DMC P940029

EPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date . NOV - 8 1995

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Neuromedical Systems, Incorporated's PAPNET® Testing System - Action

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D. M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION.

Approved _____ Disapproved _____ Date _____

Prepared by Louise E. Magruder, CDRH, HFZ-440, 9/19/95, 594-1293

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Neuromedical Systems, Inc.; PREMARKET APPROVAL of PAPNET® Testing System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Neuromedical Systems, Inc., Suffern, NY, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of PAPNET® Testing System. After reviewing the recommendation of the Hematology and Pathology Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on November 8, 1995, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Peter E. Maxim, Ph.D.,
Center for Devices and Radiological Health (HFZ-440),
Food and Drug Administration,
2098 Gaither Rd.,
Rockville, MD 20850,
301-594-1293.

SUPPLEMENTARY INFORMATION: On September 21, 1994, Neuromedical Systems, Suffern, NY, submitted to CDRH an application for premarket approval of PAPNET® Testing System. The device is a semi-automated test indicated to aid in the rescreening of cervical Papanicolaou (Pap) smears previously reported as negative. The PAPNET® Testing System is intended to detect evidence of cervical epithelial abnormalities including the following categories of the

Bethesda System for classification of cervical cytology results:

(a) primary squamous cell carcinoma of the cervix and its possible precursor lesions, i.e., low grade squamous intra epithelial lesions (LGSIL), high grade intra epithelial (HGSIL), and atypical squamous cells of undetermined significance (ASCUS).

(b) primary endocervical adenocarcinoma and its possible precursor lesion, atypical glandular cells of undetermined significance (AGUS).

PAPNET® testing is intended as an adjunct to all standard laboratory quality control and mandated re-screening procedures.

On August 7, 1995, the Hematology and Pathology Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On November 8, 1995, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA

will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d))), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Mr. Mark Rutenberg
Chairman and Chief Executive Officer
Neuromedical Systems, Inc.
Two Executive Boulevard
Suffern, New York 10901-4164

NOV - 8 1995

Re: P940029
PAPNET® Testing System
Filed: September 21, 1994
Amended: December 5, 1994 and March 27, March 31, June 23, June 30, July 19, August 2, August 29, and September 15, 1995

Dear Mr. Rutenberg:

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) for the PAPNET® Testing System. This device is a semi-automated test indicated to aid in the rescreening of cervical Papanicolaou (Pap) smears previously reported as negative. The PAPNET® Testing System is intended to detect evidence of cervical epithelial abnormalities including the following categories of the Bethesda System for classification of cervical cytology results:

(a) primary squamous cell carcinoma of the cervix and its possible precursor lesions, i.e., low grade squamous intraepithelial lesions (LGSIL), high grade intraepithelial (HGSIL), and atypical squamous cells of undetermined significance (ASCUS).

(b) primary endocervical adenocarcinoma and its possible precursor lesion, atypical glandular cells of undetermined significance (AGUS).

PAPNET® testing is intended as an adjunct to all standard laboratory quality control and mandated re-screening procedures. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device 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.

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In addition to the postapproval requirements in the enclosure, the postapproval reports must include the submission of examples of proposed advertising and promotional material to be distributed for both professional use as well as any information intended for the lay public.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, 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, that you must submit an amendment to this PMA submission with copies of all approved labeling 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,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

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SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name: Semi-automated Cervical Papanicolaou Smear Rescreening System

Device Trade Name: PAPNET® Testing System

Applicant's Name and Address: Neuromedical Systems, Inc.
Two Executive Boulevard
Suffern, New York 10901

Premarket Approval Application (PMA) Number: P940029

Date of Panel Recommendations: August 7, 1995

Date of Notice of Approval of Application: November 8, 1995

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II. Indications for Use

A. Intended Use

The PAPNET® Testing System is a semi-automated test indicated to aid in the rescreening of cervical Papanicolaou (Pap) smears previously reported as negative. The PAPNET® Testing System is intended to detect evidence of cervical epithelial abnormalities missed on prior manual microscopic examination of Pap smears. These abnormalities include the following categories of the Bethesda System for classification of cervical cytology results:

(a) primary squamous cell carcinoma of the cervix and its possible precursor lesions, i.e., low grade squamous intraepithelial lesions (LGSIL), high grade intraepithelial lesions (HGSIL), and atypical squamous cells of undetermined significance (ASCUS).

(b) primary endocervical adenocarcinoma and its possible precursor lesion, atypical glandular cells of undetermined significance (AGUS).

PAPNET® testing is intended as an adjunct to all standard laboratory quality control and mandated re-screening procedures.

B. Patient Population

The intended patient population consists of all women who are screened for atypical cells and cervical neoplasia or its precursor lesions i.e., low grade squamous intraepithelial lesion (LGSIL) and high grade squamous intraepithelial lesion (HGSIL).

C. Background

Cervical cancer is the fourth most common malignancy among females in North America and Europe (Munoz, 1989). Since cervical cancer can often be successfully treated when detected at an early stage, detection of precancerous lesions can expedite complete ablation of the disease with inexpensive office procedures which generally maintain patients' reproductive capacity.

The error associated with the manual Pap smear is a false negative one: i.e., failing to detect the relatively few abnormal cells on a slide, and therefore falsely classifying the specimen as negative. The implications of false negatives as they relate to the development of invasive cervical cancer are a public health concern (Koss, 1993).

III. Device Description

A. Device Components

The PAPNET® Testing System consists of four components; the first three components are located at the Slide Scanning Center which is owned and operated by Neuromedical Systems, Inc. (NSI) and the fourth, the PAPNET® Review Station, will be located at participating pathology laboratories.

- PAPNET® Slide ID Unit - generates barcode labels which are shipped to the pathology laboratory.

- PAPNET® Map Unit - readies each slide for scanning by reading the barcode number and marking the area under the coverslip of the slide to be scanned.

- PAPNET® Scanning Station - scans conventional cervical smears, selects and records color images of 128 potentially abnormal cells and clusters from each slide, and copies the images onto digital tape which is returned with the slides to the laboratory.

- PAPNET® Review Station - a certified cytotechnologist located at each pathology laboratory reviews the 128 images from each slide. If any one of the images appears to be abnormal, the cytotechnologist triages the slide as "Review" and then re-examines the entire slide microscopically. If all of the images appear normal, the slide is triaged as "Negative" and no further examination is done.

B. Device Operation

The PAPNET® Testing System operates as follows:

1. The PAPNET® Slide ID Unit prints barcode labels which are then sent to the laboratory. The pathology laboratory attaches one of the two matched barcode labels to a slide; the matching label is attached to the patient's laboratory records and remains at the client site. The slides are packed and shipped in a specially designed container, the PAPNET® Slide Shipping Container, to the PAPNET® Slide Scanning Center operated by NSI.

   A unique "Run Name" is assigned which specifies the client pathology laboratory, the batch identifier, and the date of scanning. Processing includes counting the slides to verify the correct quantity and cleaning each slide to assure optical quality.

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2. The PAPNET® Map Unit readies each slide for scanning by reading the barcode number and marking the area under the coverslip to be scanned. The unit also marks the corners of the coverslip and the location and size of air bubbles.

   The batch's slides are loaded into a cassette which is used while transporting the slides through the succeeding processing steps. A cassette is not loaded with slides from more than one laboratory. Uniquely labeled magnetic media (a diskette and digital tape) are used to store information about a batch of slides (the "Run") in a cassette. These media and associated paperwork accompany the cassette through each processing step. The diskette stores the barcode number and slide map for each slide.

3. The PAPNET® Scanning Station selects and records color images of 128 potentially abnormal cells and clusters from each slide. The images are copied onto digital tape and returned with the slides to the laboratory. The selection of images is accomplished using a hierarchical design incorporating both algorithmic image and neural network processing.

   The Algorithmic Image Processor ("AIP") is designed for high-speed digital image processing. Using standard algorithmic programs, it analyzes images to identify objects whose morphometric parameters (gray scale intensity, size, and local contrast) fall within predetermined limits. For the PAPNET® Testing System, the AIP was programmed to identify as many objects as possible (cells, clusters of cells, overlapping cytologic material, or material resembling cells) that represent potentially abnormal cytologic scenes. The AIP's analysis is designed to be sensitive, but not specific.

   The Neural Network Processor ("NNP") receives the object images selected by the AIP and gives a numerical score to each scene reflecting its general resemblance to the abnormal cells, upon which the NNP was trained. Neural networks are non-algorithmic, connectionist systems patterned after neurobiologic models and implemented using standard computer software and hardware.

   A robot in the PAPNET® Scanning Station loads each slide onto the microscope's automated stage. The slide's mapped area is scanned to locate fields of cellularity. The AIP examines each field sequentially as the slide is moved under the microscope to identify

objects of interest for the NNP. The NNP scores each object according to the similarity of its appearance to the abnormal cells or cell clusters used in its training. The 128 highest scoring single cells and cell cluster images are stored on a digital tape for subsequent review by a cytotechnologist.

Scanning is performed automatically at three magnifications: low power equivalent to a microscope magnification of 50X; medium power equivalent to 200X; and high power equivalent to 400X. Two images of each scene are stored on the Scanning Station computer's hard disk. Before each image is taken, the microscope automatically focuses to ensure that the image is clear and crisp. The coordinates specifying the location of each selected scene on the slide are also recorded. Each scene image is called a "Tile." When all of the slides have been scanned, the stored images and coordinates from the Run are copied to a digital tape and sent to the subscriber laboratories.

4. The PAPNET® Review Station is located at a pathology laboratory. When the slides and digital tape are received at the pathology laboratory, the images and associated information on the digital tape are loaded into the PAPNET® Review Station so that the images can be displayed and reviewed. The review process permits a cytotechnologist to use the high resolution color monitor to triage each slide as either "Review" or "Negative" from the 128 Tiles selected from that slide.

   If any of these scenes exhibits potential cytologic abnormality, the cytotechnologist triages the Case as Review. If triaged as Review, the cytotechnologist rescreens the entire slide microscopically in the conventional manner to determine whether it should be referred further. If no evidence of abnormality is noted among the 128 scenes, the slide is categorized as Negative and no further examination is performed.

   The 128 Tiles from one slide are contained together in a single computer file. The file is placed into a directory on the Review Station's hard disk. The unique identifiers given to each slide and Run help to prevent the mis-identification of slides and their associated images by the laboratory.

   The Review Station's software obligates the cytotechnologist to display and view individually all of the images from a slide through a series of explicit actions leading to a final triage designation of either Negative or Review. A completed status is given for

the Run only after all the slides have been triaged. Review slides are then referred for a cytotechnologist's manual microscopic examination and slides triaged as Negative are sent to the archive.

IV. Alternative Practices and Procedures

At this time, laboratories are required by law to participate in a 10 percent quality control (QC) rescreen of those smears initially evaluated as "negative." The Clinical Laboratories Improvement Amendment (CLIA) and the Health Care Financing Administration (HFCA) regulations specify that the 10 percent sample is to be selected by combining randomly selected negative smears with other negative smears from patients whose clinical profiles place them at higher risk for developing cervical cancer.

V. Marketing History

Since January, 1992, PAPNET® Review Stations have been marketed in Austria, Belgium, Canada, Hong Kong, The Netherlands, and Switzerland. The PAPNET® Testing System has not been withdrawn from any market for any reason related to safety and effectiveness of the device.

VI. Potential Adverse Effects of the Device on Health

Cytologic screening errors may result in delayed treatment for precancerous changes. This may be especially pernicious for women who, for one reason or another, do not undergo routine Pap smear testing at the recommended intervals. A false negative smear report for these women may delay diagnosis and allow the disease to progress. Also, this device has not been validated for all categories of the Bethesda System; therefore a false negative slide containing a malignant neoplasm other than primary squamous cell carcinoma or endocervical adenocarcinoma may be missed.

VII. Contraindications

The PAPNET® Testing System has not been approved for primary screening and has only been evaluated for rescreening conventionally prepared Pap smears that have previously been categorized as negative by manual microscopic screening.

This device has only been validated for the Bethesda System categories of primary squamous cell carcinoma of the cervix and its possible precursor lesions i.e., LGSIL, HGSIL, ASCUS, and primary endocervical adenocarcinoma and its possible precursor lesion, AGUS.

This device has not been evaluated for detection of endocervical components to assess smear adequacy, benign cellular changes due to infection, reactive changes associated with inflammation, atrophy with inflammation, radiation, and intrauterine contraceptive devices, other malignant neoplasms, such as nonepithelial neoplasms and extrauterine epithelial malignant neoplasms, reparative changes, or evaluation of hormonal effects.

The PAPNET Testing System may not display the cells that represent the most severe cytologic abnormalities of any particular Pap smear. For this reason, the cytotechnologist must rescreen the entire slide of all Pap smears triaged for "Review" by manual microscopy . The images displayed in the tiles of the video display and their corresponding slide coordinate locations serve to assist, but do not substitute for the cytotechnologist's manual microscopic evaluation of the entire microscopic slide.

The PAPNET Testing System is to be operated only by licensed and certified cytologists or cytopathologists who have been trained and certified to use the PAPNET Testing System by the applicant, one of the applicant's subsidiaries, or an educational institution certified by the applicant to conduct PAPNET Testing System training.

VIII. Summary of Studies

A. Preclinical Studies

Reproducibility Study

A study was conducted to evaluate the reproducibility of the PAPNET® Testing System. Two separate sets of 100 slides were used for the studies. Both sets consisted of 50 positive slides from biopsy-confirmed high grade or malignant cervical lesions and 50 slides previously screened as negative by conventional cervical cytology. The two sets of slides were screened by the PAPNET® Testing System to make two tapes, A and B.

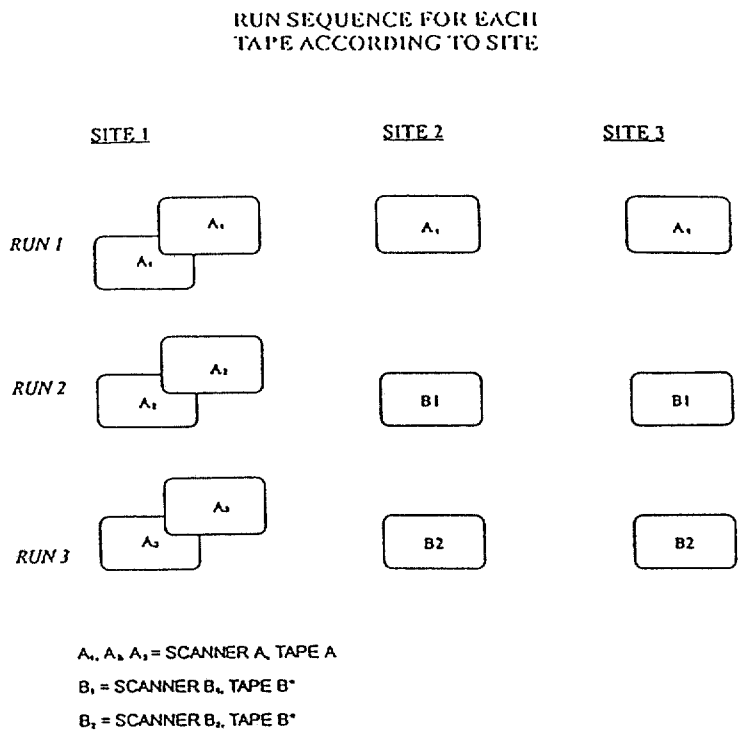
Tape A contained three runs (A1, A2, and A3) of the same set of slides using the same PAPNET® Scanning Station. The first run on tape A (A1) was analyzed by three different cytotechnologists at three different laboratories. Analysis of this data gave an estimate of between laboratory/cytotechnologist reproducibility.

In addition, each run (A1, A2, and A3) of the same set of slides (A) on tape A was analyzed twice by the one cytotechnologist at site 1. Each review of the same images was separated by a minimum of 24 hours. Analysis of these

results gave an estimate of within observer/within scanner reproducibility.

Tape B consisted of two parts (B1 and B2) made from the second set of slides (B) on two different PAPNET® scanning Stations. The two parts (B1 and B2) were analyzed by two different cytotechnologists at two different laboratories. This analysis determined between scanner variability and gave a second look at between cytotechnologist/laboratory variability.

Figure 1



Results of the Reproducibility Studies

The PAPNET® Scanner does not create a video tape of identical images when the same slide is scanned two and three times. Thus PAPNET® reproducibility cannot be evaluated simply by evaluating PAPNET® images. The pathologists' final diagnosis must be the endpoint evaluated.

The reproducibility studies evaluated three endpoints: (1) the cytologists' triage from the PAPNET® screen, (2) the cytologists referral of positive slides triaged in the first endpoint to the pathologist, and (3) an evaluation of the reproducibility of the pathologists final diagnosis.

1. Results of the Three Endpoints Associated with Within Cytotechnologist/Scanning Station Reproducibility. (Evaluation of Sets A1, A2, and A3 within Site 1.)

Table 1 shows the results of the analysis. This table was the control against which the remaining reproducibility results were measured as these results show how consistent the cytotechnologist and pathologist were within themselves, with or without the aid of PAPNET®.

Table 1

Intraobserver Reproducibility Analysis

Percent Concordance at Each Phase of the Slide Review Process:
Analysis of Slide Set Scanned by the Same PAPNET Scanner
(Same Tape Reviewed Twice by the Same Cytotechnologist
and the Same Pathologist)

Type of Reproducibility	Comparison	Intraobserver Reproducibility (Percent Concordance)			
		Cytotechnologist Triage (PAPNET Image)	Cytotechnologist Referral (Glass Slide)	Pathologist Diagnosis (Glass Slide)	
				Full Agreement[1]	Working Agreement[2]
Intraobserver	Tape A1/Site 1 vs Tape A1/Site 1	87.0% (87/100)	88.4% (61/69)	73.2% (41/56)	92.9% (52/56)
	Tape A2/Site 1 vs Tape A2/Site 1	81.0% (81/100)	91.5% (54/59)	54.7% (29/53)	84.9% (45/53)
	Tape A3/Site 1 vs Tape A3/Site 1	79.0% (79/100)	96.3% (52/54)	62.7% (32/51)	96.1% (49/51)
	Mean	82.3% (247/300)	91.8% (167/182)	63.8% (102/160)	91.3% (146/160)

[1] Full Agreement = Diagnoses at the same diagnostic level.

[2] Working Agreement = Diagnoses within ±1 diagnostic level.

The study showed that the same cytotechnologist triaged 87, 81, and 79 of 100 slides on tapes A1, A2, and A3, respectively, concordantly, as either positive or negative from the PAPNET® video screen when they were observed on two different days at least 24 hours apart. From the slides, 69, 59 and 54 were referred for further observation. Of these, 61, 54, and 52, respectively, were referred to the pathologist for diagnosis. The pathologist read the slides and had the same diagnosis 41/56 (73.2 percent), 29/53 (54.7 percent), and 32/51 (62.7 percent) of the time. The pathologist' review was within plus or minus one diagnostic level 52/56 (92.9 percent), 45/53 (84.9 percent) and 49/51 (96.1 percent) of the time. See Table 1.

2. Intrascanner Reproducibility Analysis.

When the same cytotechnologist looked at three different runs of the same slides through the same scanner, the number of slides triaged concordantly as either positive or negative dropped slightly from an average of 82.3 to 78.7 percent (Table 2). In the three different runs, a total of 163/181 (90.1 percent) were concordantly either referred to the pathologist or not, compared to 167/182 (91.8 percent) when set A1 only was examined above. Within scanner reproducibility appeared very consistent. The pathologist received a total of 160 potentially positive referrals using set A1 alone and 157 when all three sets, A1, A2, and A3 were all examined. The pathologist's diagnoses were very similar also. The findings showed that 102/160 (63.8 percent) versus 98/157 (62.4 percent) for full agreement in diagnosis and 146/160 (91.3 percent) versus 143/157 (91.1 percent) for within plus or minus one diagnostic level. See Table 2.

