap® Primary Screening System and require manual review. All **Review** slides that are classified as WNL by the cytotechnologist are eligible for rescreening.

Classification of QC Review (Rescreen) Slides

The AutoPap® Primary Screening System also classifies at least 15% of *all* successfully processed slides as eligible for rescreening. The slides in this enriched group have the highest likelihood of being abnormal. This enriched population of slides may be used as a substitute for the 10% random selection of slides that constitutes laboratory quality control review.

3.3 **AutoPap[®] Reports**

The AutoPap[®] reports including the Archive Report, Ranked Review Report, and Quality Control (QC) Ranked Review Report, provide the following information.

Ranking Information

To assist the cytotechnologist during manual review, the device ranks the slides for probable abnormality. Each slide is individually ranked from 1 to n , where a rank of 1 indicates a slide most likely to contain abnormality and n is the slide least likely to contain abnormality (n is the number of slides in a print set). Additionally, each slide is assigned a group ranking, ranging from 1 to 5, where a rank of 1 indicates the group most likely to contain abnormalities.

The AutoPap Archive Report for **No Further Review** slides does not provide slide ranks for probable abnormality or a slide adequacy evaluation of unsatisfactory because these slides are classified as WNL and archived.

Evaluation of Slide Adequacy

The device evaluates slide adequacy according to The Bethesda System slide adequacy criteria. The device reports three adequacy parameters: squamous component (detected, not detected), endocervical component (detected, not detected), and inflammation/obscuration (a percentage of the coverslip area). The AutoPap[®] Primary Screening System uses the combination of these parameters to classify the slide as satisfactory, satisfactory but limited by (SBLB), or unsatisfactory.

Processing Information

The device confirms that the slide was completely and successfully processed by the AutoPap[®] Primary Screening System.

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4 Instructions and Instrumentation

Pap Smear Preparation

The AutoPap[®] Primary Screening System generally does not require special preparation of conventional Pap smear slides with glass coverslips by the laboratory. Refer to the Operator's Manual for slide labeling and loading instructions.

The compatibility of a laboratory's staining process will be assessed by NeoPath prior to clinical use of the device by the laboratory as described in the Operator's Manual.

Materials Provided

The AutoPap[®] Primary Screening System consists of the following components:

- AutoPap[®] Instrument
- Slide trays
- AutoPap[®] Workstation:
 - Computer (CPU)
 - Monitor, keyboard, mouse, mouse pad
 - Modem
 - Printer
 - Ethernet transceiver unit
 - Cart
- Electronic cables: Ethernet, printer to Ethernet, AutoPap[®] Instrument to CPU, monitor to CPU, tape drive to CPU, modem to CPU, keyboard to CPU
- Power strip (6-outlet)
- Power cords: Instrument, CPU, monitor, printer, modem

Additional Items Supplied:

- Printer paper (starter package)
- Head cleaning tape
- Slide barcode labels
- Backup tapes
- SCSI bus terminator
- Line protector and/or power supply (optional, at additional cost)

Materials Required but Not Provided

- Instrument: dedicated 20 amp supply, (100–200 volts), or dedicated 10, 15, or 16 amp supply (220–240 volts)
- Workstation: dedicated 10 amp supply (100–240 volts)
- Dedicated analog telephone line
- Dustproof bins to store empty slide trays
- 70% Isopropyl Alcohol
- Cotton swabs or soft bristle brush
- Lint-free cloths
- Glass cleaning solution

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5 Warnings



Broken Glass Hazard when Handling Slides

Do not drop or break slides during slide preparation and when loading and unloading slides into trays. If slides are broken, injuries may occur.



Moving Parts Hazard when Loading/Unloading Trays

Remove all potentially obstructive jewelry and clothing before loading or unloading trays. After opening a hopper door, be sure all moving parts in the hopper have stopped before inserting or removing a tray. If trays are inserted before all moving parts have stopped, injuries may occur or the device may jam.



Shock Potential when Cleaning the Monitor

Failure to remove power to the monitor before performing the procedure could result in an electric shock. See the Operator's Manual.



Shock Potential when Power Applied Improperly

The symbol next to the power connector indicates potential shock hazard. Ensure that the system is connected to a power receptacle that provides voltage and current within the specified rating for the system. Use of an incompatible power receptacle may produce electrical shock and fire hazards.



Shock Potential when Improperly Grounded

Never use a two-prong plug adapter to connect primary power to the system. Use of a two-prong adapter disconnects the utility ground, creating a potential shock hazard. Always connect the system power cord directly to an appropriate receptacle with a functional ground.



Shock Potential when Cleaning with Power Applied

Always turn off the power switch and unplug the power cord before cleaning the outer surfaces or internal components of the device to avoid a potential shock hazard.

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Shock Potential from Spilled Liquids

Do not place containers with liquids on the device or the workstation cart. Do not spill liquids on the system; fluid seepage into internal components creates a potential shock hazard. Shut down the device, disconnect from the power source and wipe up all spills immediately. Do not operate the system if internal components have been exposed to fluid.



Electromagnetic Fields

This is a Class A product. In a domestic environment, this product may cause radio interference with other electronic devices, such as telephones and other medical equipment, in which case the user may be required to take measures to reduce such interference.

6 Precautions

Slide and Coverslip Requirements

This device is intended for use only with glass microscope slides and glass coverslips. This device cannot be recommended for use with slides and coverslips that do not comply with the specifications provided in the Operator's Manual, particularly slides with plastic coverslips, broken slides, dirty or marked slides and non-standard slide or coverslip sizes.

Staining Procedures

Staining procedures should be conducted carefully so that as many slides as possible may be processed on the device. See the Operator's Manual for additional information.

Backup Procedures

When performing the backup procedures, NeoPath recommends that two tapes be used in rotation; each tape would be used every other day. This will ensure minimum loss of data in the unlikely event of a workstation failure.

Shutdown Procedures

Except in an emergency situation, such as those described in the **Warnings** section, shutting down the AutoPap[®] Primary Screening System should only be performed with prior authorization of a company representative to avoid loss of data. If no emergency situation exists, consult the Operator's Manual for the appropriate procedures or contact NeoPath, Inc., or its designated representative. before attempting to shut down the device.

Power Down Procedures

It is important to shut down the system components in the proper order. See the Operator's Manual for additional information.

Restart Procedures

The AutoPap[®] Workstation must always be turned on and booted BEFORE the AutoPap[®] Instrument is turned on. It is important to apply power to the system components in the proper order. See the Operator's Manual for additional information.

Replacement Fuses

Use replacement fuses with the required current rating and specification. Using improper fuses or short-circuiting the fuse holders may cause fire or damage the device.

Installation and Service

The device should be installed only by company authorized personnel. Only technically qualified personnel, trained by NeoPath, Inc., should perform troubleshooting and service procedures on internal components.

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7 **Report of Clinical Studies**

A Prospective, Intended Use Study was conducted at five cytology laboratories to evaluate the effectiveness of the AutoPap® Primary Screening System in detecting abnormal and normal Pap smears when the device was used as a combined primary screener and quality control rescreener.

Of the 31,507 Pap smear slides in the study, 25,124 were evaluated in a two-arm study comparing current practice with an AutoPap® Primary Screening System-assisted practice (referred to in this section and in the data tables as the AutoPap® Assisted Practice). These two study arms were defined as follows:

- Current Practice consisted of 100% manual initial screening and 10% random rescreening (designated as *quality control*)
- AutoPap® Assisted Practice consisted of 100% AutoPap® System initial screening, at least 75% AutoPap®-assisted manual screening, and 15% AutoPap®-assisted manual rescreening

Slides not meeting the inclusion criteria for the study, such as high risk slides, were excluded from the analysis. The AutoPap® Primary Screening System is not intended to replace individual laboratory processes for screening high risk slides.

The goal of the clinical study was to demonstrate that, compared to current practice, the AutoPap® Primary Screening System detected more slides with epithelial abnormality in the following diagnostic categories:

ASCUS+ (All abnormal slides <i>combined</i>)	Atypical squamous cells of undetermined significance and above; additionally includes the categories AGUS, LSIL, HSIL, AIS, and cancer
LSIL	Low-grade squamous intraepithelial lesion
LSIL+	In addition to LSIL, includes the categories HSIL, AIS, and cancer

An additional goal was to demonstrate that, compared to current practice, the device detected an equivalent number of satisfactory but limited by (SBLB) and unsatisfactory slides.