Table 2

Intrascanner Reproducibility Analysis

Percent Concordance at Each Phase of the Slide Review Process
Analysis of Slide Set Scanned by the Same PAPNET Scanner

Type of Reproducibility	Comparison	Intrascanner Reproducibility (Percent Concordance)			
		Cytotechnologist Triage (PAPNET Image)	Cytotechnologist Referral (Glass Slide)	Pathologist Diagnosis (Glass Slide)	
				Full Agreement[1]	Working Agreement[2]
Intraobserver[3]	Tape A1/Site 1 vs Tape A2/Site 1	75.0% (75/100)	87.9% (51/58)	62.0% (31/50)	86.0% (43/50)
	Tape A2/Site 1 vs Tape A3/Site 1	79.0% (79/100)	92.9% (52/56)	62.7% (32/51)	92.2% (47/51)
	Tape A1/Site 1 vs Tape A3/Site 1	82.0% (82/100)	89.6% (60/67)	62.5% (35/56)	94.6% (53/56)
	Mean	78.7% (236/300)	90.1% (163/181)	62.4% (98/157)	91.1% (143/157)
Interobserver[4]	Tape A1/Site 1 vs Tape A1/Site 2	59.0% (59/100)	92.7% (38/41)	54.1% (20/37)	89.2% (33/37)
	Tape A1/Site 2 vs Tape A1/Site 3	84.0% (84/100)	90.2% (37/41)	55.9% (19/34)	85.3% (29/34)
	Tape A1/Site 1 vs Tape A1/Site 3	71.0% (71/100)	83.0% (44/53)	68.3% (28/41)	90.2% (37/41)
	Mean	71.3% (214/300)	88.1% (119/135)	59.8% (67/112)	88.4% (99/112)

[1] Full Agreement = Diagnoses at the same diagnostic level.

[2] Working Agreement = Diagnoses within ±1 diagnostic level.

[3] Different tapes of the same set of slides, produced by the same scanner, and reviewed by the same cytotechnologist.

[4] The same tape reviewed by cytotechnologists at different sites.

3. Interobserver/Intrascanner Reproducibility Analyses.

The data (Table 2) showed a drop in between-cytotechnologist concordance. All three cytotechnologists observed the same tape A1. Compared to results obtained when one cytotechnologist looked at the slides, there was concordance in only 59, 84, and 71 of 100 slides. This would indicate that human variability is a greater contributor to variability than are the PAPNET® video images.

There was a combined total of 135 slides triaged as positive from the PAPNET® video versus 181 when one cytotechnologist at site 1 was involved. Since fewer slides were referred on to the pathologist, fewer ended up diagnosed as positive; sixty-seven versus 98 for full agreement and 99 versus 143 for within plus or minus one diagnostic category. However, the percentages finally diagnosed as positive were similar (59.8 percent versus 62.4 percent).

4. Intraobserver and Interobserver/Interscanner Reproducibility Analysis.

The data shown in Table 3 demonstrate that different scanners contributed little to imprecision of Pap smear analysis.

Table 3

Interscanner Reproducibility Analysis

Percent Concordance at Each Phase of the Slide Review Process
Analysis of Slide Set Scanned by Different PAPNET Scanners

Type of Reproducibility	Comparison	Interscanner Reproducibility (Percent Concordance)			
		Cytotechnologist Triage (PAPNET Image)	Cytotechnologist Referral (Glass Slide)	Pathologist Diagnosis (Glass Slide)	
				Full Agreement[1]	Working Agreement[2]
Intraobserver[3]	Tape B1/Site 2 vs Tape B2/Site 2	88.0% (88/100)	93.3% (42/45)	72.5% (29/40)	95.0% (38/40)
	Tape B1/Site 3 vs Tape B2/Site 3	90.0% (90/100)	94.0% (47/50)	68.9% (31/45)	97.8% (44/45)
	Mean	89.0% (178/200)	93.7% (89/95)	70.6% (60/85)	96.5% (82/85)
Interobserver[4]	Tape B1/Site 2 vs Tape B1/Site 3	88.0% (88/100)	89.6% (43/48)	45.2% (19/42)	90.5% (38/42)
	Tape B2/Site 2 vs Tape B2/Site 3	90.0% (90/100)	89.4% (42/47)	65.9% (27/41)	100.0% (41/41)
	Mean	89.0% (178/200)	89.5% (85/95)	55.4% (46/83)	95.2% (79/83)

[1] Full Agreement = Diagnoses at the same diagnostic level.

[2] Working Agreement = Diagnoses within ±1 diagnostic level.

[3] Two tapes of the same set of slides, produced by different scanners, and reviewed by the same cytotechnologist.

[4] Two tapes of the same set of slides, produced by different scanners, and reviewed by cytotechnologists at different sites.

5. Overall Conclusion

The reproducibility of PAPNET® semi-automated screening is comparable to the reproducibility of unassisted, manual microscopic examination.

B. Clinical Studies

Two separate clinical studies were undertaken. The first clinical study tested a selected assembly of various slides at six medical institutions as a preliminary validation of the frozen (training is stopped) neural network system to determine that it was ready for full scale clinical trials. The second clinical study was the full scale clinical trial performed at 10 medical institutions.

1. Preliminary System Validation Study

The approximate starting and ending dates of the validation studies were September 1991 to March 1993. The objective of the studies was to measure the sensitivity of the PAPNET® System to detect cervical abnormalities missed by routine manual screening and to stress the PAPNET® System with purposive sampling of an abnormally large number of abnormal slides representing a wide variety of disease presentations, staining variables, etc.

Preliminary validation studies were performed at the following six institutions under the direction of the following investigators:

F. Rilke, M.D., Milan Institute (Istituto Nazionale per lo Studio e la Cura dei Tumori), Divisione di Anatomia Patologica e Cytologia, Milano, Italy.

J.K.Kish, M.D., Hinsdale Hospital, Department of Pathology, Hinsdale, Illinois.

E. Malberger, M.D., Rambam Medical Center, Department of Cytopathology, Ministry of Health, Haifa, Israel.

Klaus Schreiber, M.D., Montefiore Medical Center, Department of Pathology, Bronx, New York.

S. Keyhani-Rofagha, M.D., Ohio State University, Department of Pathology, Columbus, Ohio.

Michael B. Cohen, M.D., University of Iowa Hospital, Department of Pathology, Iowa City, Iowa.

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At each site, the investigator(s) purposely selected conventionally prepared and routinely screened cervical Papanicolaou (Pap) smears from the laboratory's archives. Depending on the site protocol, the investigator selected either sequential smears in a series, challenging examples of abnormal entities, or abnormal smears associated with biopsy-confirmed lesions.

A total of 1247 cervical smears were analyzed at the six locations. This represented 1247 slides from 1227 patients. 534 of the smears had previously been classified as abnormal, either cytologically or histologically. The 534 smears included 19 cases of adenocarcinomas, 46 cases of squamous cell carcinoma, 2 other malignant neoplasms, 189 HGSIL, 252 LGSIL, and 26 ASCUS.

Study Results

Cytologists using the PAPNET® System detected abnormality in 517 of 534 (sensitivity equals 96.8 percent, 95 percent confidence interval (CI): 95 to 98.1 percent) of the smears previously diagnosed cytologically or histologically as abnormal. The 517 smears included 16 cases of adenocarcinomas, 46 cases of squamous cell carcinoma, 2 other malignant neoplasms, 187 HGSIL, 241 LGSIL, and 25 ASCUS. Triaged as negative with the aid of PAPNET® were 3 additional adenocarcinomas, 2 HGSIL, 11 LGSIL, and 1 ASCUS. The sponsor postulates that the misclassification of 8 of the LGSIL and the 3 adenocarcinomas was due to no abnormal cells collected in the sample because the slides were called negative by previous manual screening also. Exclusion of the 11 samples from the calculation of sensitivity would bring PAPNET's preliminary sensitivity up to 98.8 percent. Details of the breakdown of the types of samples detected can be seen in Table 4 (next page).

Table 4

Site	Initial Method of Diagnosis	Number of Smears	PAPNET System Triage	Total	Initial Diagnosis: WNL	Benign Cellular Changes	Epithelial Cell Abnormalities: Squamous: ASCUS	LG SIL	HG SIL	Sq Ca	Glandular: Adeno Ca	Other Malignant Neoplasms	PAPNET System Sensitivity*
Milan Institute	Cytology	200	Review	88	40	15	3	11	15	2	2	0	33/33
			Negative	112	110	2	0	0	0	0	0	0	
Hinsdale Hospital	Cytology	184	Review	69	0	7	5	52	2	0	3	0	62/63
			Negative	115	70	44	0	1	0	0	0	0	
Rambam Medical	Cytology	126	Review	66	23	15	0	11	8	2	7	0	28/29
			Negative	60	54	5	0	1	0	0	0	0	
Montefiore Medical	Cytology	172	Review	168	0	0	1	36	116	9	4	2	168/172
			Negative	4	0	0	1	1	2	0	0	0	
Ohio State University	Histology	357	Review	261	61	0	10	119	38	33	0	0	200/211
			Negative	96	85	0	0	8**	0	0	3**	0	
University of Iowa	Cytology	208	Review	53	27	0	6	12	8	0	0	0	26/26
			Negative	155	155	0	0	0	0	0	0	0	
Total Smears		1247											Mean Sensitivity
Total Triage			Review	705	151	37	25	241	187	46	16	2	517/534
			Negative	542	474	51	1	11	2	0	3	0	96.8%

Results for Six Validation Studies of PAPNET Testing System

WNL: Within Normal Limits
LG SIL: Low Grade Squamous Intraepithelial Lesion
Sq Ca: Invasive Squamous Cell Carcinoma
ASCUS: Atypical Squamous Cells of Undetermined Significance
HG SIL: High Grade Squamous Intraepithelial Lesion
Adeno Ca: Adenocarcinoma

* PAPNET system sensitivity is defined as the number of true abnormals triaged for "Review" using PAPNET testing, divided by the number of true abnormals.
** These were also missed by conventional microscopy and were considered sampling errors.

2. Clinical Study

The clinical study began January, 1993, and ended in July, 1994. This study was designed to test the efficacy of the PAPNET® System in detecting abnormalities missed by conventional methods. The sponsor had three specific objectives for the final clinical study.

(1) The first objective was to demonstrate the percentage of women with biopsy-confirmed high grade lesions or malignant cervical lesions who could have had an abnormality identified earlier with the use of the PAPNET®-assisted 100% rescreen.

(2) The second objective was to estimate how many months prior to the positive biopsy an earlier abnormality could have been detected by PAPNET® testing.

(3) The third objective was to estimate an increase in the detection of abnormal smears afforded by supplementing conventional microscopic screening with PAPNET®-assisted 100 percent rescreen of all slides previously called negative.

Study Populations

Two cohorts of slides were collected to demonstrate the three objectives:

(1) The first cohort (Index Women) consisted of 573 slides previously triaged as negative using current practice manual microscopy (including primary screening and current practice rescreening). These 573 slides represent 487 smears (separate visits to the doctor) from 228 women with biopsy-confirmed high grade or malignant cervical lesions that went undetected in their prior cervical smear(s). Biopsy diagnoses of the 228 women included 55 cases of cervical intraepithelial neoplasia (CIN) levels II and III, 134 cases of CIN III, 32 cases of carcinoma in situ, 1 case of endocervical adenocarcinoma, and 6 cases of squamous cell carcinoma.

(2) The second cohort of 11,354 slides from 9666 smears presumed to originate from 9666 women (Control Women) consisted of the laboratories' next 20 consecutive cervical cytology cases diagnosed as negative following each Index Negative woman. These women were accessioned at the same pathology laboratory on the same or the following day. It is possible, but unlikely, that the same woman would be included as a matched control more than once. If it did occur, the samples would probably be taken at least a year apart, the minimum routine screening protocol for negative women.

The 11,354 slides of the matched control cohort were randomly mixed with the 573 index negative slides for the final clinical study. The purpose of the Matched Control cohort was twofold:

a) to provide a background of negative slides to approximate usual prevalence of positive cytology and to minimize bias in the detection of any positivity in the index negative cohort of slides.

b) to serve as the basis for the unbiased estimate of the increase in sensitivity of the combination of manual screening with the PAPNET® system compared to manual screening alone. (Objective #3 above.)

Exclusion Criteria

Slides were excluded from this study if sufficient physical damage rendered them completely unsuitable for testing with PAPNET®. Only 48 slides were excluded based on this criteria. Table 5 lists the total number of slides excluded from each site.

Table 5

Site	A	B	C	D	E	G	H	I	J	TOTAL
No. of Slides	3	7	1	17	9	2	3	1	5	48

Number of Slides Excluded per Site

The 10,153 smears were collected from the following 10 institutions under the direction of the following investigators:

Mark E. Sherman, M.D., Johns Hopkins University Hospital, Baltimore, Maryland.

Philip T. Valente, M.D., University of Texas Health Center, San Antonio, Texas.

Allen Anes, M.D., Associated Pathology Laboratory, Las Vegas, Nevada.

Betty Jane McClellan, M.D., Oklahoma University Hospital, Oklahoma City, Oklahoma.

Luciano B. Lemos, M.D., University of Mississippi Medical Center, Jackson, Mississippi.

Terry M. Darragh, M.D., University of California San Francisco, San Francisco, California.

Dorothy L. Rosenthal, M.D., University of California Los Angeles, Los Angeles, California.

Michael B. Cohen, M.D., University of Iowa Hospitals and Clinics, Department of Pathology, Iowa City, Iowa.

S. Keyhani-Rofagha, M.D., Ohio State University Hospital, Department of Pathology, Columbus, Ohio.

Klaus Schreiber, M.D., Montefiore Medical Center, Department of Pathology, Bronx, New York.

The numbers of samples analyzed at each of the 10 sites for cohorts (1) and (2) (called "Index" and "Control", respectively) can be seen in Table 6.

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Table 6

ACCOUNTABILITY
NUMBER OF WOMEN, PAP SMEARS, AND SLIDES ACCORDING TO INSTITUTION AND CASE/CONTROL STATUS

	SITE													
	A		B		C		D		E		F		G	
	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control	Index	Control
# of Women[1]	18	639	18	460	27	1013	45	1816	12	757	5	200	45	1738
# of Smears	32	639	23	460	51	1013	91	1816	38	757	10	200	87	1738
# of Slides	36	672	24	486	51	1015	91	1818	43	922	13	261	92	1780

	SITE						TOTAL	
	H		I		J			
	Index	Control	Index	Control	Index	Control	Index	Control
# of Women[1]	24	1454	13	419	21	1170	228	9666
# of Smears	75	1454	21	419	59	1170	487	9666
# of Slides	84	1650	22	442	117	2308	573	11354

[1] The number of matched control women is assumed to be the same as the number of matched control smears. Since no patient identifying information was collected on the matched control slides, there is no way to confirm this assumption.

Study Results

(1) Objective 1, Increased Sensitivity for Cervical Neoplasia.

PAPNET®-assisted rescreening detected positive cells in 72 of the 228 women to show that 31.6 percent (95 percent CI: 25.5 to 37.6 percent) of the women with biopsy-confirmed cervical neoplasia have a prior false negative Pap smear identified as positive through the use of the PAPNET® System. See Table 7.

Index women identified as positive were 23/55 (41.8 percent, 95 percent CI: 28.7 to 55.9 percent) of cases of CIN II-III, 36/134 (26.9 percent, 95 percent CI: 19.4 to 34.4 percent) of cases of CIN III, 12/32 (37.5 percent, 95 percent CI: 21.1 to 56.3 percent) of cases of CIS, 1/1 (100 percent) of cases of endocervical adenocarcinoma, and 0/6 (0 percent, 95 percent CI: 0.0 to 45.9 percent) cases of squamous cell carcinoma.

Table 7

PAPNET TESTING RESULTS

DISTRIBUTION OF FALSE NEGATIVE INDEX WOMEN BY MOST SEVERE DIAGNOSIS* ACCORDING TO SITE

False Negative Diagnosis	STUDY SITE																				TOTAL	
	A		B		C		D		E		F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
ASCUS	4	50.0	.	.	3	50.0	6	42.9	3	100.0	0	0.0	5	50.0	3	21.4	1	25.0	3	27.3	28	38.9
LG SIL	.	.	1	50.0	2	33.3	4	28.6	.	.	0	0.0	.	.	6	42.9	.	.	3	27.3	16	22.2
HG SIL	4	50.0	1	50.0	1	16.7	4	28.6	.	.	0	0.0	4	40.0	5	35.7	3	75.0	4	36.4	26	36.1
CARCINOMA	.	.	.	.	.	.	.	.	.	.	0	0.0	1	10.0	.	.	.	.	1	9.1	2	2.8
TOTAL FALSE NEGATIVE INDEX WOMEN	8	100.0	2	100.0	6	100.0	14	100.0	3	100.0	0	0.0	10	100.0	14	100.0	4	100.0	11	100.0	72	100.0

* Diagnosis severity hierarchy = ASCUS, AGUS, LG SIL, HG SIL, Carcinoma.

PAPNET®-assisted rescreening detected positive cells in 98 of 487 smears (20.1 percent, 95 percent CI: 16.6 to 23.7 percent) called negative using conventional screening practices taken at one or more visits to the physician from women that subsequently developed biopsy-confirmed cervical neoplasia. The 487 smears were from the 228 Index women. See Table 8.

Table 8

PAPNET TESTING RESULTS

DISTRIBUTION OF INDEX NEGATIVE SMEARS BY PAPNET TESTING RESULT ACCORDING TO SITE

PAPNET Testing Result	SITE																				TOTAL	
	A		B		C		D		E		F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Concordant Negative	23	71.9	21	91.3	42	82.4	74	81.3	34	89.5	10	100.0	77	88.5	48	64.0	16	76.2	40	67.8	385	79.1
Inadequate					2	3.9			1	2.6									1	1.7	4	0.8
False Negative:	9	28.1	2	8.7	7	13.7	17	18.7	3	7.9			10	11.5	27	36.0	5	23.8	18	30.5	98	20.1
Carcinoma													1	1.1					1	1.7	2	0.4
HG SIL	4	12.5	1	4.3	1	2.0	4	4.4					4	4.6	6	8.0	3	14.3	5	8.5	28	5.7
LG SIL			1	4.3	2	3.9	4	4.4							8	10.7	1	4.8	3	5.1	19	3.9
ASCUS	5	15.6			4	7.8	9	9.9	3	7.9			5	5.7	11	14.7	1	4.8	9	15.3	47	9.7
AGUS															2	2.7					2	0.4
Total Smears	32	100.0	23	100.0	51	100.0	91	100.0	38	100.0	10	100.0	87	100.0	75	100.0	21	100.0	59	100.0	487	100.0

(2) Objective 2, Earlier Detection of Cervical Neoplasia.

The data indicate that 66 of the 228 women with biopsy-confirmed cervical neoplasia (29 percent, 95 percent CI: 23.1 to 34.9 percent) might have had their abnormalities identified at least one year earlier with the aid of PAPNET® rescreening. Twenty-eight (12.3, 95 percent CI: 8.0 to 16.5 percent) might have had their abnormalities identified at least two (2) years earlier, and 12 (5.3 percent, 95 percent CI: 2.75 to 9.0 percent) at least three or more years earlier than with a single manual screening alone. See Table 9.

Table 9

RANGE	NO. WOMEN	CARCIN	HGSIL	LGSIL	ASCUS/ AGUS
≥3 YEARS	12			2 (16.7%)	10 (83.3%)
2-3 YEARS	16		6 (37.5%)	4 (25.0%)	6 (37.5%)
1-2 YEARS	38	2 (5.3%)	13 (34.2%)	7 (18.4%)	16 (42.1%)
6 MOS.-1 YEAR	6		2 (33.3%)	2 (33.3%)	2 (33.3%)
TOTAL	72	2 (2.8%)	21 (29.2%)	15 (20.8%)	34 (47.2%)

(3) Objective 3. Estimation of the increase in sensitivity for cervical neoplasia of a 100 percent PAPNET® rescreen of negative smears.