7.1 Slide Accountability

As shown in Table 7.1, the clinical study analyzed a total of 25,124 slides.

Table 7.1 Slide Accountability

Number of slides in study	31,507
Excluded (High risk)	-3,200
Excluded (Device exclusions)*	-1,132
Excluded (Lab exclusions) [†]	-1,004
Entered in study	26,171
Failed processing on AutoPap	-963
Processed on AutoPap	25,208
Excluded from analysis (no truth determination) [‡]	-84
Total Slides Analyzed	25,124

* Broken slides, slides with plastic coverslips, non-Pap smear slides

† Multiple slides from one patient, dotted slides, markings, etc.

‡ Slides not available from labs for truth determination

7.2 Study Truth (Truth Determination Process)

Study truth was determined by cytologic confirmation, not by histologic biopsy. The true diagnosis for the slides analyzed during the clinical trial was determined as follows:

- When the cytotechnologists' screening diagnoses from the AutoPap[®] Assisted Practice and Current Practice agreed, this diagnosis was considered to be the true cytological diagnosis for the slide, or truth.
- When the cytotechnologists' screening diagnoses from the AutoPap[®] Assisted Practice and Current Practice disagreed, an external discrepancy panel (EDP) was convened. An external discrepancy panel consisted of a group of three cytopathologists who independently diagnosed a slide. If two out of three agreed, a diagnosis was determined; otherwise, the slide was reviewed at a multi-head microscope until a consensus diagnosis was achieved. A total of 24 cytopathologists, or 8 groups of 3, participated in this process.
- When adequacy determinations between the two study arms agreed, this was also considered to be truth.
- When adequacy determinations between the two study arms disagreed, a single, independent senior cytotechnologist reviewed the slide to determine truth.

7.3 Definition of High Risk

During the study, each laboratory applied its own definition of high risk. A high risk definition consisted of one or more of the reasons listed below:

Physician-designated high risk patients; prior abnormal gynecological history; postmenopausal or abnormal vaginal bleeding; DES patients; previous breast cancer or history of malignancy; previous tissue or Pap diagnosis of HPV, dysplasia, or HIV infection; multiple sex partners; visible lesion; early age of sexual intercourse; smoker.

All known high risk slides were excluded from the study at all sites. Table 7.2 shows the percentage of slides excluded for high risk reasons at each site.

Table 7.2 High Risk Exclusion Rates by Site

Site	High Risk Exclusion%
1	5.7%
2	6.1%
3	7.1%
4	11.8%
5	14.3%

7.4 Clinical Study Results

In this clinical study, 25,124 slides were analyzed in a comparison of two study arms: the AutoPap[®] Assisted Practice and Current Practice. The slides were submitted to the truth determination process described in Section 7.2 so that each slide had a final cytologic diagnosis (study truth). The cytotechnologist diagnoses from one study arm could be compared to the other study arm as well as to study truth. The distribution of these 25,124 slides is shown in the following tables:

Table 7.3 Distribution of Study Slides

Diagnosis	Number of Slides
Unsatisfactory	171
WNL	23,556
All Abnormals	1,397
Total	25,124

Table 7.4 Distribution of Abnormal Slides

Diagnosis	Number of Slides
ASCUS	998
AGUS	51
LSIL	278
HSIL	67
AIS	1
Cancer	2
Total	1,397

7.4.1 Summary of the Analyses of Diagnostic Categories

In this study, the AutoPap® Primary Screening System was used to detect abnormal and normal Pap smears, whereby up to 25% of the slides could be classified as **No Further Review** and archived by the laboratory.

The results of this study showed that the AutoPap® Assisted Practice improved the laboratories' ability to detect abnormal cervical cells and precursors, while also effectively assessing specimen adequacy. The AutoPap® Primary Screening System improved sensitivity by increasing the detection of abnormalities in the **Review** population and by enhancing the recovery of abnormalities that may have been missed during initial manual screening in the rescreen population (termed **QC Review**), without decreasing specificity.