In a sample of 9666 cervical smears previously triaged as negative by conventional Pap screening practices in the 10 cytology laboratories, evidence of abnormality was found in 464 smears to give an average of 4.8 percent, (95 percent CI: 4.37 to 5.23 percent) false negative smears detected. This varied among the 10 study sites from a low of 0.8 percent to high of 10.8 percent. The average false negatives detected was compared to the historical average of 12.7 percent (95 percent CI: 12.7 to 12.8 percent) of abnormalities found in the 10 laboratories over the past 3 to 8 years. Overall, nearly 3 million smears were encompassed in the historical data used to estimate the 12.7 percent. This 12.7 percent included abnormalities detected during routine manual screening of Pap smears and during whatever

protocol was used for the quality control rescreening. Some labs rescreen more than the mandated 10 percent of negative slides.

The 4.8 percent additional positives determined with the aid of the PAPNET® Testing System represented a 30 percent average increase in detection of abnormal smears at the 10 cytology laboratories (range 9 to 94 percent). The estimate of a 30 percent increase is a weighted average, using site-specific number of smears as the weights. (See Table 10 and Statistical Analysis section on following page for specific details).

Table 10

PAPNET TESTING RESULTS
RELATIVE SENSITIVITY OF PAPNET AS A RESCREENING DEVICE ACCORDING TO INSTITUTION

	Historical Data[1]					Clinical Study Results	Estimated Additional Abnormal Smears Identified With Aid of PAPNET		Estimated Abnormal Smears With PAPNET Included as Rescreening Device		Relative Sensitivity[5]	
	Total Smears Screened	Abnormal Diagnoses		Negative Diagnoses		Percent False Negative for Matched Control Smears						
Site		N	%	N	%		N[2]	%[3]	N[4]	%[3]	Weighted	Unweighted
A	99,116	18,926	19.1%	80,190	80.9%	10.8%	8,661	8.7%	27,587	27.8%	1.46	1.49
B	378,949	34,480	9.1%	344,469	90.9%	3.5%	12,056	3.2%	46,536	12.3%	1.35	1.36
C[6]	622,624	54,830	8.8%	567,794	91.2%	2.0%	11,356	1.8%	66,186	10.6%	1.21	1.21
D	956,095	142,607	14.9%	813,488	85.1%	6.2%	50,436	5.3%	193,043	20.2%	1.35	1.38
E	84,304	3,579	4.2%	80,725	95.8%	0.8%	646	0.8%	4,225	5.0%	1.18	1.18
F	114,904	34,025	29.6%	80,879	70.4%	5.0%	4,044	3.5%	38,069	33.1%	1.12	1.15
G	117,517	14,190	12.1%	103,327	87.9%	1.6%	1,653	1.4%	15,843	13.5%	1.12	1.13
H	129,293	16,950	13.1%	112,343	86.9%	4.3%	4,831	3.7%	21,781	16.8%	1.29	1.28
I	180,964	24,480	13.5%	156,484	86.5%	1.4%	2,191	1.2%	26,671	14.7%	1.09	1.09
J	126,212	13,186	10.4%	113,026	89.6%	10.1%	11,416	9.0%	24,602	19.5%	1.87	1.94
Total	2,809,978	357,253	12.7%	2,452,725	87.3%	4.4%[7]	107,290	3.8%	464,543	16.5%	1.30	1.30
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)	(k)	(l)	(m)

[1] Historical data were only available at Site A for 1987 - 1992, at Site B for 1990 - 1992, and at Site I for 1989 - 1992. At all other sites, data were reported for 1985 - 1992.

[2] Negative Diagnoses (Historical Data) X Percent False Negative for Matched Control Smears (Clinical Study Data)

[3] Denominator = Total Smears Screened (Historical Data)

[4] Positive Diagnoses (Historical Data) + Additional Abnormal Smears Identified With Aid of PAPNET

[5] Relative sensitivity is the ratio of smears diagnosed as abnormal when PAPNET is used as a rescreening device to smears diagnosed as positive by manual screening alone (historical data).

[6] Site C: Abnormal Diagnoses (Historical Data) and Percent False Negative for Matched Control Smears (Clinical Study Results) exclude Atypia diagnoses from abnormal / false negative figures.

[7] The Total Matched Control False Negative Percentage (Clinical Study Results) reported in this table is weighted by the number of Negative Diagnoses at each site (Historical Data). When the estimates are weighted by the number of Matched Control Smears at each site in the clinical study, the overall relative sensitivity is 1.33.

The abnormalities described in the 464 additional positive smears were as follows: 29 HGSIL, 98 LGSIL, 318 ASCUS, and 19 AGUS. No carcinomas were identified. None of the abnormalities detected were confirmed. The results of the by site can be seen in Table 11.

Table 11

PAPNET TESTING RESULTS

DISTRIBUTION OF MATCHED CONTROL WOMEN/SMEARS BY PAPNET TESTING RESULT ACCORDING TO SITE

PAPNET Testing Result	SITE																				Total	
	A		B		C		D		E		F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Concordant Negative	564	88.3	443	96.3	962	95.0	1702	93.7	734	97.0	183	91.5	1704	98.0	1386	95.3	409	97.6	1049	89.7	9136	94.5
Inadequate	6	0.9	1	0.2	15	1.5	2	0.1	17	2.2	7	3.5	6	0.3	5	0.3	4	1.0	3	0.3	66	0.7
False Negative:	69	10.8	16	3.5	36	3.6	112	6.2	6	0.8	10	5.0	28	1.6	63	4.3	6	1.4	118	10.1	464	4.8
Carcinoma																						
HG SIL	16	2.5	5	1.1	2	0.2							2	0.1	1	0.1			3	0.3	29	
LG SIL	15	2.3	9	2.0	28	1.8	21	1.2			1	0.5	5	0.3	15	1.0	3	0.7	11	0.9	98	
ASCUS	34	5.3	2	0.4	14	1.4	91	5.0	5	0.7	7	3.5	20	1.1	46	3.2	1	0.2	98	8.4	318	
AGUS	4	0.6			2	0.2			1	0.1	2	1.0	1	0.1	1	0.1	2	0.5	6	0.5	19	
Total Smears	639	100.0	460	100.0	1013	100.0	1816	100.0	757	100.0	200	100.0	1738	100.0	1454	100.0	419	100.0	1170	100.0	9666	100.0

Statistical Analysis

(1) Studies for Objective #1, Increased Sensitivity for Cervical Neoplasia.

Sensitivities were calculated as ratios. The 95 percent confidence intervals of single ratios were also calculated.

(2) Studies for Objective #2, Earlier Detection of Cervical Abnormality.

Ratios and their 95 percent confidence intervals were determined.

(3) Studies for Objective #3.

An estimate of the increase in sensitivity of PAPNET®-assisted 100 percent rescreen of all slides triaged as negative compared to the current practice of screening and rescreening using manual microscopy alone was calculated.

Table 10 shows how this estimate was made. The percent of additional positive smears detected at each site in the matched control population

(column g) was multiplied by the number of smears triaged as negative since 1985. (This information was not available for three laboratories, thus fewer years were used for them.) This multiplication gave an estimate of how many additional smears would have been called positive if PAPNET® Testing System had been used for each of those years (column h). The additional positive smears were added to the number of smears actually triaged as positive for the same time period at each site (column c) to give an estimate of the total number of smears that would have been called positive at each laboratory since 1985 if PAPNET® would have been in use to rescreen 100 percent of negative smears (column j). The figure in column c included positives found during routine screening and rescreening. The figure in column j was divided by the positives actually found at each site (column c) to determine a ratio representing an estimated unbiased increase in positive slides found with the aid of PAPNET® rescreening (column l). This estimate can be seen for each site and for an average of all sites in Table 10.

IX. Conclusions Drawn From the Studies

1. Preliminary System Validation Study

The results of the studies indicated the PAPNET® System neural network was sufficiently trained to be frozen and undergo full clinical trials to test it's effectiveness in detecting missed cervical abnormality.

2. Clinical Study

a) Objective #1. Increased Sensitivity.

PAPNET®-assisted rescreening detected cervical neoplasias missed by conventional manual microscopy practices. In this study, the PAPNET® System is not consistently missing any cancer category with the exception of squamous cell carcinoma.

b) Objective #2. Earlier Detection of Cervical Neoplasia.

Use of PAPNET-assisted rescreening might result in earlier detection of cervical neoplasia.

c) Objective #3. Estimation of the increase in sensitivity for cervical neoplasia of a 100 percent PAPNET® rescreen of negative smears.

One hundred percent rescreen of negative smears with the aid of the PAPNET® Testing System can increase the sensitivity of Pap screening by an estimated 30 percent.

General Conclusions

The results of the clinical studies demonstrate with reasonable assurance that the PAPNET® Testing System is relatively safe and effective for the stated intended use which is a semi-automated test indicated to aid in the rescreening of cervical Papanicolaou (Pap) smears previously reported as negative.

X. Panel Recommendation

The Hematology and Pathology Devices Panel recommended at the panel meeting on August 7, 1995 that the PMA for the PAPNET® Testing System be approved with conditions and recommended the following list of limitation statements.

(1) The PAPNET® Testing System has not been approved for primary screening and has only been evaluated for rescreening conventionally prepared Pap smears that have previously been diagnosed as negative by manual microscopic screening and federally-mandated CLIA 10 percent manual microscopy rescreening.

(2) This device has only been validated for the Bethesda System categories of primary squamous cell carcinoma of the cervix and its possible precursor lesions i.e., LGSIL, HGSIL, ASCUS, and primary endocervical adenocarcinoma and its possible precursor lesion, AGUS.

(3) This device has not been evaluated for detection of endocervical components to assess smear adequacy, benign cellular changes due to infection, reactive changes associated with inflammation, atrophy with inflammation, radiation, and intrauterine contraceptive devices, other malignant neoplasms, such as nonepithelial neoplasms and extrauterine epithelial malignant neoplasms, hormonal evaluation, and reparative changes.

(4) The PAPNET Testing System may not display the cells that represent the most severe cytologic abnormalities of any particular Pap smear. For this reason, the cytotechnologist must rescreen by manual microscopy the

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entire slide of all Pap smears triaged for "Review". The images displayed in the tiles of the video display and their corresponding slide coordinate locations serve to assist, but do not substitute for the cytotechnologist's manual microscopic evaluation of the entire microscopic slide.

(5) The PAPNET Testing System is to be operated only by licensed and certified cytologists or cytopathologists who have been trained and certified to use the PAPNET Testing System by the sponsor, one of the sponsor's subsidiaries, or an educational institution certified by the sponsor to conduct PAPNET Testing System training.listed in Section VI under Contraindications and Precautions.

XI. CDRH Action on The Application

CDRH concurred with the recommendations of the Panel. CDRH issued an approvable letter to the applicant on September 1, 1995, requesting submission of examples of proposed advertising and promotional material to be distributed for both professional use as well as any information intended for the lay public, yearly follow-up in the annual reports, and a concurrence with the "Conditions of Approval." The applicant satisfactorily responded to the approvable letter. An approval letter was issued to Neuromedical Systems, Ins. on November 8, 1995.

The applicant's manufacturing and control facilities were inspected on October 13, 1995, and the facilities were found to be in compliance with the Good Manufacturing Practice (GMP) Regulations.

XII. Approval Specifications

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

XIII Bibliography

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Description of Samples by Site

The Milan Institute provided a collection of 200 cervical smears obtained from 200 patients during 1990-2. Included were 150 consecutive routine negative smears, 17 smears with benign negative changes (BCC), and 33 abnormal smears with 2 adenocarcinomas, 2 squamous carcinomas, 15 HGSIL, 11 LGSIL, and 3 ASCUS.

The Hinsdale Hospital provided 184 smears from 184 patients. This study sample included 70 normals, 3 adenocarcinomas, 2 HGSIL's, 53 LGSIL's, and 5 ASCUS as well as 51 BCC.

Rambam Medical Center contributed a total of 126 smears from 106 patients. Twenty (20) had BCC, 7 adenocarcinoma, 2 squamous carcinoma, 8 HGSIL, and 12 LGSIL and 77 were normal.

Montefiore Medical Center contributed 172 cytologically abnormal smears with histologically confirmed lesions, obtained from 172 patients between 1983 and 1988. These included 4 adenocarcinomas, 9 squamous carcinomas, 118 HGSIL, 37 LGSIL and 2 ASCUS. Many of the cases contained very scanty evidence of abnormality.

The Ohio State University provided 357 cervical smears collected during 1990-2 from 357 patients having had biopsies at the time of cytology or within one year after the smear. The histologic diagnoses of the subsequent biopsies confirmed the presence of 3 adenocarcinomas, 33 squamous carcinomas, 38 HGSIL, 127 LGSIL, and 10 ASCUS as well as 146 normals.

The University of Iowa Hospital contributed 208 consecutive cervical smears from 208 patients during October 1990. They included 8 HGSIL, 12 LGSIL, 6 ASCUS and 182 normal smears.

PAPNET®

PAPNET TESTING SYSTEM

PAPNET Review Station Operator's Manual

For In Vitro Diagnostic Use

☎ **PAPNET® Testing System technical support 1-800-PAPNET4.**

NSI Document # 721A0016, Revision E
November, 1995
for REVIEW version 1.6

This document supersedes all prior versions of the PAPNET Review Station Operator's Manual.

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1.0 PAPNET® TESTING SYSTEM INTENDED USE

The PAPNET Testing System is a semi-automated test indicated to aid in the rescreening of cervical Papanicolaou (Pap) smears** previously reported as negative. The PAPNET Testing System is intended to detect evidence of cervical epithelial abnormalities missed on prior manual microscopic examination of Pap smears. These abnormalities include the following categories of the Bethesda System for classification of cervical cytology results:

(a) primary squamous cell carcinoma of the cervix and its possible precursor lesions, i.e., low grade squamous intraepithelial lesions (LGSIL), high grade squamous intraepithelial lesions (HGSIL) and atypical squamous cells of undetermined significance (ASCUS).

(b) primary endocervical adenocarcinoma and its possible precursor lesion, atypical glandular cells of undetermined significance (AGUS).

PAPNET testing is intended as an adjunct to all standard laboratory quality control and mandated rescreening procedures.

2.0 LIMITATIONS

2.1 The PAPNET Testing System is to be used *only* on conventionally prepared cervical Papanicolaou (Pap) smears that previously have been assessed to be normal by conventional, manual microscopic screening.

2.2 Performance characteristics of the PAPNET Testing System have not been determined for its use in primary screening of cervical Pap smears or its use as a substitute for the federally-mandated CLIA 10% manual microscopy rescreen.

2.3 The PAPNET Testing System is not intended for detection of the following categories of the Bethesda System for classification of cervical cytology results:

(a) endocervical component to assess smear adequacy;[2,12]
(b) benign cellular changes due to infection;

** A smear is defined as a gynecologic, cytologic specimen obtained during a single visit or examination and is contained on one or more glass slides.

(c) reactive changes associated with inflammation, atrophy with inflammation, radiation and intrauterine contraceptive devices;
(d) malignant neoplasms other than primary squamous or endocervical adenocarcinomas, such as nonepithelial neoplasms and extrauterine epithelial malignant neoplasms;
(e) hormonal evaluation;
(f) reparative changes.

2.4 The PAPNET Testing System may not display the cells that represent the most severe cytologic abnormalities of any particular Pap smear. For this reason, all Pap smears triaged for "Review" must be rescreened by manual microscopy in their entirety. The cell tile images and their corresponding slide coordinates serve to assist but not to substitute for the cytologist's manual microscopic evaluation of the entire microscopic slide.

2.5 PAPNET Testing System testing is to be performed only by licensed and certified cytologists who have been trained and certified to use the PAPNET Testing System by NSI, one of NSI's subsidiaries, or an educational institution certified by NSI to conduct PAPNET Testing System training.

3.0 WARNINGS

3.1 ELECTRO-MAGNETIC FIELDS

Though there is no conclusive evidence that the electro-magnetic fields (EMF) of computer monitors are a health hazard, NSI has endeavored to use equipment that has been certified as producing a low level of emission. MPR-II is the most widely accepted low emission standard in Europe. It has also been accepted by the Institute of Electrical Engineers (IEEE), a U.S. standards organization. Your PAPNET monitors are certified by their manufacturers as being in compliance with MPR-II, both within the extremely low frequency (ELF) and the very low frequency (VLF) ranges.

Monitor emissions are their weakest from the front of the monitor; EMF field strengths diminish with the square of distance, and after a couple of feet, drop down to those of a typical office with fluorescent lights. These are additional steps that NSI recommends that you take to reduce your exposure risks, especially if you are a pregnant woman or nursing mother

1) Stay at arm's length (about 28 inches) from the front of the monitor
2) Keep at least three feet from the sides and back of neighboring monitors

3.2 SPILLS

Liquid spills on the PAPNET Review Station components must be avoided, as they may lead to electrical shock or electrical problems. If a liquid spill occurs, turn OFF the power to all of the PAPNET Review Station components and disconnect the power cords from their source before attempting to clean the liquid spill.

3.3 COVERS AND PANELS

The system covers and panels must not be removed, since they protect the operator and others from exposure to electrical hazards, as well as protect the internal parts of the PAPNET Review Station components from damage.

4.0 PRECAUTIONS

Certain precautions are necessary during operation of the PAPNET Review Station to ensure that data are not lost or that the system is not damaged. These precautions are listed below.

4.1 POWER ON/OFF

The power switches to all of the PAPNET Review Station components must be switched OFF before any of the cables that interconnect the components, such as the mouse, are disconnected. Failure to follow this procedure may cause damage to the PAPNET Review Station components.

CAUTION
NEVER SHUT OFF THE POWER TO THE PAPNET REVIEW STATION WITHOUT EXITING IN THE MANNER DESCRIBED ABOVE. FAILURE TO FOLLOW CORRECT PROCEDURE MAY RESULT IN LOSS OF DATA.

The power switch on the PAPNET Review Station computer must not be turned OFF while the diskette drive or the tape drive indicator light is illuminated. If the

power is turned off while either of these drives is active, the drive or the data contained on the tape or diskette may be damaged.

Before switching the power to the PAPNET Review Station computer OFF, ensure that the Startup menu (Figure 7) is displayed on the command monitor.

4.2 SUPERVISORY FUNCTIONS

To ensure that only authorized personnel may customize the site location information, the SETSITE diskette should be kept in a locked cabinet and individual user IDs should be kept confidential.

4.3 LABELING OF TAPES AND DISKETTES

Verify the labeling of tapes or diskettes before inserting them in their respective drives, to guard against erroneous labeling of data transferred to or from the diskette or tape.

4.4 SYSTEM REBOOTING

Rebooting of the system software by pressing Ctrl, Alt, and Del simultaneously must only be done while the diskette drive or the tape drive indicator light is not illuminated, to prevent damage to the drive or loss of data.

4.5 MONITOR DEGAUSSING

Before degaussing the monitor (see troubleshooting section), be sure that all digital tapes and diskettes have been removed from the vicinity of the monitor, to prevent accidental erasure of the data contained on the tape or diskette.

4.6 LOSS OF POWER

In the event of a utility failure (blackout, brownout, or power sag), the UPS will transfer the Review Station equipment to power derived from a battery source within the UPS. This provides the Operator ample time to save files and properly shut down the system, preventing data loss. During this time, the UPS will emit a beep every *five seconds* to remind the Operator that the power duration is limited. If the power is not restored to normal, a loud tone will alert the Operator when there is less than *two minutes* remaining.

The UPS also contains EMI/RFI (Electro-Magnetic and Radio Frequency) noise and suppression circuitry to protect the Review Station from surges and high frequency noise at all times.

5.0 REQUIREMENTS FOR GLASS SLIDES

The performance of the PAPNET Testing System may be affected by the presence of artifacts such as dirt, fibers, air bubbles, water bubbles, or "cornflakes" (dried, curled cells from an improperly prepared specimen) in the slide. The presence of macroscopic bubbles precludes the scanning of the underlying smear area. When these artifacts are present in sufficient numbers to potentially affect the results obtained during scanning of slides, a message is appended to the results and displayed during the REVIEW process. The appearance of such a message or any other message that is displayed with the TECH CODE notation on the triage menu, should alert the reviewer that a second manual review of that slide may be necessary.

Specifications for slides scanned by the PAPNET Testing System include:

- Glass slides cannot exceed 25.7 mm (1.01") in width and/or 77.5 mm (3.05") in length.
- The slide ID label cannot overhang the edges of the glass slide and must be flush with the slide edges.
- The coverslip cannot be misaligned with the edges of the glass slide and must be flush with the slide edges.
- Permount leaks from the specimen area cannot extend over the slide edges to the bottom or top of the slide.
- Slides must not be broken or cracked.
- Slides cannot be excessively over or under-stained (extremely light or dark).
- Slide coverslips should not extend more than 50 mm (1.97") from the slide edge opposite the slide ID label.

6.0 SUMMARY AND DESIGN PRINCIPLES

The Papanicolaou-stained cervical smear has long been recognized as one of the greatest advancements in oncologic prevention. Since its introduction as a method of screening for abnormalities of the uterine cervix, the "Pap smear" has been a critical element in significantly decreasing patient morbidity and mortality associated with cervical cancer. With over 40 years application as a screening tool in gynecology, the Pap smear is unchallenged for the detection of cervical cancerous and precancerous abnormalities. Properly obtained and prepared, the cervical smear contains much of the information needed to detect an array of abnormalities, including those associated with varying degrees of precancerous lesions.

Detection of precancerous states and small, curable, invasive carcinomas of the uterine cervix by analysis of the Pap smear is based on a complex system of clinical and laboratory procedures. The conventional preparation of the specimen, consisting of fixation and staining, preserves biological context, background milieu, and architecture such as syncytia and mucous strands. It also provides diagnostically useful information about the type and degree of inflammation, which is critical in assessing the origins of cytological change. As a practical manner, however, individual preparations can vary greatly in staining, thickness, and the presence of artifacts. Each smear can contain hundreds of thousands of cells, many of them overlapping or clustered. This architectural complexity, intrinsic to the cervical smear, makes Pap smear screening a great challenge.

Historical attempts to automate the analysis of cervical smears have relied on classical algorithmic information processing techniques. These techniques generally have depended on finding the boundaries of objects and then defining simple morphological features, such as area and density. While these techniques worked well with simple objects in uncomplicated scenes, they were not capable of handling the complex and infinitely variable combinations of overlapping material typically found on conventionally prepared Pap smears.

To address these technical challenges, the PAPNET Testing System uses a patented combination of neural network image recognition plus standard algorithmic image processing to analyze conventionally prepared Pap smears[9,10,11]. Neural networks represent a non-algorithmic branch of artificial intelligence and are ideally suited for recognizing patterns in natural scenes. Unlike algorithms, they do not utilize rules but rather they learn from training sets in much the same way that cytologists learn. Neural networks can generalize from examples, and are both fault tolerant and robust.

Furthermore, the interpretation of cytological abnormality is a subjective task which cannot be defined absolutely by a standard set of rules. Many types, stages and degrees of abnormality exist, representing a disjointed set of morphologies.

Completely automated diagnosis of cytological smears is thus neither feasible nor desirable. Therefore, the PAPNET Testing System automates only the search for abnormality (See Figure 1). The system is designed to select and display 128 images from every smear for cytologist evaluation and directed microscopic re-examination when indicated.

The PAPNET system tolerates variations in staining and preparation in two ways. First, the system utilizes neural network processing, which is a robust type of pattern recognition, also characterized by a tolerance for such variations. Secondly, the system selects the 128 objects based on neural network ranking relative to the other objects on that particular smear. No minimum threshold level of ranking is required in order for an object to be selected among the 128 Tiles.

Therefore, the PAPNET system's primary design goal is to select and display evidence of abnormality sufficient to trigger the cytologist to triage the case for microscopic "Review" if the smear does in fact contain missed abnormality. This cytologic evidence of abnormality may consist of merely a single Tile, and may not be representative of the highest degree of abnormality on the smear. The 128 Tiles are thus not designed to direct a diagnosis, but rather to direct an indication for a microscopic re-examination.

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Conventionally prepared and stained cervical smears, barcoded at the subscribing pathology laboratory, are shipped by express delivery service to a PAPNET Slide Scanning Center. There, each smear is cleaned, and the area under the coverslip to be scanned is delineated. Each smear is then automatically scanned at 50X, 200X, and 400X magnification, and the cell images are classified by algorithmic image processing and neural network processing as to the degree of potential abnormality. Between tens of thousands and hundreds of thousands of objects on each slide are analyzed, and the 128 objects determined to have the highest level of potential abnormality according to the PAPNET neural network processors are selected. The images of each of the 128 objects are centered in an image field, termed a "Tile," and are stored on digital tape, along with each object's corresponding X and Y slide coordinate location.

The slides and the digital tape containing the 128 images from each slide are returned by express delivery service to the subscribing pathology laboratory. There, the cytologist evaluates the digital tape images on a PAPNET Review Station. The X and Y coordinates of all 128 objects are displayed automatically, so that suspicious cells may be located and re-examined under the microscope. Those smears that are triaged for microscopic "Review" by the cytologist must be rescreened in their entirety.

This operator's manual provides a detailed description of the PAPNET Review station and its operation. The manual also provides an overview of the PAPNET Testing System for rescreening of cervical Pap smears.

7.0 PERFORMANCE CHARACTERISTICS

7.1 MULTICENTER CLINICAL TRIAL

The effectiveness of the PAPNET Testing System was evaluated by a longitudinal, multicenter, blinded clinical trial involving 10,153 conventionally prepared cervical smears originally reported and archived as negative by the investigating institutions. Smears from two patient cohorts, case and control, were included in this trial.

The case or "Index" cohort consisted of patients with high grade or malignant cervical histopathologic diagnoses reported between 1985 to 1992 and essentially negative cervical smear histories. The prior negative smears from this Index case cohort (termed "Index Negative Smears") were the focus of the first two objectives of the clinical trial: (1) to estimate the percentage of women with high grade or malignant cervical lesions who could have had an abnormality identified earlier using PAPNET testing; and (2) to estimate how many months prior to the positive biopsy an earlier abnormality could have been detected by PAPNET testing.

The second cohort included in this trial, the "Matched Controls," consisted of twenty reportedly negative smears sequentially accessioned after each Index Negative case smear. These Matched Control smears served to mask the investigators as to case or control status and to address the third trial objective: (3) to measure the increased detection of abnormal smears afforded by supplementing conventional microscopic screening with PAPNET testing.

The Index Negative cohort constituted a total of 228 patients from the ten investigating institutions whose histories met all of the protocol inclusion criteria. Their corresponding Index Negative smears consisted of all negative smears obtained prior to the positive biopsies and available in the institutions' archives. There were a total of 487 such available Index Negative smears which constituted the case cohort.

The Matched Control cohort, the series of sequentially accessioned negative smears following each Index Negative smear, consisted of a total of 9666 smears.

The trial was designed to reflect intended use and minimize bias. Bias was minimized by masking the smear labels and mixing the Index Negative and Matched Control smears using random barcode number labels. All smears were scanned at a PAPNET Slide Scanning Center, and the resulting digital tapes and smears returned to their originating institutions for PAPNET rescreening. Each investigating cytologist used a PAPNET Review Station to evaluate the cytologic images and triage smears accordingly. Smears triaged for "Review" were examined microscopically, and if judged abnormal referred to the investigating cytologist for final microscopic diagnosis.

7.2 MULTICENTER CLINICAL TRIAL RESULTS

Clinical Trial Objective 1:
To estimate the percentage of women with high grade or malignant cervical lesions who could have had an abnormality identified earlier using PAPNET testing:

PAPNET testing resulted in the detection of one or more false negative Index Negative smears obtained from 72 of the 228 (31.6%; 95% CI: 25-38%) Index Negative women. (See Table 1)

Table 1 - Distribution of Index Women by PAPNET Testing Result According to Site

PAPNET Testing Result	STUDY SITE									
	A		B		C		D		E	
	N	%	N	%	N	%	N	%	N	%
False Negative	8	44.4	2	11.1	6	22.2	14	31.1	3	25.0
Concordant Negative	10	55.6	16	88.9	21	77.8	31	68.9	9	75.0
TOTAL INDEX WOMEN	18	100.0	18	100.0	27	100.0	45	100.0	12	100.0

PAPNET Testing Result	STUDY SITE										TOTAL	
	F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%
False Negative	.	.	10	22.2	14	58.3	4	30.8	11	52.4	72	31.6
Concordant Negative	5	100.0	35	77.8	10	41.7	9	69.2	10	47.6	156	68.4
TOTAL INDEX WOMEN	5	100.0	45	100.0	24	100.0	13	100.0	21	100.0	228	100.0

Table 2 - Distribution of False Negative Index Women by Most Severe Diagnosis* According to Site

False Negative Diagnosis	STUDY SITE									
	A		B		C		D		E	
	N	%	N	%	N	%	N	%	N	%
CARCINOMA	.	.	.	.	.	.	.	.	.	.
HG SIL	4	50.0	1	50.0	1	16.7	4	28.6	.	.
LG SIL	.	.	1	50.0	2	33.3	4	28.6	.	.
ASCUS	4	50.0	.	.	3	50.0	6	42.9	3	100.0
TOTAL FALSE NEGATIVE INDEX WOMEN	8	100.0	2	100.0	6	100.0	14	100.0	3	100.0

False Negative Diagnosis	STUDY SITE										TOTAL	
	F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%
CARCINOMA	0	0.0	1	10.0	.	.	.	.	1	9.1	2	2.8
HG SIL	0	0.0	4	40.0	5	35.7	3	75.0	4	36.4	26	36.1
LG SIL	0	0.0	.	.	6	42.9	.	.	3	27.3	16	22.2
ASCUS	0	0.0	5	50.0	3	21.4	1	25.0	3	27.3	28	38.9
TOTAL FALSE NEGATIVE INDEX WOMEN	0	0.0	10	100.0	14	100.0	4	100.0	11	100.0	72	100.0

* Diagnosis severity hierarchy = ASCUS, AGUS, LG SIL, HG SIL, Carcinoma.

The diagnosis of the most severe false negative smear detected by PAPNET testing for each of the 72 Index Negative women is presented below:

2	Invasive Carcinoma	(2.8%)	95% CI: 0-7.3%
26	HG SIL	(36.1%)	95% CI: 24.3-47.9%
16	LG SIL	(22.2%)	95% CI: 11.9-32.5%
28	ASCUS	(38.9%)	95% CI: 26.9-50.8%

The diagnosis of the earliest false negative smear detected for each of the 72 Index Negative women identified by PAPNET testing is presented below:

2	Invasive Carcinoma	(2.8%)	95% CI: 0-7.3%
26	HG SIL	(27.8%)	95% CI: 16.8-38.8%
16	LG SIL	(20.8%)	95% CI: 10.7-30.9%
28	ASCUS	(48.6%)	95% CI: 36.4-60.8%

Examining the results by Index Negative smear, 98 of the 487 (20.1%; 95% CI: 17-24%) case smears were determined to have a missed abnormality using PAPNET testing. (See Table 3.)

Table 3 - Distribution of Index Negative Smears by PAPNET Testing Result According to Site

PAPNET Testing Result	SITE									
	A		B		C		D		E	
	N	%	N	%	N	%	N	%	N	%
Concordant Negative	23	71.9	21	91.3	42	82.4	74	81.3	34	89.5
Inadequate					2	3.9			1	2.6
False Negative:	9	28.1	2	8.7	7	13.7	17	18.7	3	7.9
Carcinoma										
HG SIL	4	12.5	1	4.3	1	2.0	4	4.4		
LG SIL			1	4.3	2	3.9	4	4.4		
ASCUS	5	15.6			4	7.8	9	9.9	3	7.9
AGUS										
Total Smears	32	100.0	23	100.0	51	100.0	91	100.0	38	100.0

PAPNET Testing Result	SITE										TOTAL	
	F		G		H		I		J			
	N	%	N	%	N	%	N	%	N	%	N	%
Concordant Negative	10	100.0	77	88.5	48	64.0	16	76.2	40	67.8	385	79.1
Inadequate									1	1.7	4	0.8
False Negative:			10	11.5	27	36.0	5	23.8	18	30.5	98	20.1
Carcinoma			1	1.1					1	1.7	2	0.4
HG SIL			4	4.6	6	8.0	3	14.3	5	8.5	28	5.7
LG SIL					8	10.7	1	4.8	3	5.1	19	3.9
ASCUS			5	5.7	11	14.7	1	4.8	9	15.3	47	9.7
AGUS					2	2.7					2	0.4
Total Smears	10	100.0	87	100.0	75	100.0	21	100.0	59	100.0	487	100.0

The diagnoses of these false negative Index Negative smears are as follows:

2	Invasive Carcinoma	(2.0%)	95% CI: 0-5.4%
28	HG SIL	(28.6%)	95% CI: 19.1-38.0%
19	LG SIL	(19.4%)	95% CI: 11.1-27.7%
47	ASCUS	(48.0%)	95% CI: 37.6-58.4%
2	AGUS	(2.0%)	95% CI: 0-5.4%

Clinical Trial Objective 2:
To estimate how many months prior to the positive biopsy an earlier abnormality could have been detected by PAPNET testing.

Of the 228 Index Negative Women included in the clinical trial, 72 were detected by PAPNET testing to have had one or more prior year false negative smears. Of these 72 women, 66 (66/72=91.7%) had an abnormality detected by PAPNET testing on a smear obtained more than one year prior to the positive biopsy. Of these 72 women, 28 (28/72=38.9%) had an abnormality detected by PAPNET testing on a smear obtained more than two years prior to the positive biopsy.

RANGE	NO. WOMEN	CARCIN	HGSIL	LGSIL	ASCUS/ AGUS
≥3 YEARS	12			2 (16.7%)	10 (83.3%)
2 -3 YEARS	16		6 (37.5%)	4 (25.0%)	6 (37.5%)
1 -2 YEARS	38	2 (5.3%)	13 (34.2%)	7 (18.4%)	16 (42.1%)
6 MOS.- 1 YEAR	6		2 (33.3%)	2 (33.3%)	2 (33.3%)
TOTAL	72	2 (2.8%)	21 (29.2%)	15 (20.8%)	34 (47.2%)

Clinical Trial Objective 3:
To measure the increased detection of abnormal smears afforded by supplementing conventional microscopic screening with PAPNET testing.
(See table below.)

Table 4 -Study Results: Distribution Of Matched Control Smears By PAPNET Testing Result According To Site

PAPNET Testing Result	SITE																					
	A		B		C		D		E		F		G		H		I		J		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Concordant Negative	564	88.3	443	96.3	962	95.0	1702	93.7	734	97.0	85	91.5	1704	98.0	1386	95.3	409	97.6	1049	89.7	9136	94.5
Inadequate	6	0.9	1	0.2	15	1.5	2	0.1	17	2.2		3.5	6	0.3	5	0.3	4	1.0	3	0.3	66	0.7
False Negative:	69	10.8	16	3.5	36	3.6	112	6.2	6	0.8	1	5.0	28	1.6	63	4.3	6	1.4	118	10.1	464	4.8
HG SIL	16		5		2								2		1				3		29	
LG SIL	15		9		18		21						5		15		3		11		98	
ASCUS	34		2		14		91		5				20		46		1		98		318	
AGUS	4				2				1				1		1		2		6		19	
Total Negative Smears	639	100	460	100	1013	100	1816	100	757	100	10	100	1738	100	1454	100	419	100	1170	100	9666	100

The diagnoses of these false negative Matched Control smears are as follows:

29	HG SIL	(6.3%)	95% CI: 4.0 - 8.6%
98	LG SIL	(21.1%)	95% CI: 17.3 - 24.9%
318	ASCUS	(68.5%)	95% CI: 64.2 - 72.8%
19	AGUS	(4.1%)	95% CI: 2.2 - 6.0%

A. STUDY RESULTS: DISTRIBUTION OF FALSE NEGATIVE MATCHED CONTROL SMEARS BY PAPNET TESTING RESULT ACCORDING TO SITE

PAPNET Testing Result	SITE																					
	A		B		C		D		E		F		G		H		I		J		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
False Negative:	69	10.8	16	3.5	36	3.6	112	6.2	6	0.8	1	5.0	28	1.6	53	4.3	6	1.4	118	10.1	464	4.8

B. HISTORICAL DATA: PERCENTAGE OF SMEARS REPORTED AS ABNORMAL BY CLINICAL STUDY SITES (INCLUDES INITIAL MANUAL SCREEN AND CLIA MANDATED RESCREENING)

	A	B	C	D	E	F	G	H	I	J	Overall
% Abnormal at Initial Screen	19.1%	9.1%	8.8%	14.9%	4.2%	29.6%	12.1%	13.1%	13.5%	10.4%	12.7%

C. COMBINING STUDY RESULTS AND HISTORICAL DATA

1. Formula for

Estimated increased detection of abnormals = Proportional increase in sensitivity over historical rates of abnormals on initial screen

$$= \frac{(100\% - \%\ \text{Abnormal on Initial Screen}) \times (\%\ \text{False Negative})}{\%\ \text{Abnormal on Initial Screen}}$$

2. *Example: Site A*

$$\text{Estimated increased detection of abnormals} = \frac{(100 - 19.1)x(10.8)}{19.1} = 46\%$$

D. ESTIMATED INCREASE IN DETECTION OF ABNORMAL SMEARS

	A	B	C	D	E	F	G	H	I	J	Overall
Estimated Increase in Detection of Abnormals[1]	46%	35%	21%[2]	35%	18%	12%	12%	29%	9%	87%	30%

Overall PAPNET rescreening identified 464 (4.8%) abnormal smears among the 9,666 supposedly negative controls. This results in an overall estimated increase of up to 30% in the identification of abnormal smears; overall historical average 12.7%, with PAPNET testing 16.9%.

[1] Total Estimated Increased Detection of Abnormals is weighted according to the relative distribution of negative smears in historical rates.

[2] *Historical data reported by Site C exclued ASCUS and AGUS diagnoses. Estimated increased detection of abnormals* at this site is calculated excluding these diagnostic categories from % False Negative

8.0 REFERRED SLIDES DIAGNOSED AS NEGATIVE FROM CLINICAL TRIAL

Table 5 presents the number of slides triaged as Review by the cytologist and subsequently diagnosed as Negative by the pathologist (grouped by site), comparing the Index Negative cohort and the Matched Control cohort and total slide cohort for each site.

Table 5 Referred Slides Diagnosed as Negative

Referred Slides Diagnosed as Negative											
	A	B	C	D	E	F	G	H	I	J	Total
Index	1/36	6/24	1/51	0/91	1/43	2/13	0/92	3/84	0/22	6/117	20/573
	3%	25%	2%	0%	2%	15%	0%	4%	0%	5%	3%
Controls	19/672	68/486	25/1015	4/1818	31/922	25/261	12/1780	35/1650	4/442	115/2308	338/11354
	3%	14%	2%	0%	3%	10%	1%	2%	1%	5%	3%
Total	20/708	74/510	26/1066	4/1909	32/965	27/274	12/1872	38/1734	4/464	121/2425	358/11927
	3%	14%	2%	0%	3%	10%	1%	2%	1%	5%	3%

9.0 SYSTEM OVERVIEW AND DEVELOPMENT

9.1 OVERVIEW OF THE PAPNET TESTING SYSTEM

The PAPNET Testing System utilizes a centralized automated PAPNET Slide Scanning Center to identify, map, and scan Pap smear slides. Images selected by the Scanning station are reviewed at individual PAPNET Review Stations installed at participating laboratories. Work flow occurs in four stages within the PAPNET Testing System:

- Slide Identification
- Slide Mapping
- Slide Scanning
- PAPNET Image Review

Slide Identification is carried out by the participating laboratory using conventionally prepared and stained Pap smear slides. Slide identification consists of attaching a special slide ID label, provided by NSI, to each slide. The participating laboratory then packages the slides in shipping containers provided by NSI, and sends them to a PAPNET Slide Scanning Center.