Table 7.5 compares the AutoPap® Assisted Practice to Current Practice for all diagnostic categories. The diagonal values (shaded) in the table show where the two study arms agreed on the diagnosis. The off-diagonals show where the study arms disagreed. These discordances were used to compare the diagnostic performance between the two study arms.

The *total* columns in the table show the number of abnormal slides for each diagnostic category that were correctly classified by each study arm. The values shown in parenthesis are the total number of slides in each diagnostic category as determined by truth.

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**Table 7.5 AutoPap Assisted Practice Diagnosis vs.
Current Practice Diagnosis**
(N) = Total Number of Slides in the Diagnostic Category as Determined by Truth

	Current Practice Diagnosis								Total
	Unsat (171)	WNL (23,566)	ASCUS (998)	AGUS (51)	LSIL (278)	HSIL (67)	AIS (1)	Cancer (2)	
AutoPap- Assisted Practice Diagnosis Unsat (171)	99	38	0	0	0	0	0	0	137
WNL (23,566)	34	23,556	163	8	25	1	1	0	23,788
ASCUS (998)	0	232	603	0	0	0	0	0	835
AGUS (51)	0	9	0	34	0	0	0	0	43
LSIL (278)	0	45	0	0	208	0	0	0	253
HSIL (67)	0	3	0	0	0	63	0	0	66
AIS (1)	0	0	0	0	0	0	0	0	0
Cancer (2)	0	2	0	0	0	0	0	0	2
Total	133	23,885	766	42	233	64	1	0	25,124

7.4.1.1 Epithelial Abnormalities

This section provides the results for the epithelial abnormality categories of ASCUS+ (includes ASCUS, AGUS, LSIL, HSIL, AIS, and cancer) ASCUS/AGUS, LSIL, LSIL+ (includes LSIL, HSIL, AIS, and cancer), and HSIL+ (includes HSIL, AIS, and cancer). To determine whether a statistically significant greater number of slides in these categories were detected by the cytotechnologists in the AutoPap[®] Assisted Practice arm, a one-sided exact conditional binomial test was used.

Note that the lower right cells in the following 2x2 tables are blank because only abnormal slides are considered for the analysis of performance.

ASCUS+

Table 7.6 shows the results for slides identified by the truth determination process to be ASCUS+. The laboratories detected a statistically significant greater number of ASCUS+ slides in the AutoPap[®] Assisted Practice compared to Current Practice.

Table 7.6 Classification of ASCUS+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	908	291	1,199
	WNL (-)	198		198
		1,106	291	1,397

ASCUS/AGUS

The following two tables show the results for slides identified by the truth determination process to be ASCUS and AGUS, respectively. When ASCUS and AGUS are combined for analysis, the laboratories detected a statistically significant greater number of ASCUS/AGUS slides in the AutoPap® Assisted Practice arm compared to the Current Practice arm.

Table 7.7 Classification of ASCUS Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	603	232	835
	WNL (-)	163		163
		766	232	998

Table 7.8 Classification of AGUS Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	34	9	43
	WNL (-)	8		8
		42	9	51

LSIL

Table 7.9 shows the results for slides identified by the truth determination process to be LSIL. The laboratories detected a statistically significant greater number of LSIL slides in the AutoPap® Assisted Practice compared to Current Practice.

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Table 7.9 Classification of LSIL Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	208	45	253
	WNL (-)	25		25
		233	45	278

LSIL+

Table 7.10 shows the results for slides identified by the truth determination process to be LSIL+, which includes the categories LSIL, HSIL, AIS, and cancer. The laboratories detected a statistically significant greater number of LSIL+ slides in the AutoPap® Assisted Practice compared to Current Practice.

Table 7.10 Classification of LSIL+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	271	50	321
	WNL (-)	27		27
		298	50	348

HSIL+

In the prospective study of over 25,100 slides, only 70 HSIL+ slides were available for analysis. HSIL+ includes the categories HSIL, AIS, and cancer. Table 7.11 shows that the laboratories detected more HSIL+ slides in the AutoPap® Assisted Practice as compared to Current Practice. There were an insufficient number of smears to determine whether this increased detection was statistically significant.

Table 7.11 Classification of HSIL+ Slides

		Current Practice		
		Abnormal (+)	WNL (-)	
AutoPap Assisted Practice	Abnormal (+)	63	5	68
	WNL (-)	2		2
		65	5	70

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7.4.1.2 Specimen Adequacy

This section provides the results for the specimen adequacy categories of satisfactory but limited by (SBLB) and unsatisfactory. The AutoPap[®] Primary Screening System evaluates slide adequacy according to The Bethesda System criteria. The device reports three adequacy parameters: squamous component (detected, not detected), endocervical component (detected, not detected), and inflammation/obscuration (a percentage of the coverslip area).

Satisfactory But Limited By (SBLB)

Out of 5,873 slides identified by the truth determination process to be SBLB, the laboratories detected 5,059 slides in the AutoPap[®] Assisted Practice compared to 4,728 detected by Current Practice. The AutoPap[®] Assisted Practice is equivalent to Current Practice in identifying SBLB slides.

Unsatisfactory (Unsat)

Out of 171 slides identified by the truth determination process to be unsatisfactory, the laboratories detected 137 slides in the AutoPap[®] Assisted Practice compared to 133 detected by Current Practice. The AutoPap[®] Assisted Practice is equivalent to Current Practice in identifying unsatisfactory slides.

7.4.1.3 Benign Cellular Changes (BCC)

The cytotechnologists on each arm of the study assessed the slides for evidence of epithelial abnormality and the presence or absence of benign cellular changes.

The results were compared to study truth for the slides and showed that the detection of BCC, reactive changes, and infection was equivalent in the AutoPap[®] Assisted Practice and Current Practice arms of the study.

Out of 5,156 slides identified by the truth determination process to be BCC, the AutoPap[®] Assisted Practice detected 3,276 compared to 3,431 detected by Current Practice.

Reactive Changes

The WNL slide population was evaluated for the presence of reactive changes. Of the 23,556 WNL slides, 3,037 were noted for reactive changes by the cytotechnologists on either arm of the study. Of the 3,037 slides with reactive changes, 2,978 were noted for inflammation (without atrophy).

Infections

In the study, cytotechnologists on both study arms examined slides for the presence of infections, including actinomyces, herpes, coccobacilli, trichomonas, and candida. If a cytotechnologist on either or both study arms detected the presence of infection on a Pap smear, this was considered truth for the slide.

The following table provides a breakdown by infection subcategories of the 2,925 slides noted for infections.

Table 7.12 Detection of Infections
(N) = Total number of slides noted for each infection category

Infections	AutoPap® Assisted Practice	Current Practice
All infections (2,925)	1,985	2,141
Actinomyces (17)	12	8
Candida (1,282)	865	983
Coccobacilli (1,375)	869	897
Herpes (14)	11	9
Trichomonas (343)	275	293

7.4.2 Site-Specific Comparison of Sensitivity Performance

This section compares the sensitivity results by diagnostic category for each arm of the study. These results are provided for each site. The sensitivity is calculated as:

$$\frac{\text{All slides called abnormal by the cytotechnologist}}{\text{All study truth abnormal slides}}$$

In this study, the sensitivity for all abnormal, ASCUS+, (which includes the categories of ASCUS, AGUS, LSIL, HSIL, AIS, and cancer) for each study arm is:

$$\text{AutoPap® Assisted Practice: } \frac{1,199}{1,397} = 85.8\%$$

$$\text{Current Practice: } \frac{1,106}{1,397} = 79.2\%$$

The following table shows the site-specific sensitivity results for the categories of ASCUS+, ASCUS/AGUS, LSIL, LSIL+, and HSIL+. The AutoPap® Assisted Practice sensitivities are greater than Current Practice at all sites for all diagnostic categories except for HSIL+ at site 5.