Slide Mapping is performed at the PAPNET Slide Scanning Center. Each slide is cleaned and examined, and the maximum area under the coverslip to be scanned is electronically recorded.

Slide Scanning is performed on a PAPNET Scanning Station consisting of slide handling robotics, an automatic microscope with video camera, a host computer, an algorithmic image processor, a neural network processor, and various control electronics. During scanning, the area under the coverslip is systematically examined by the automatic microscope and converted to a series of digitized images. Each digitized image is analyzed by the algorithmic image processor, which selects a subset of objects for processing. Each of the objects is then scored by the neural network processor with respect to how closely each resembles abnormal cells or groups of cells.

At the completion of the scanning process for each slide, the 128 images (64 cellular images and 64 cell clusters) scored as the most potentially abnormal are copied to digital tape, along with their locations on the slide. After all slides have been scanned, the tape and slides are returned to the participating laboratory.

PAPNET Image Review is carried out at the participating laboratory on a PAPNET Review Station utilizing desktop computer technology. The digital tape is loaded into the PAPNET Review Station and the potentially abnormal cell images are viewed on a large-screen high-resolution color monitor. After viewing the selected images, the participating laboratory decides whether further conventional review of that slide is warranted.

The workflow that occurs within each of these stages is described in Figure 1.

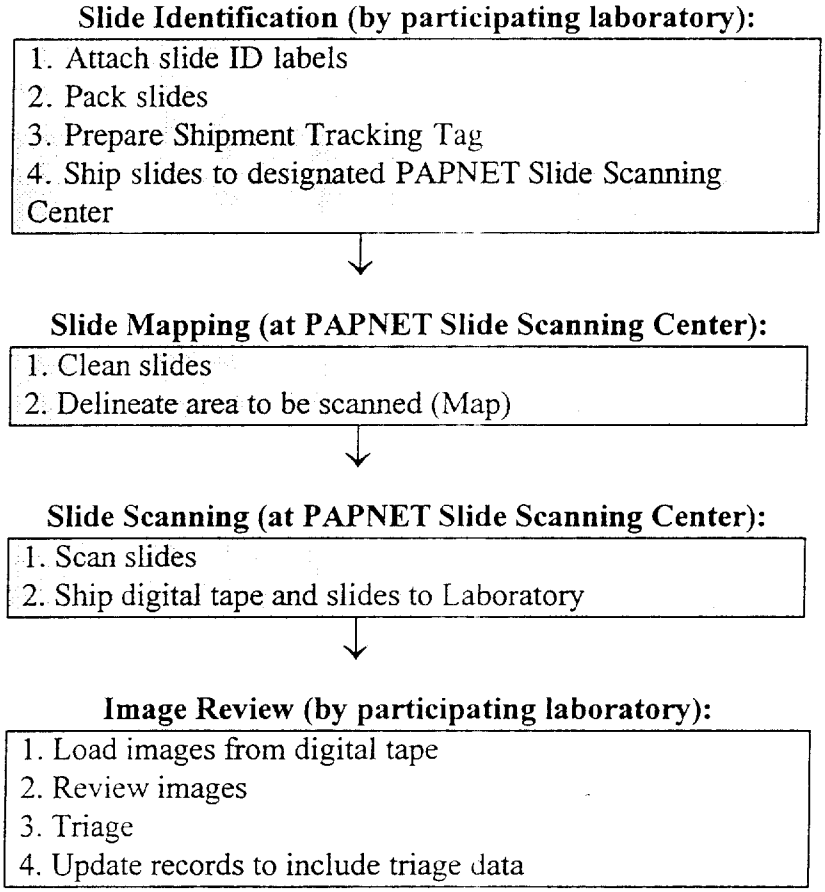


Figure 1 PAPNET® TESTING SYSTEM Workflow

The detailed steps associated with **PAPNET Image Review** are the subject of this manual. The **Slide Identification**, **Slide Mapping**, and **Slide Scanning** operations are only performed at the Slide Scanning Center and therefore are not detailed in this manual.

9.2 GENERAL TERMINOLOGY

The terminology used with the PAPNET Testing System is the same as that used in cytology laboratories. In addition, certain specific terms are used for description of an operation or identification of the resulting data. These terms and their definitions are described below:

Term	Definition
Case	A slide and its corresponding 128 images. A smear may consist of more than one such case.
DRESTORE	See "Load Cases"
High-Resolution Monitor	The high-resolution video screen, a component of the PAPNET Review Station, that is used to view the digital images that are selected from each slide during scanning.
Load Cases	The copying all the images from one Run from a digital tape cartridge to the Review Station hard disk drive.
Magnify	The process of displaying a "high power" image of the center of the selected tile by clicking the right mouse button.
Page	An array of 64 tiles (images) presented on the high-resolution monitor. There are two pages of tiles for each Case.
Quadrant	A magnified section of a page containing 16 of the 64 tiles. Each page has four quadrants.
Restore	See "Load Cases"
Review	The process of interpreting the images of the 128 cell scenes recorded from each slide.
Run	The images produced from the scanning of a series of slides. Images from one Run are contained on one digital tape cartridge. A maximum of 100 slides may constitute one Run.
Run Name	The code that is assigned to a Run. The code contains the account number, the date on which the Run was performed, and the Run letter, if there was more than one Run on that day for that account.

Scan	The automated analysis of each slide, performed at the PAPNET Slide Scanning Center, to identify the 128 objects with the highest neural network scores (highest potential for abnormality) from each slide.
Slide ID	The identifying barcode number on the PAPNET label that is affixed to each slide.
Tag	The demarcation of a tile (a cell image) with the mouse for further review. The slide coordinates are displayed for the cell selected.
Tile	A rectangular image of a single microscopic field. An array of 64 tiles or 16 tiles (magnified) is displayed on the high resolution monitor at one time during review.
Triage	The categorization of each Case, after examining its images, according to whether microscopic referral is required. Triage categories of the slide are either "Negative" or "Review".
Zoom	The process of enlarging the images displayed on the high resolution monitor by switching the array of tiles displayed on the high resolution screen from the page mode (64 tiles) to the quadrant mode (16 tiles).

9.3 PAPNET Scanning Station Principles

At the Scanning Center, each slide is cleaned to optimize optical quality and the boundaries of the coverslipped area are delineated. The slides are then placed into a cassette and placed on the Scanning Station. A robotic arm sequentially unloads each slide and places it on a motorized microscope stage where a barcode label identifying the slide is read to ensure proper identification of the slide.

The PAPNET scanning process involves three separate scans by the microscope across the slide. The low power scan (50X) defines the areas (*fields*) which contain cellular material. During the second, or medium power scan (200X), cell images in the selected fields are analyzed. The Algorithmic Image Processor (AIP) identifies objects that represent potentially abnormal cytologic scenes. The Neural Network Processor (NNP) assigns a numerical score to each object reflecting its resemblance to the abnormal cells and clusters upon which the NNP was trained.

The NNP contains two neural networks. Both are feed-forward, back-propagation networks. During system development, one neural network was trained with grey-scale images of single cells; the other was trained with images of cell clusters. The neural networks were trained to correlate positive (abnormal) library

images, with maximum output values and negative (normal) library images with minimum output values.

High power image capture (the third and final scan) records high resolution color images at 400X magnification of the 128 objects with the highest neural network scores. The slide coordinates for each of these objects are recorded on digital tape along with a 128 micron by 100 micron image of each cell or cluster, including the cell's contextual surroundings.

Once all the slides have been scanned, they are returned to the cytology laboratory, accompanied by the digital tape containing the images. The images are then reviewed by a PAPNET-trained cytologist using the PAPNET Review Station.

9.4 PAPNET Review Station Principles

The PAPNET Review Station is installed at each participating cytology laboratory. The Review Station includes a MS-DOS computer equipped with a mouse and keyboard, a tape drive for reading the digital tapes, a 20" High Resolution Color Monitor on which the images are displayed, and a color printer.

The 128 image scenes are displayed on two separate *pages* (monitor screen displays). The first page displays 64 single-cell scenes and the second page displays 64 cell-cluster scenes. All 64 tiles (image scenes)on each page are initially presented at low power (50x) so that the cytologist can gain an initial, overall assessment of the smear.

The tiles are then viewed in the *quadrant mode* (200x), displaying 16 tiles at a time, for analysis and interpretation of potential abnormalities. Manual microscopy location coordinates are provided for all 128 Tiles. Any tile may be further magnified (400x), for more detailed inspection, and tagged (electronically dotted). Another feature allows the user to create a montage of tagged tiles for display on the monitor, representing a summary screen of suspicious cell scenes that can be used for an overall assessment of abnormalities on the smear.

A PAPNET trained cytologist reviews the selected images from the cervical smear on the Review Station High Resolution Color Monitor. The cytologist then classifies (*triages*) the smear into one of two categories: "**Review**" or "**Negative.**" Cases triaged as "**Review**" require further examination with the microscope; cases triaged as "**Negative**" indicate that the selected scenes represent objects that are considered to be within normal limits and that no further microscopic examination is required. For those cases triaged as "Review," the cytologist can readily locate the suspicious cells on the smear using a calibrated laboratory microscope and the slide coordinates provided by the PAPNET Review Station. The color printer can be used to produce a copy of selected images.

10.0 THE PAPNET REVIEW STATION

At least one PAPNET Review Station is installed at each participating laboratory. It is used to:

- Review the images obtained during scanning of each slide.
- Obtain the X and Y coordinates of any of the suspected abnormal objects.
- Record the conclusions reached after triage of each slide.
- Print the results of the review.

10.1 HARDWARE COMPONENTS

The hardware components of the PAPNET Review Station are shown in Figure 2. The Review Station consists of a desktop computer equipped with keyboard, mouse, tape drive, printer, and two video monitors. The first monitor is a conventional monitor that is used to display commands and messages. The second monitor is a larger, high-resolution video monitor that is used to display the images from each slide.

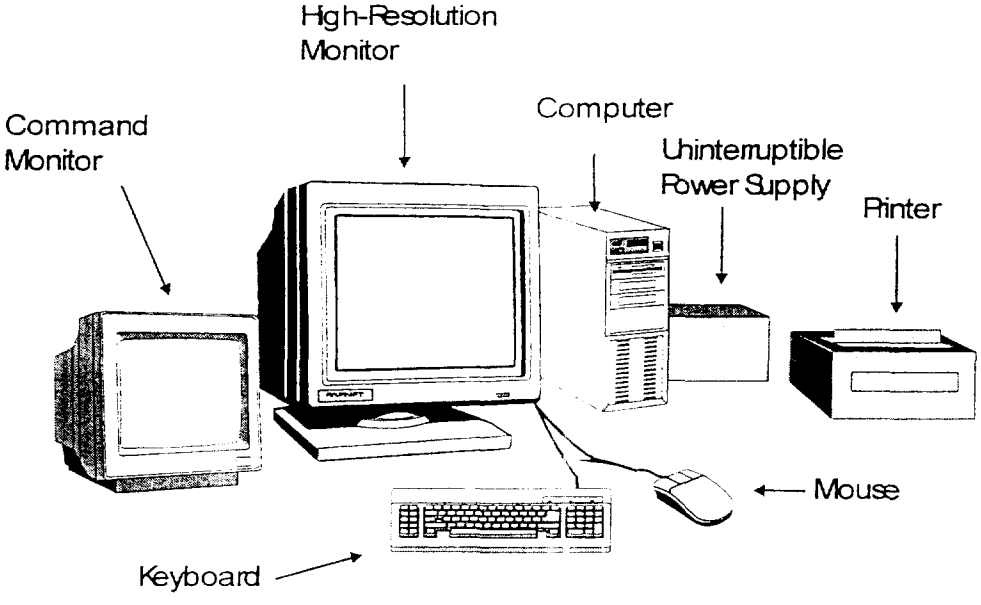
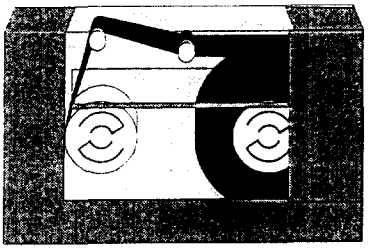


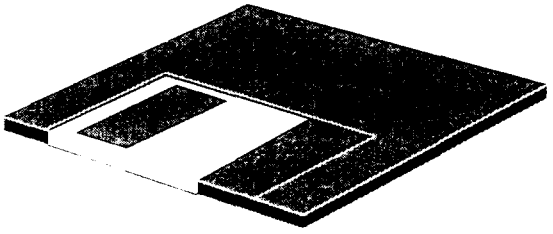
Figure 2 PAPNET REVIEW STATION Hardware Components

A microscope with an aligned stage is also required but is not provided by NSI. For further information refer to Section A.1.2 on page 73.

Two forms of media (refer to Figure 3) are used, in addition to the keyboard and mouse, for transferring data to and from the computer. Digital tape is used to store the images obtained during scanning of the slides. The image data are copied to the PAPNET Review Station computer by the pathology laboratory in preparation for review. A diskette is used to transfer software or data.



Digital Tape



Diskette

Figure 3 Magnetic Data Storage Media Used With The PAPNET® REVIEW STATION

10.2 SOFTWARE COMPONENT

The **REVIEW** software program is the primary operating software of the PAPNET Review Station. This program is used to display the images on the high-resolution monitor.

10.3 CONTROLS AND INDICATORS

A diagram of the controls and indicators on the PAPNET Review Station is shown in Figure 4. Consult this diagram for assistance in locating the various components described in the following paragraphs.

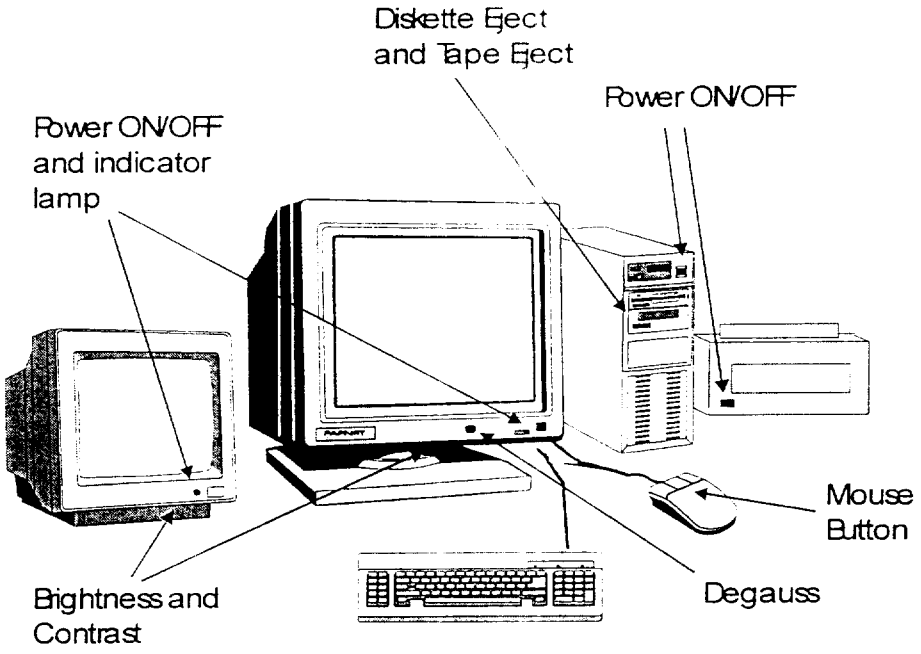


Figure 4 PAPNET® REVIEW STATION Control and Indicator Locations

Power ON/OFF switches and power indicator lamps for the computer, command monitor, high-resolution monitor and printer are located on the front panel of these components. Press the power ON/OFF switches once to activate the power to the component and again to turn off the power.

The digital tape drive and the diskette drive are located on the front panel of the computer. Each drive has an EJECT button as shown. Press the button to eject the diskette or tape from its respective drive.

Each monitor has a BRIGHTNESS and CONTRAST adjustment knob as shown. Adjust the BRIGHTNESS control to obtain brightness that is consistent with the room illumination and allow easy viewing of images on the command and high-resolution monitors. Adjust the CONTRAST control to allow easy viewing and maintain optimum focus and clarity. The high-resolution monitor has a DEGAUSS button on the front panel. This button should be pressed for approximately 5 seconds when colors (especially at the borders of the monitor screen) become distorted. This function demagnetizes the monitor.

The mouse has either two or three buttons. The mouse is moved on the desktop to move the pointer that is displayed on the screen. The pointer movement corresponds to the direction of your hand movement. The left and right mouse buttons are used to select items shown on the command monitor or the high-resolution monitor. The center button, of a three button mouse, is not used for any function.

The keyboard (Figure 5) is a conventional personal computer keyboard. The Esc, Tab, Enter, arrows, Page Up, and Page Down keys are used for special functions when operating the PAPNET Review Station. The other (alpha - numeric) keys are utilized in a conventional manner for entering information or comments.

NOTE: In this manual, the following convention is used to show keyboard keys: [Esc], [Tab], [Enter], [↑], [↓], [←], [→], [Pg Up], and [Pg Dn].

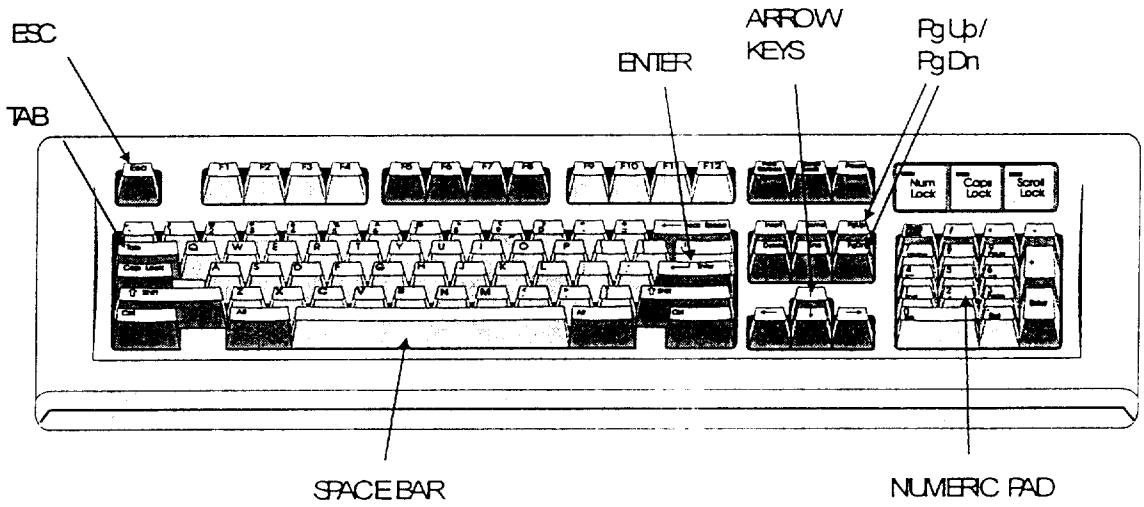


Figure 5 Keyboard and Key Locations

10.4 PAPNET REVIEW STATION

The PAPNET Review Station consists of a desktop computer with a high-resolution monitor on which to view images. The PAPNET Review Station computer contains a 1.2 GB (Gigabyte) hard disk which has a capacity that is sufficient to store the images from approximately 600 slides. To operate the PAPNET Review Station, the images from a Run (up to 100 slides) are loaded into the computer by copying the digital image data from the digital tape to the computer hard drive. Each image from each slide is then viewed, and a determination is made as to whether the series of images displayed for that Case contain potentially abnormal cells. The location of the center of each image on the slide is encoded as X and Y coordinates, enabling each selected object to be easily reviewed on a microscope with an aligned stage. The recommended positioning of the PAPNET Review Station components is shown in Figure 6.

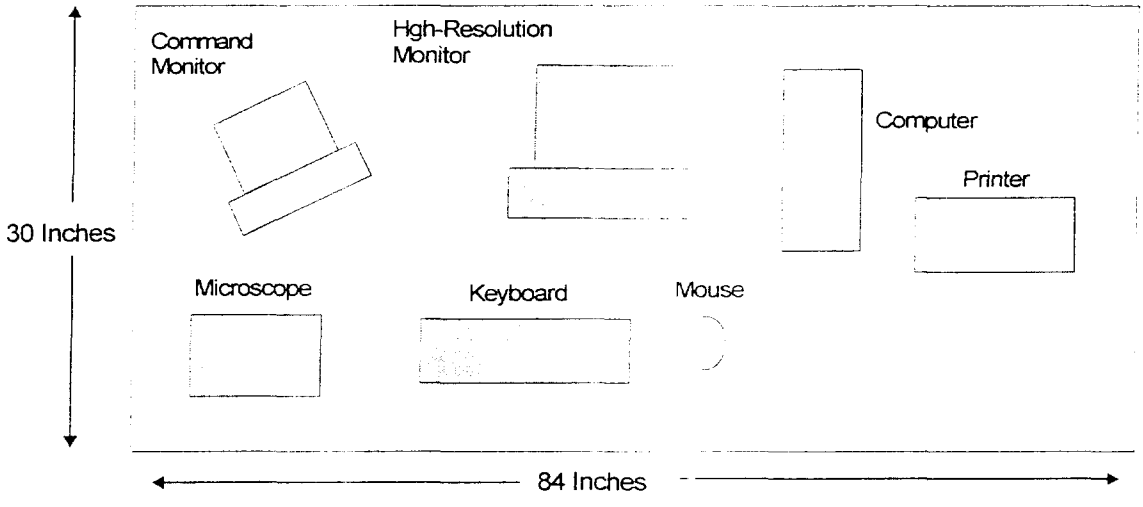


Figure 6 REVIEW STATION Recommended Spacing and Positioning

10.5 MATERIALS PROVIDED/NOT PROVIDED

Materials provided:

- PAPNET Review Station
- Barcode labels for slide identification
- Slide shipping containers
- Shipment tracking tag labels

Materials required but not provided:

- Standard clinical microscope with Vernier graduated stage

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11.0 REVIEW STATION OPERATION

11.1 OVERVIEW

Operation of the PAPNET Review Station consists of first loading image data from the digital tape into the computer, then viewing the images and selecting a triage classification for each Case, and finally printing out final results. Additionally, comments can be entered for each Case, however, they are not required.

To load image data from tape into the computer, use the **Load Cases** selection on the REVIEW STATION MENU, described in Section 11.5.

You can review images using the **Review Cases** function on the REVIEW STATION MENU, described in Section 11.6. Images are displayed when you select a Case or Run. Examine the images in page mode (64 tiles per screen) or in quadrant mode (16 tiles per screen), and tag any cells or group of cells that appear to require further examination. After you have examined each image in its entirety, select a triage classification for the Case (**Negative** or **Review**), described in Section 11.6.10.

You can print images and view and print reports of session information and Run results using the review session reporting features (REPORT MENU), described in Section 11.7.

Other information, including startup and shutdown, erasing cases from the hard disk drive, and general maintenance of the Review Station equipment are also detailed in the following sections.

11.2 USE OF THE MOUSE

The **mouse** is a hand-held pointing and switching device that enables you to select functions or images without having to use the keyboard, although, for many functions, either the keyboard or the mouse may be used. Whenever the mouse can be used in a particular application, a pointer, or mouse arrow, will be displayed on the screen of the monitor.

When using the mouse, hold the mouse flat on your desk or a table top and slide it gently to move the pointer around on the monitor. The pointer on the monitor moves a corresponding distance and direction. Move the pointer in this manner until it is positioned over the cell (on the high-resolution monitor) or function (on the command monitor) that is to be selected. When the pointer is positioned properly, select the cell or function by pressing either the left or right mouse button as directed.

11.3 STARTUP

Move the computer power switch to the **ON** position. Press the push-button power switches on both monitors and switch the printer power switch to the **ON** position. After a brief warm-up period, the REVIEW STATION MENU screen (Figure 7) is displayed on the command monitor.

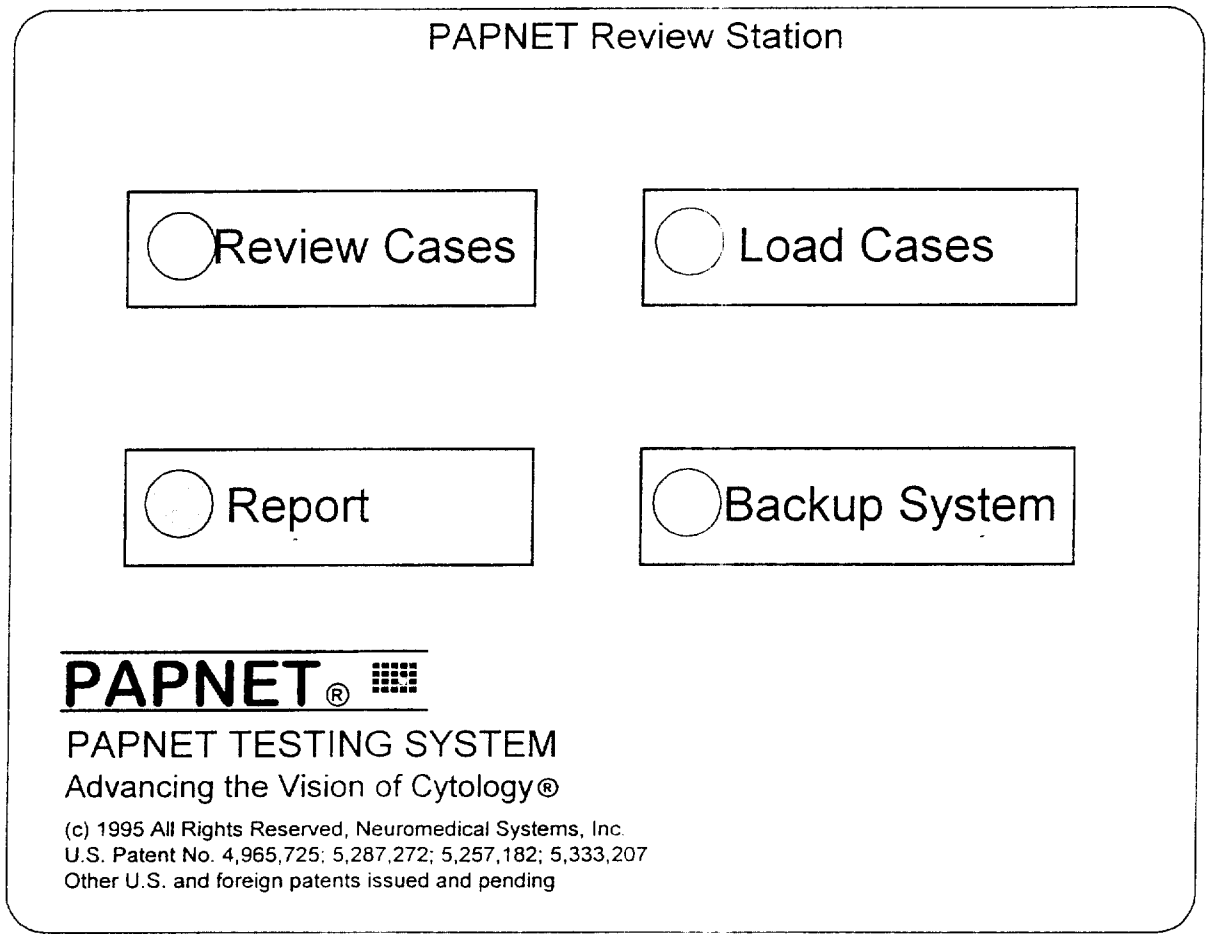

Figure 7 REVIEW STATION MENU Screen

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11.4 SELECTING A TAPE

The image data for each slide to be reviewed are contained on the digital tape prepared at the PAPNET Slide Scanning Center. Select the appropriate digital tape by examining the labels on the tape. The label contains the name of your laboratory, and the Run Name (a code containing your laboratory identification), as well as a reference slide ID (barcode) number (usually from the first case).

Select the tape containing the slide ID numbers that are to be reviewed. Verify that the laboratory name on the tape label is correct, and verify that the reference slide ID number listed on the label is contained in the Run you wish to review.

11.5 LOADING CASES

After verifying that you have selected the correct tape, insert the tape cartridge into the tape drive of the computer as shown in Figure 8. When inserting the tape, position it so that the arrow imprinted on the tape by the manufacturer is pointing away from you, and the labeled edge of the tape is closest to you. Gently push the tape into the tape drive until it locks in place.

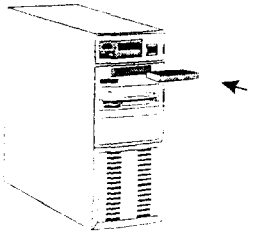

Figure 8 Digital Tape Insertion Into DAT Drive

To load cases from tape, position the mouse arrow on the **Load Cases** option in the REVIEW STATION MENU screen (on the command monitor), and then press and release either the left or the right mouse button. Several messages, including "INITIALIZING DRIVE," "READING DAT HEADER INFORMATION," and "SYSTEM READY" are displayed before the LOAD CASES (DRESTORE) screen (Figure 9) is displayed on the command monitor.

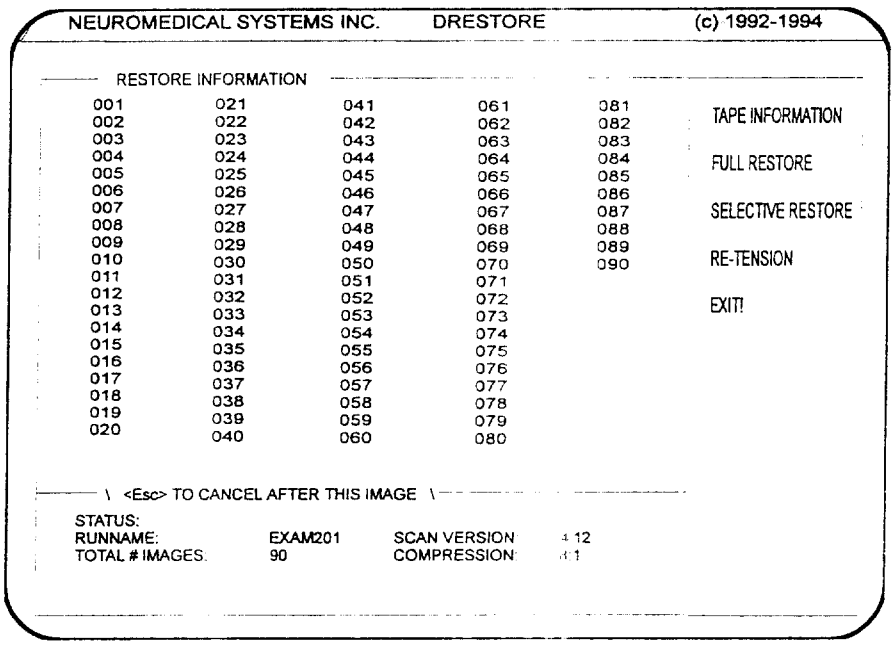

Figure 9 The LOAD CASES Screen

The window in the upper left hand portion of the LOAD CASES screen displays information concerning each of the cases contained on the tape. The window at the lower left hand portion of the screen describes the operation that is in progress (for example, "RESTORING"), as well as the Run Name, total number of cases contained on the tape, and other information.

The window at the right of the screen contains functions that are used to initiate various operations while in the LOAD CASES mode. A description of each of these functions and a summary of their purpose is outlined in Table 6:

Command:	What it Does:
Tape Information	Displays the slide ID numbers of all cases on the tape.
Full Restore	Copies all of the cases on the tape to the computer hard disk. (See Section 11.5.1.)
Selective Restore	Copies selected cases to the computer hard disk. (See Section 11.5.2.)
Re-Tension	Re-tensions the tape. Select this command if the message "NON-PAPNET TAPE" is displayed. (See Section 11.5.4)
Exit	Exits the LOAD CASES screen and returns to the PAPNET REVIEW STATION MENU screen.

Table 6 Command Functions Available on the LOAD CASES Screen

11.5.1 FULL RESTORE

The FULL RESTORE function is used to copy all of the cases that are on the digital tape. To restore all cases:

1. Highlight the **FULL RESTORE** function on the LOAD CASES screen using [↑] and [↓].

2. Select the highlighted function by pressing [Enter]. The tape drive is activated, and the program information window displays the status of the operation. As each Case is copied to the computer hard disk, the slide ID number of the Case currently being copied is displayed, along with the number of blocks (pieces of the data) that remain to be copied. It will take approximately ten minutes for 50 cases to be copied to the computer hard disk. After all the data have been transferred to the computer hard disk, the message "FUNCTION COMPLETED" is displayed in the program information window.

Note that you can press Esc at any time to interrupt the restore function. Refer to Section 11.5.3 for more information.

3. Return to the REVIEW STATION MENU screen by selecting the **EXIT** function (use the arrow keys to highlight **EXIT**, and then press Enter).

> **NOTE**: To eject a tape, you must exit out of the LOAD CASES screen and return to the REVIEW STATION MENU screen. Once there, press the eject button on the tape drive. The tape will rewind itself, and, after about 30 to 45 seconds, the tape will be ejected.

11.5.2 SELECTIVE RESTORE

The SELECTIVE RESTORE function is used to select some but not all of the cases that are on the digital tape. To restore selected cases:

1. Highlight the **SELECTIVE RESTORE** function on the LOAD CASES screen using ↑ or ↓.

2. Select the highlighted function by pressing Enter.

   The slide ID numbers of all of the cases that are recorded on the digital tape are displayed on the command monitor, with the slide ID number of the first Case highlighted.

3. If the highlighted slide ID number is to be restored, press Space to select it. The slide ID number will be displayed in yellow, indicating that it has been selected.

4. Highlight additional slide ID numbers by pressing the arrow keys to highlight the appropriate slide ID number, and then pressing Space to select it. Previously selected slide ID numbers can be deselected by again highlighting the number and then pressing Space.

5. Review the slide ID numbers of the cases displayed in yellow to ensure that the appropriate cases have been selected. Select and deselect cases as necessary.

6. Press [Enter]. The tape drive is activated, and the program information window displays the status of the operation. As each Case is copied to the computer hard disk, the slide ID number of the Case currently being copied is displayed, along with the number of blocks (pieces of data) that remain until the entire Case is copied. After all the data for the selected cases have been transferred to the computer hard disk, the message "FUNCTION COMPLETED" is displayed in the program information window.

7. Return to the REVIEW STATION MENU screen by selecting the **EXIT** command function (use [↑] and [↓] to highlight it, and then press [Enter]).

> **NOTE**: To eject a tape, you must exit out of the LOAD CASES screen and return to the REVIEW STATION MENU screen. Once there, press the eject button on the tape drive. The tape will rewind itself, and, after about 30 to 45 seconds, the tape will be ejected.

11.5.3 INTERRUPTING THE RESTORE PROCEDURE

Loading cases may be interrupted at any time by pressing [Esc]. After all the data from the current Case are copied, a dialog box is displayed on the command monitor with the message "**OK: to stop the restore now**" and "**Cancel: to Continue**", with **OK** highlighted. Press [Enter] to select the **OK** choice, and terminate the RESTORE function, or press [→] and then [Enter] to select **Cancel** and continue restoring cases.

The message "FUNCTION COMPLETED" is displayed in the program information window if the RESTORE function is terminated, otherwise, the restoration is resumed.

11.5.4 RE-TENSIONING A TAPE

Occasionally during shipping the tape itself loosens around the spools and the Review Station tape drive cannot read the information. When this occurs, it is necessary to re-tension the tape. To do so:

1. Highlight the **RE-TENSION** function on the LOAD CASES screen using ↑ or ↓.

2. Select the highlighted function by pressing Enter.

   The tape drive winds the tape to tighten the tension, and the message "RE-TENSIONING TAPE (30 sec. - 3 min.) is displayed in the program information window. Once the tape has been re-tensioned, the message "DRIVE/TAPE READY" is displayed in the program information window.

11.6 REVIEWING A CASE

Position the mouse arrow on the **Review Cases** option in the REVIEW STATION MENU screen, and then press and release either the left or right mouse button. The message "Enter review name:" is displayed on the command monitor, and the PAPNET Testing System logo is displayed on the high resolution monitor.

Enter the user ID assigned to you by your laboratory manager or your system administrator and press Enter. If this is a practice or demonstration session, or if you simply wish to review a Case without recording the results, type

DEMO

and press Enter. Remember that if you use the DEMO user ID, none of your review results will be saved.

The REVIEW screen is displayed on the monitor. The menu choices across the top of the screen are selections that initiate various operations available while in the review mode. A description of each of these selections and a summary of their functions is outlined in Table 7.

Selection:	What it Does:
CASES/RUNS	Allows review of selected cases or of all cases in the Run.
UTILITIES	Displays the space available on the hard disk drive, and provides the ability to erase images to make room for new cases.
F1-HELP	Activates a help screen.
QUIT	Returns to the PAPNET Review Station Menu.

Table 7 The REVIEW Menu

Select one of the menu choices by using [←] or [→] to highlight the menu item. Press [Enter] to display the submenu for that selection.

Select **CASES/RUNS** by using [←] or [→], and pressing [Enter]. A submenu offering the choices **View by Run, View by Case,** or **Main Menu** is displayed (Figure 10). To view all cases from a single Run one at a time, continue with Section 11.6.1. To view only selected cases, continue with Section 11.6.2. To return to the REVIEW MAIN MENU screen, select **Main Menu.**

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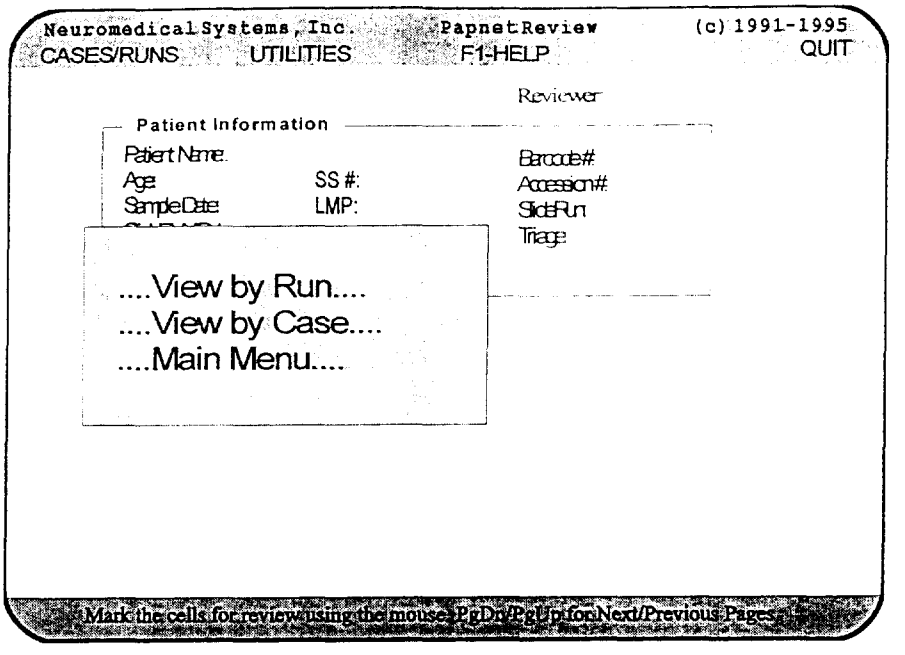

Figure 10 The REVIEW Screen

11.6.1 VIEWING BY RUN

To review all cases in a particular Run, select the **View by Run** option by highlighting it and then pressing Enter. A listing of the Run Names that are loaded in the computer hard drive will be displayed. Each Run Name is displayed in green, yellow, or red letters to signify the review status of the Run as summarized in Table 8.