Table 7.13 Site-Specific Sensitivity Results
Sensitivity%, (N)

		Site 1	Site 2	Site 3	Site 4	Site 5	Total
ASCUS+ (all abnormals)	AutoPap® Assisted Practice	90.6% (163/180)	81.3% (169/208)	90.3% (93/103)	83.5% (406/486)	87.6% (368/420)	85.8% (1,199/1,397)
	Current Practice	80.0% (144/180)	76.4 (159/208)	67.0% (69/103)	80.7% (392/486)	81.4% (342/420)	79.2% (1,106/1,397)
ASCUS/AGUS	AutoPap® Assisted Practice	88.4% (114/129)	78.1% (114/146)	85.1% (57/67)	81.9% (307/375)	86.1% (286/332)	83.7% (878/1,049)
	Current Practice	77.5% (100/129)	76.7% (112/146)	58.2% (39/67)	78.7% (295/375)	78.9% (262/332)	77.0% (808/1,049)
LSIL	AutoPap® Assisted Practice	95.7% (45/47)	87.0% (47/54)	100% (30/30)	86.5% (77/89)	93.1% (54/58)	91.0% (253/278)
	Current Practice	85.1% (40/47)	75.9% (41/54)	86.7% (26/30)	85.4% (76/89)	86.2% (50/58)	83.8% (233/278)
LSIL+	AutoPap® Assisted Practice	96.1% (49/51)	88.7% (55/62)	100% (36/36)	89.2% (99/111)	93.2% (82/88)	92.2% (321/348)
	Current Practice	86.3% (44/51)	75.8% (47/62)	83.3% (30/36)	87.4% (97/111)	90.9% (80/88)	85.6% (298/348)
HSIL+	AutoPap® Assisted Practice	100% (4/4)	100% (8/8)	100% (6/6)	100% (22/22)	93.3% (28/30)	97.1% (68/70)
	Current Practice	100% (4/4)	75% (6/8)	66.7% (4/6)	95.5% (21/22)	100% (30/30)	92.8% (65/70)

7.4.3 Comparison of False Negative Performance

The AutoPap® Primary Screening System classified 5,109 slides as **No Further Review**. Of these, 21 had unresolved diagnostic or adequacy truth (1 and 20 slides, respectively), leaving 5,088 slides. Table 7.14 shows the false negatives (FNs) in this population as determined by study truth.

**Table 7.14 False Negative Performance in the No Further Review Population
(As Determined by Study Truth)**

Diagnosis	No Further Review FNs
Unsat	9
WNL	5,036
ASCUS	31
AGUS	1
LSIL	11
HSIL	0
AIS	0
Cancer	0
Total	5,088

Within the population of 5,036 WNL slides, 4,800 slides were classified as WNL by the cytotechnologists in the Current Practice arm and as **No Further Review** by the AutoPap® Primary Screening System. After the study was completed, these slides were subjected to further rescreening by a senior cytotechnologist. If the senior cytotechnologist determined that a slide was not WNL, the slide was sent for pathologist confirmation. The results of this rescreening and confirmation showed that an additional 11 unsatisfactory, 10 ASCUS, 1 AGUS, and 3 LSIL slides were detected in the **No Further Review** population. There were no HSIL, AIS, or cancer slides found by the senior cytotechnologist.

Table 7.15 compares the false negative performance of the AutoPap® Assisted Practice with Current Practice. The table shows the total number of false negative slides for each study arm. In all diagnostic categories (except AIS) the AutoPap® Assisted Practice had fewer false negatives; that is, the AutoPap® Assisted Practice detected more abnormal slides.

Table 7.15 Comparison of False Negative Performance for the 25,124 Study Slides

Diagnosis	AutoPap Assisted Practice FNs*	Current Practice FNs
Unsat	34	38
ASCUS	163	232
AGUS	8	9
LSIL	25	45
HSIL	1	3
AIS	1	0
Cancer	0	2
Total	232	329

*Includes the **No Further Review** false negatives (FNs) shown in Table 7.14

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7.4.4 Site-Specific Comparison of Specificity Performance

In this study, specificity was defined as the percentage of WNL slides determined to be normal and adequate according to the truth determination process, defined as:

$$\frac{\text{All slides called WNL by cytotech \& confirmed as WNL by truth}}{\text{All study truth WNL slides}}$$

Therefore, the specificity change is defined as:

$$\frac{(\% \text{Specificity of the AutoPap Assisted Practice}) - (\% \text{Specificity of Current Practice})}{\% \text{Specificity of the Current Practice}}$$

In the clinical study, 23,556 slides were diagnosed as WNL according to study truth. Table 7.16 compares the specificity results for each arm of the study. A positive percent change in specificity indicates improved specificity for the AutoPap[®] Assisted Practice arm; a negative percent change indicates improved specificity for the Current Practice arm.