Type Color:	What it Means:
Green	The Run has not been reviewed by the current reviewer.
Yellow	The Run has been partially reviewed by the current reviewer.
Red	The Run has been totally reviewed by the current reviewer.

Table 8 Coding (Color) of RUN Status

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Select the Run Name to be reviewed by using the arrow keys to highlight the Run Name and then pressing Enter. The TRIAGE MENU is displayed on the command monitor and the first image is displayed on the high-resolution monitor.

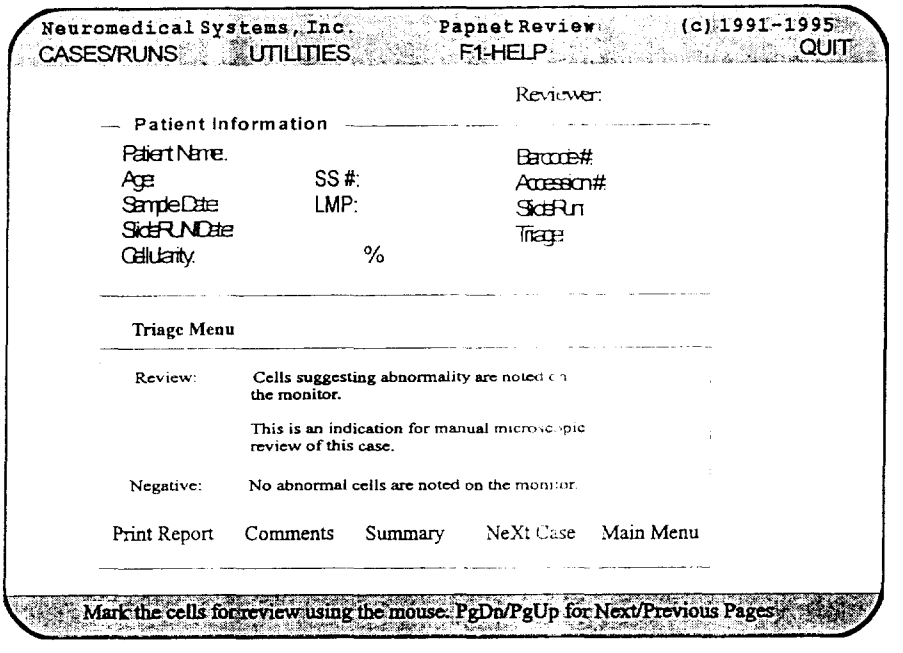

Figure 11 The TRIAGE MENU Screen

The window in the upper half of the TRIAGE MENU screen displays information concerning the cases being reviewed (**Patient Information**). The window in the bottom half of the screen contains the TRIAGE MENU items labeled **REVIEW** and **NEGATIVE.** It also contains a menu bar at the bottom of the window listing alternatives for various operations available while in the TRIAGE MENU (refer to Figure 11).

A description of each of the alternatives and a summary of the functions of the TRIAGE window is outlined in Table 9.

Selection:	What it Does:
Print Report	Displays the TRIAGE SUMMARY screen which contains results of review for cases in the current Run. Printing options are executed from this screen.
Comments	Opens a window into which comments concerning the Case can be typed.
Summary	Displays all image tiles that have been tagged for further review.
Next Case	Moves to the next Case selected in the Run.
Main Menu	Returns to main menu.

Table 9 The TRIAGE MENU

Information about the first Case that has not yet been reviewed is displayed in the Patient Information window on the monitor screen, and an array of images (tiles) from that Case is displayed on the high-resolution monitor.

11.6.2 VIEWING BY CASE

To review only some of the cases in the Run, select the **View by Case** option by making sure the selection is highlighted and then pressing Enter. A listing of the Run Names in the computer hard drive will be displayed in green, yellow or red letters to signify the status of the Run as summarized in Table 8.

Select the Run Name to be reviewed, using the arrow keys to highlight the Run Name and then pressing Enter. A listing of slide IDs representing the cases in the Run chosen will be displayed, with previously reviewed cases displayed in red and the remaining cases displayed in green.

The slide ID of the first Case will be highlighted in blue. If the highlighted Case number is to be selected, press the Space bar on the keyboard, and that slide ID will be displayed in white, indicating that the Case has been selected. Highlight adjacent slide IDs by pressing the up or down arrow keys and select appropriate slide IDs by pressing the Space bar. Previously selected slide IDs can be deselected by highlighting again and pressing the Space bar.

Review the slide IDs of the cases displayed in white on the screen to ensure that the appropriate cases have been selected. Press Enter. Information about the first Case is displayed in the **Patient Information** window on the monitor screen, and an array of images (tiles) from that Case is displayed on the high-resolution monitor.

11.6.3 IMAGE PRESENTATION

The arrays of images from each Case are presented in two viewing pages, with each page consisting of 64 images (Figure 12). The first array, consisting of 64 tiles containing images of single isolated cells, is labeled as Page 1. A second array, consisting of 64 additional images containing cell clusters, is labeled as Page 2. Each array of images is presented in a matrix of 8 x 8 tiles, with each tile containing an image of a cell or group of cells.

After viewing the first page of images, the second page is displayed by using PgDn. Page 2 images may not be viewed until all four quadrants are reviewed on Page 1 (in zoom mode) a minimum of once (one quadrant of 16 tiles displayed). Move in the reverse direction by using PgUp.

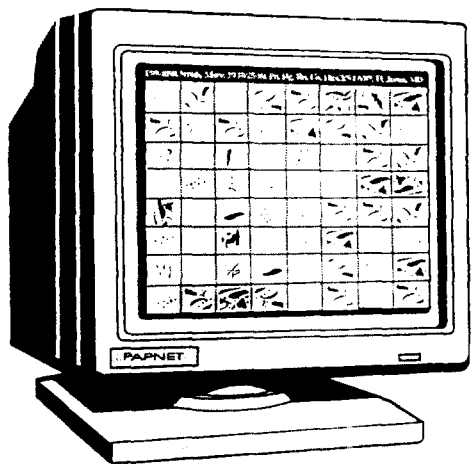

Figure 12 Review Station Displaying One (Full) Video Page

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11.6.4 DISPLAYING IMAGES IN QUAD MODE

During review of each page, it will be necessary to increase the magnification of one or more images. All of the images may be electronically enlarged (zoomed) by pressing [Z] to expand the tiles so that one fourth of each page (called a quadrant) is displayed on the high-resolution monitor (Figure 13). Move from one quadrant to the next by pressing [Tab]. The full-page display may be resumed by pressing [Z].

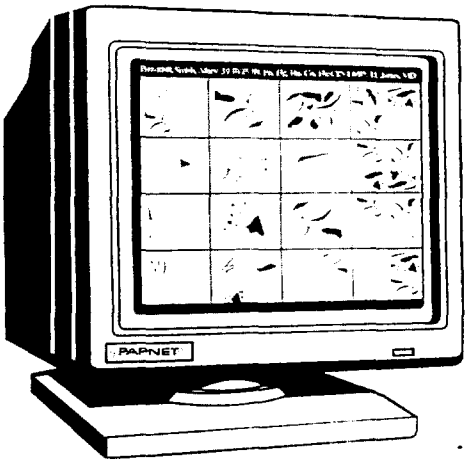

Figure 13 Displaying One Quadrant of 16 Tiles

11.6.5 SAVING QUADRANT IMAGES FOR PRINTING

While in Quad mode it is possible to save the current quadrant of Tiles for printing at a later time (see Section 11.7.1 "PRINTING IMAGES").

To save a quadrant for printing:

1. Display the image (from either Case review or Summary) to be printed in Quad mode. Note that the mouse cursor is displayed in the printed quadrant image and should be positioned on the screen accordingly. Also, magnified Tiles and coordinates, if displayed, are displayed in the printed image; ensure that these features are not in use if they are not desired as part of the printed output.

2. Press [F2] to save the quadrant for printing with the mouse pointer displayed in the output, or [F9] to save the quadrant for printing without the mouse pointer displayed n the output. Note that saving the same Quadrant image for print a second time replaces the image and data that was saved for that Quadrant previously.
3. If hardcopy printouts of additional quadrants are required, press [Tab] to view another quadrant, and repeat steps one and two until all required quadrants have been saved for printing.
4. Continue with the instructions outlined in Section 11.7.1, "PRINTING IMAGES".

11.6.6 MAGNIFYING A CELL

Alternately, an optically magnified view of the central portion of each image (obtained during scanning) can be selected by positioning the mouse pointer near the center of the tile and momentarily pressing the right mouse button. A green letter "**M**" is displayed and remains in the lower right hand corner of the tile while it is in the magnified view. The original unmagnified image can be selected by positioning the mouse pointer near the center of the tile and momentarily pressing the right mouse button.

11.6.7 TAGGING A CELL

Each of the 64 images on each page should be reviewed. If, during review of the images, it appears that one or more cells may require further review under the microscope, the cell should be tagged using the mouse. Position the pointer on the cell in question, and momentarily press the left mouse button. A red border appears around that tile, and the coordinates of the cell will be displayed in the tile. The "tag" can be removed from the tile at any time by repositioning the mouse pointer within the tile and then momentarily pressing the left mouse button.

11.6.8 ENTERING COMMENTS

Comments concerning a Case may be entered after reviewing a Case by highlighting the **Comments** selection in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [C]. A green comment window will open, and comments of up to 65 characters can be entered. After the comments have been typed, press [Enter].

Comments entered for the Case may then be viewed, and edited at any time before proceeding to the next Case. Comments may be viewed and edited by either highlighting the **Comments** selection in the Triage Menu box (use the arrow keys) and pressing [Enter] or by simply pressing [C].

Comments may be revised by pressing [←]. To exit, press [Esc] at any time during comment entry. Note that pressing [Esc] before pressing [Enter] causes any text entered to be lost.

11.6.9 VIEWING ALL TAGGED CELLS

All of the tiles that have been tagged during review of the Case can be viewed at any time by selecting the **Summary** option in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [S]. Images of all of the tagged tiles are displayed on the high resolution monitor with their coordinates. To view this tagged summary in the quadrant mode, press [Z]. To conceal the coordinates of the tagged Tiles, press [D]. To display the coordinates, press [D] again. To save summary Quadrant images for printing with the mouse pointer visible, press or [F2]. To save summary Quadrant images for printing without the mouse pointer visible, press [F9].

To continue reviewing the Case after viewing images of tagged cells in the **Summary** option, press [Esc], followed by [PgUp] and [PgDn] to further view images in the first and second pages. To record triage information or

to proceed to the next Case, press [X] or follow the procedures outlined in the following sections.

11.6.10 TRIAGE

Triage is the process of determining which cases should be referred for microscopic evaluation. If one or more of the 128 tiles of the Case cells appears to be abnormal, the triage classification of **Review** is selected, and the slide must be subsequently manually re-examined under the microscope. If all of the cells appear to be normal, the triage classification of **Negative** is selected.

The "zoom" feature must be used to review each of the four quadrants on both pages of a Case prior to making a triage assessment.

After all of the tiles have been reviewed, the triage assessment for the Case can be made by highlighting either the **Review** or **Negative** selection in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [R] (for "Review") or [N] (for "Negative").

If any of the tiles in the Case is tagged and a **Negative** triage classification is entered, a prompt is displayed on the screen to verify the negative triage. The negative triage can be confirmed by pressing [Enter], or the Case can be reconsidered by highlighting the **Cancel** selection and pressing [Enter].

11.6.11 TRIAGE GUIDELINES

A Case should be classified as **Review** whenever there is definitive or suggestive cytological abnormality. The abnormality may range from atypia to malignancy, and may involve cells of any type. In addition, the **Review** classification should be used for any other instance suggesting manual microscopic confirmation. In additional to definitive or suspicious abnormalities, examples of circumstances that may require manual microscope evaluation include, but not limited to:

- the presence of excessive blood, inflammation, or cytolysis.
- hormonal pattern inconsistent with age and patient history.

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- presence of endometrial or endocervical cells.
- confirmation of microorganisms.
- evaluation due to suspicious background.
- cases displaying select Tech Codes

A Case should be classified as **Negative** when all of the fields displayed for that Case appear within normal limits and there is no suggestion of cellular abnormality.

11.6.12 TECH CODES

Occasionally, a message (refer to Table 10) is displayed in a red window on the command monitor prior to image display. After a key is pressed, a notation of **TECH** is displayed following the TRIAGE heading on the control monitor screen.

This message and the appearance of the **TECH** notation alerts the reviewer either that the scanning of this slide was affected by the presence of artifacts, or that other problems may have been detected during scanning of the slide. The particular problem that caused the **TECH** notation to be displayed is indicated by a numerical code that follows the notation. A listing of the various TECH codes, the message that accompanies each, and an explanation of their meaning is shown in Table 7.

For cases with the **TECH** notation, a triage classification does not have to be selected. This may be desirable if the smear or images are suboptimal. The default triage, if NEGATIVE or REVIEW are not selected, is TECH*xx*, where *xx* is a two digit numeric code.

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Code	Message:	Reason:
01-09, 11-15, 17-19, 22-24	Due to technical difficulties, the processing of this slide on the PAPNET system is incomplete. Please examine further if indicated.	A problem, such as focus failure, occurred during the automatic scanning of this slide and was unable to be corrected.
10,16	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	Not enough cells were found.
20	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	Not enough squamous cells were found.
21	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	Not enough cell clusters were found.
50	Due to physical problems with this slide, the scanning of this slide cannot be performed.	The slide was broken.
51	Due to physical problems with this slide, the scanning of this slide cannot be performed.	The mounting agent was wet.
52	Due to physical problems with this slide, the scanning of this slide cannot be performed.	The slide was cracked or chipped
53	Due to physical problems with this slide, the scanning of this slide cannot be performed.	Two coverslips or coverslips on wrong side
54	Due to physical problems with this slide, the scanning of this slide cannot be performed.	Double slide
60	This slide contains a significant number of artifacts. Please examine further if indicated.	Many artifacts such as graphite, dirt, or fibers were detected.
61	Excessive bubbles (>30%) prevented a complete scan of this slide. Please examine further if indicated.	At least 30% of the area under the coverslip could not be scanned because air or water bubbles were present.
62	This slide contains a significant number of artifacts. Please examine further if indicated.	Many artifacts were detected.
70	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	The staining of the slide was inadequate.
71	Due to physical problems with this slide, the scanning of this slide cannot be performed.	The slide was still wet.
72	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	Annual rings were present.
73	Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	The coverslip was warped.

Table 10 Explanation of TECH Codes

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11.6.13 PROCEEDING TO THE NEXT CASE

Proceed to the next Case by highlighting the **Next Case** selection in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [X] from either the REVIEW screen or the SUMMARY screen once the Case has been triaged. The REVIEW screen will now display information for the next Case.

11.6.14 PRINT REPORT

Print Report is used to display and/or print a summary of triage results for the current Run. The Print Report command brings up the TRIAGE SUMMARY screen. A list of smear slide IDs, their triage status, and accession number (if available) is displayed. There are several viewing options available. Smears from the current Run, which have been reviewed in the current session, may be viewed either in their entirety or partially. Comments will be displayed below each smear slide ID, if entered.

Cases are selected for display by pressing [A] for displaying all cases, [R] for all cases classified as Review, [N] for all cases classified as Negative, or [T] to display all cases that are classified as TECH. These triage options are summarized in Table 11.

Option:	What it Does:
[A] -All	All cases are displayed.
[R] -Review	Cases with "Review" triage (or classified as Review), are displayed.
[N] -Negative	Cases with 'Negative' triage (or classified as Negative), are displayed.
[T] -Tech.	Cases with 'Tech' triage (Special conditions) are displayed.

Table 11 Sort Options for Printing Cases

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To print a report, press [P] to activate the Triage Summary option. Only the information visible on the screen that is displayed will be printed. If the review results are contained on more than one screen, scroll the list by using the 'Page Up' and 'Page Dn' keys and press [P] to print the triage summary.

11.6.15 *INTERRUPTING A RUN*

Review of the current Case must be completed before interrupting a Run.

A Run can be interrupted by highlighting the **Main Menu** selection in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [M] A screen summarizing the cases that have been reviewed in the current session and their triage classification is displayed and can be printed using [P]. Pressing [Esc] will bring up the REVIEW STATION MENU screen.

11.6.16 *EXITING REVIEW*

At the completion of any Case (see above), the REVIEW screen may be exited by highlighting the **Main Menu** selection in the Triage Menu box (use the arrow keys) and pressing [Enter], or by simply pressing [M]. The system will prompt you for verification before exiting. The next screen will be the TRIAGE SUMMARY screen. Press [Esc] . Following is the PATIENT INFORMATION screen. Select the **QUIT** function or press [Esc] to bring up the REVIEW STATION MENU screen.

The system will display a prompt for verification of exiting the review program. After verification, the REVIEW STATION MENU screen is displayed.

CAUTION
NEVER SHUT OFF THE POWER TO THE PAPNET REVIEW STATION WITHOUT EXITING IN THE MANNER DESCRIBED ABOVE. FAILURE TO FOLLOW CORRECT PROCEDURE MAY RESULT IN LOSS OF DATA.

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11.7 REPORTING OPTIONS

11.7.1 PRINTING IMAGES

The PAPNET image printing feature increases the printing capabilities of the Review Station by providing the ability to print the color images displayed on the high resolution monitor. The images are saved during Review using the method described in Section 11.6.5, "Saving Quadrant Images For Printing". These images can then be printed using the tools provided by this feature. The image printing feature provides the ability to print:

- All quadrant images saved from a selected Run, including Summary quadrants.
- One or more quadrant images saved during Review for a selected Case.

To print saved quadrant images:

1. Select PAPNET IMAGE PRINT from the Report Menu. A list of available Runs is displayed:

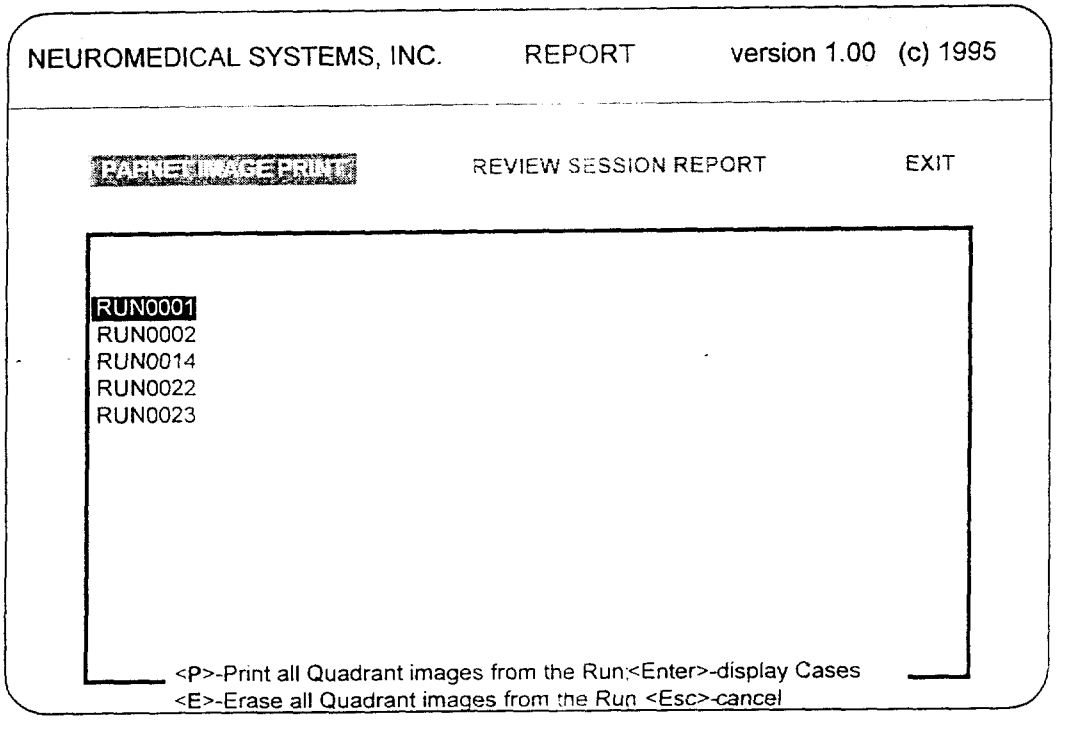

Figure 14 Sample List of Available Runs

2. From within the list of Runs:

To:	Follow these steps:
Print all saved quadrant images from a Run	1. Use ↑ and ↓ to highlight the Run. 2. Press P.
Erase all saved quadrant images for a Run	1. Use ↑ and ↓ to highlight the Run. 2. Press E. 3. At the confirmation message, press Enter to erase all saved quadrant images for that Run, or press → and then Enter to cancel the deletion.
Display Case quadrant images for a selected Run	1. Use ↑ and ↓ to highlight a Run. 2. Press Enter. 3. Continue with Section "Printing And Erasing Case Quadrant Images".
Return to the Report Menu	Press Esc.