Table 7.16 Site-Specific Specificity Comparison

	AutoPap[®] Assisted Practice Specificity%	Current Practice Specificity%	% Change in Specificity
Site 1	96.1 (3,544/3,689)	97.1 (3,583/3,689)	-1.1
Site 2	97.8 (3,862/3,950)	98.0 (3,870/3,950)	-0.2
Site 3	96.0 (3,652/3,803)	97.9 (3,725/3,803)	-1.9
Site 4	94.9 (5,459/5,751)	93.7 (5,387/5,751)	+1.3
Site 5	93.1 (5,926/6,363)	89.1 (5,669/6,363)	+4.5
Total	95.3 (22,443/23,556)	94.4 (22,233/23,556)	+1.0

Using the data in Table 7.16, the combined percent change in specificity for all sites is:

$$\frac{95.3 - 94.4}{94.4} \times 100 = +1.0\%$$

These data indicate that, for all study sites combined, the AutoPap[®] Assisted Practice improved the specificity by 1.0%.

7.4.5 Site-Specific Comparison of False Positive Performance

In this study, a false positive was defined as a WNL slide that the cytotechnologist incorrectly classified as abnormal and referred to a cytopathologist, defined as:

$$\frac{\text{All slides called abnormal by cytotech \& confirmed as WNL by truth}}{\text{All study truth WNL slides}}$$

Therefore, the false positive value change is defined as:

$$\frac{(\text{False Positive Value for Current Practice}) - (\text{False Positive Value for AutoPap Assisted Practice})}{\text{False Positive Value for Current Practice}}$$

A total of 23,556 slides were diagnosed as WNL according to study truth. Table 7.17 compares the false positive results for each arm of the study. A positive percent change in the false positive value indicates a reduction of false positives in the AutoPap[®] Assisted Practice arm; a negative percent change indicates a reduction of false positives in the Current Practice arm.

Table 7.17 Site-Specific False Positive Value Comparison

	AutoPap[®] Assisted Practice False Positive Value%	Current Practice False Positive Value%	% False Positive Value Change
Site 1	3.9 (145/3,689)	2.9 (106/3,689)	-36.9
Site 2	2.2 (88/3,950)	2.0 (80/3,950)	-9.8
Site 3	4.0 (151/3,803)	2.1 (78/3,803)	-91.8
Site 4	5.1 (292/5,751)	6.3 (364/5,751)	+19.7
Site 5	6.9 (437/6,363)	10.9 (694/6,363)	+37.0
Total	4.7 (1,113/23,556)	5.6 (1,323/23,556)	+16.0

Using the data in Table 7.17, the combined false positive value change for all sites is:

$$\frac{5.6 - 4.7}{5.6} \times 100 = +16\%$$

These data indicate that, for all study sites combined, the AutoPap[®] Assisted Practice reduced the false positive slides by 16%.

7.4.6 Ranked Review Report Analysis

Table 7.18 shows the distribution of the study truth abnormal slides with their associated group ranks. As shown in the table, the AutoPap[®] Primary Screening System placed the highest proportion of slides in the top ranks for all diagnostic categories. For example, 54 of the 70 HSIL+ slides were placed in the top rank.

Table 7.18 EDP Confirmed and Concordant Abnormal Slides by Rank

Group Rank	ASCUS	AGUS	LSIL	HSIL+
1	465	20	153	54
2	169	8	48	8
3	139	8	31	3
4	88	5	16	3
5	106	9	19	2
Total	967	50	267	70

These data demonstrate that the AutoPap[®] Primary Screening System was effective in ranking slides according to the potential for abnormality. It is important to note that all slides designated as **Review** by the device require screening since the potential for abnormality exists across all group ranks.

8 ***Storage and Operation***

Do not expose the system to direct sunlight or temperature extremes (i.e., air flow from heating or cooling systems). The operating temperature range is 10–30° C, 50–86° F.

9 Technical Service and Product Information

For technical service and assistance related to use of the AutoPap®
Primary Screening System, contact NeoPath, Inc.:

Telephone: 800-NEOPATH (outside Washington State/within
the U.S.)

(800-636-7284)

or

425-869-7284 (inside Washington State and
internationally)

Fax: 425-869-5325