Printing and Erasing Case Quadrant Images

Whenever a quadrant image is saved for printing, the PAPNET Testing System creates a copy of the quadrant image in the format that the printer can understand. These copies are saved until they are erased using the method described in "Erasing Quadrant Images" later in this section. Quadrant images can be printed or erased on a quadrant-by-quadrant basis. When Enter is pressed with a Run selected, a list of saved quadrant images is displayed:

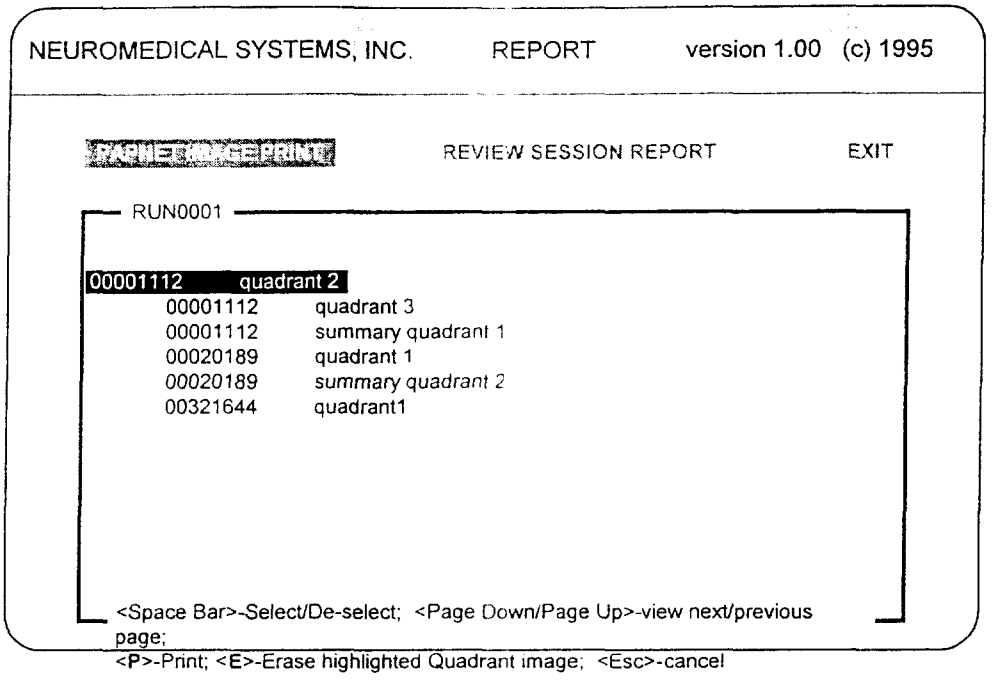

Figure 15 Sample List of Available Runs

The keystrokes available while in this menu are described in the following table:

↑ and ↓	Moves the highlight bar up and down among the saved quadrant images.
Space	Selects a quadrant image for printing, or de-selects an already selected image.
Page Down	Displays the next page of saved quadrant images (if one exists).
Page Up	Displays the previous page of saved quadrant images (if one exists).
P	Prints all selected images (see "Printing Quadrant Images" later in this section).
E	Erases the selected image (see "Erasing Quadrant Images" later in this section).
Esc	Cancels quadrant image selection and returns to the Run selection menu.

Printing Quadrant Images

1. Use [↑] and [↓] to position the highlight bar on a quadrant image to be printed.
2. Press [Space] to select the quadrant image. If the image is selected in error, press [Space] again to de-select the image.
3. Repeat steps one and two until all required images have been selected.
4. Press [P] to print the image(s). The following information is displayed:

```
Please wait. Printing image: casename quad n
```

where:

`casename`	is the name of the Case from which the quadrant was saved.
`quad`	signifies that either a Review quadrant is being printed (`quadrant`) or a Summary quadrant is being printed (`summary quadrant`).
`n`	is the number of the quadrant or summary quadrant being printed.

Notes:

- Whatever is displayed on the screen at the time the image is saved for printing will appear in the printed output. For example, if a tile is magnified at the time [F2] or [F9] was pressed, the tile will be magnified in the output.
- The image printing feature can print up to a maximum of 100 saved quadrant images from a Run.
- For guidelines on color cartridge replacement, please refer to the user manual that accompanies the printer.
- Saving the same Quadrant image for print a second time replaces the image and data that was saved for that Quadrant previously.
- If specially-coated paper is used in the color printer, ensure that the printable side (usually the shiny side) is loaded into the printer face down.

Erasing Quadrant Images

1. Use [↑] and [↓] to position the highlight bar on the saved quadrant image to be erased.
2. Press [Spacebar] to select the image to be erased.

3. Press [E] to erase the selected image.
4. At the confirmation message, press [Enter] to erase the image, or press [→] and then [Enter] to cancel the erase.

11.7.2 REVIEW SESSION REPORTING FEATURE

The Review Session Reporting feature increases the reporting capabilities of the Review Station by providing a log of Review session results that can be displayed in a variety of useful formats. This feature provides the ability to:

- Print session information reports by Run.
- Print Run results by Triage category (All, Review or Negative).
- Print Run results that received Tech codes.
- Print session information after a session has ended.
- Erase the log of Run data.

Displaying and Printing Review Session Data

To display a record of data saved from Review sessions:

1. Select REVIEW SESSION REPORT from the Report Menu. A list of available Runs is displayed:

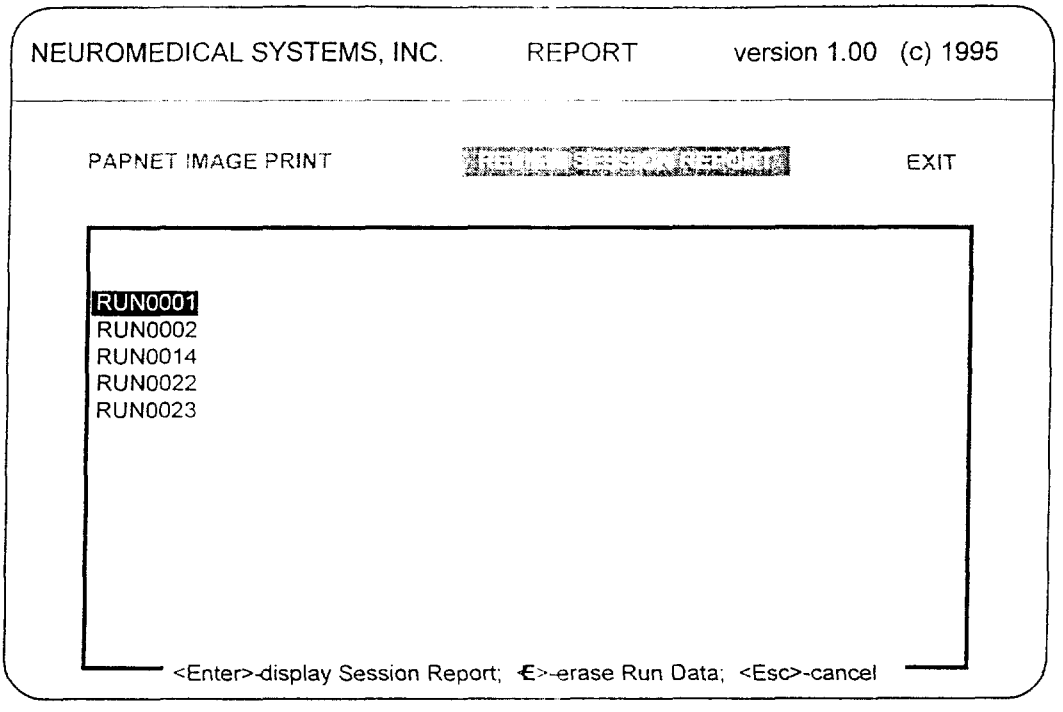

Figure 16 Session Report Options

2. Use ↑ and ↓ to highlight a Run.
3. Press Enter. The following Review results for the selected Run are displayed:
   - Casename
   - Triage result
   - Reviewer ID
   - Date reviewed
   - Coordinates of the first 25 tagged Tiles, if the Case contains any
   - Comments, if the Case contains any

Note the following example:

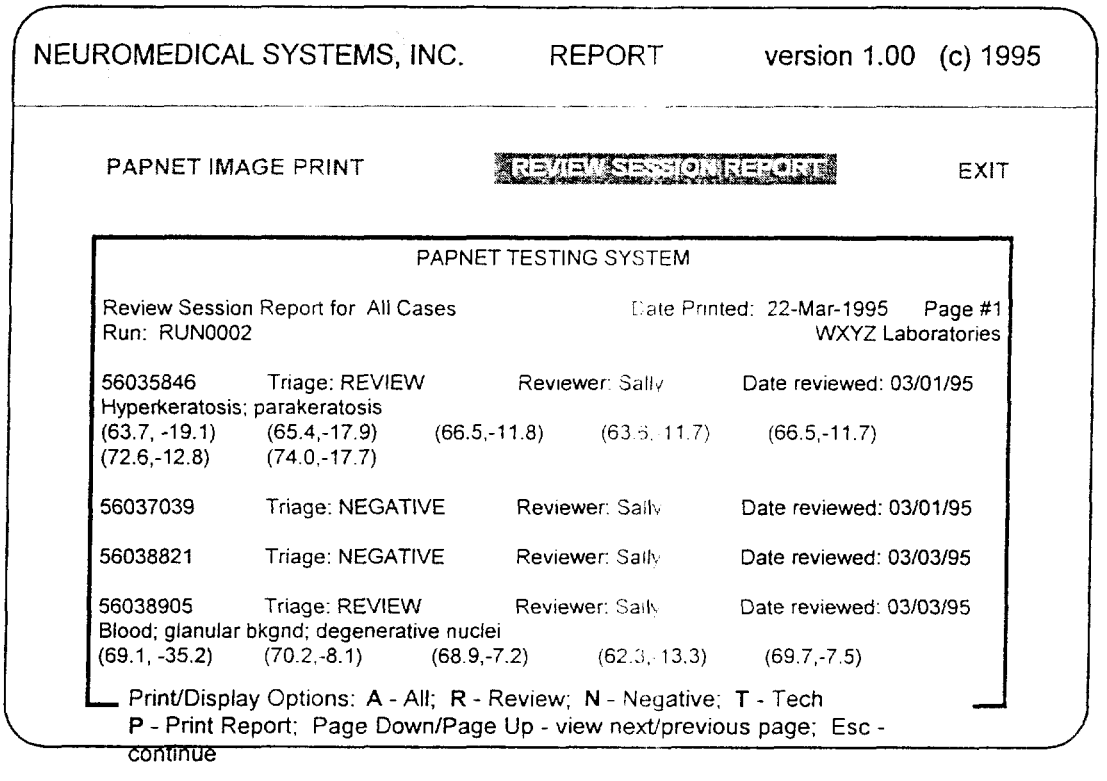

Figure 17 Sample Report Output

4. To view data for the selected Run organized in a different way, press one of the following keys:

Press:	To view:
R	Review session results triaged as Review.
N	Review session results triaged as Negative.
A	All Review results.
T	All Review results that have a Tech code.

5. To print a report, press P while the report is displayed on the screen. The report is printed on the printer attached to the Review Station. For reference, a solid double line is printed at the end of the report.
6. Repeat steps four and five until all required reports have been printed.
7. Press Esc to return to the list of Runs.

Erasing a Review Session Data Log File

Data entered during a Review session is not only saved with the Case for which is entered, it is also saved chronologically by Run in a log file. The log file of Review session data is separate from the data saved with the image and is used to create the Review session data reports. It is saved on the hard disk drive until it is manually erased.

To erase a Review session data log file:

1. Select REVIEW SESSION REPORT from the Report Menu. A list of available Runs is displayed:

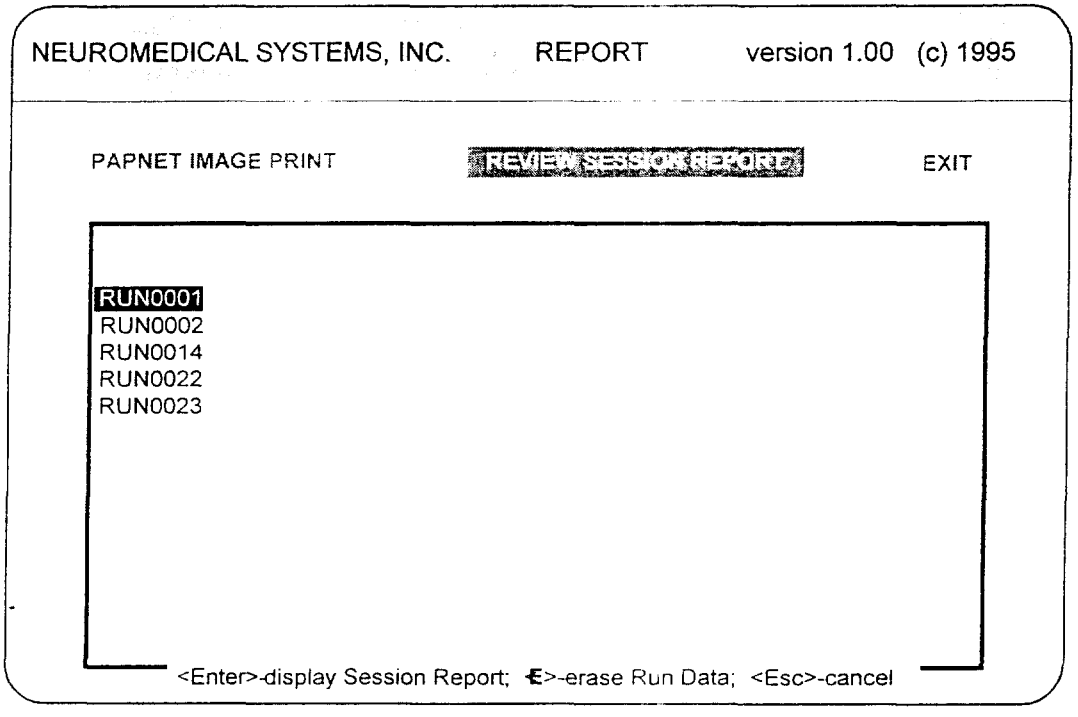

Figure 18 List of Run Log Files Available for Erasing

2. Use ↑ and ↓ to highlight the Run for which the log file is to be erased.
3. Press E to erase the log file of Review data associated with the selected Run.
4. At the confirmation message, press Enter to erase the log file, or press → and then Enter to cancel the erase.

11.7.3 EXITING REPORT

To exit from the Report Menu and return to the System Menu, use [←] or [→] to highlight **EXIT**, and press [Enter].

11.8 SYSTEM BACKUP

Position the mouse arrow on the **Backup System** option in the REVIEW STATION MENU screen, and then press and release either the left or right mouse button. The Novaback® Backup/Restore Program Menu is displayed with the selections shown in Table 12.

Selection:	What it Does:
Standard Backup	Backs up the contents of the entire disk drive.
Select Files for Backup	Backs up selected files.
Run a Backup Procedure	Runs a procedure created by the system administrator.
Restore Data from Tape	Restores back up data onto the hard drive from a tape.
Utility Functions	Provides utility information about the tape or system.
Stop	Returns you to the REVIEW STATION MENU.

Table 12 The Novaback® Backup/Restore Program Menu Options

Select one of the menu choices by using [↑] or [↓] to highlight the menu item. Press [Enter] to display the submenu for that selection. The menu items are described in detail in the following sections.

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11.8.1 PERFORMING A STANDARD BACKUP

To perform a backup of all the files on your Review Station hard disk drive:

1. From REVIEW STATION MENU, select BACKUP SYSTEM and press [Enter].

2. Insert a tape in the tape drive.

3. Select STANDARD BACKUP from the Novaback® Backup/Restore Program Menu and press [Enter].

4. If the tape is new, select OVERWRITE THE CURRENT DATA and press [Enter]. Press [Y] when prompted to format the tape.

   If the tape is not new, select WRITE AFTER THE CURRENT DATA and press [Enter] to append the data

5. Upon completion, press [Enter] to return to the BACKUP SYSTEM MENU.

6. Select Stop to return to the REVIEW STATION MENU.

11.8.2 PERFORMING A SELECTIVE BACKUP

To perform a backup of selected files on your Review Station hard disk drive:

1. From REVIEW STATION MENU, select BACKUP SYSTEM and press [Enter].

2. Insert a tape in the tape drive.

3. Select SELECT FILES FOR BACKUP from the Novaback® Backup/Restore Program Menu and press [Enter].

4. Press [Enter] to view the list of files.

5. Press [Space] to tag the file(s) or directories to be backed up.

6. Press [F10] when you are done.

7. Press [F10] to use the default options.

8. If the tape is new, select OVERWRITE THE CURRENT DATA and press [Enter]. Press [Y] when prompted to format the tape.

   If the tape is not new, select WRITE AFTER THE CURRENT DATA and press [Enter] to append the data

9. Upon completion, press [Enter] to return to the BACKUP SYSTEM MENU.

10. Select Stop to return to the REVIEW STATION MENU.

11.8.3 RESTORING BACKED-UP DATA

To restore selected files from tape to your Review Station hard disk drive:

1. From REVIEW STATION MENU, select BACKUP SYSTEM and press [Enter].

2. Insert the tape in the tape drive.

3. Select RESTORE DATA FROM TAPE from the Novaback® Backup/Restore Program Menu and press [Enter].

4. Enter the back up set number (the sequential number of the back up data to be restored - default is 1), and press [F10].

5. Press [F10] and then [Enter] to view the list of files.

6. Press [Space] to tag the file(s) or directories to restore.

7. Press [F10] when you are done.

8. When image loading is complete, press [Enter] to return to the BACKUP SYSTEM MENU.

9. Select Stop to return to the REVIEW STATION MENU.

11.9 DEMO MODE

The DEMO mode of the PAPNET Review Station may be used for viewing cases without saving triage or other review data. This mode may be used for practice, for demonstration purposes, or to simply review information.

To enter the DEMO mode, select the **Review Cases** option on the REVIEW STATION MENU screen, and then momentarily press either the left or right mouse button. When the message "Enter Reviewer Name" is displayed, type in the word **DEMO** and press [Enter].

NOTE: The **DEMO** mode should be used for practice or demonstrations only. No review information will be saved in this mode. In contrast, entry into the **REVIEW** mode followed by typing in of the correct user ID allows active entry into the **REVIEW** mode, with updating of information and entry of triage data. For security purposes, your user ID should be protected and kept confidential.

The REVIEW screen is displayed on the monitor. All of the normal operational functions of the Review Cases mode may be carried out, except that triage selections and tagged cells will not be saved

11.10 MANUAL REVIEW OF TAGGED CELLS

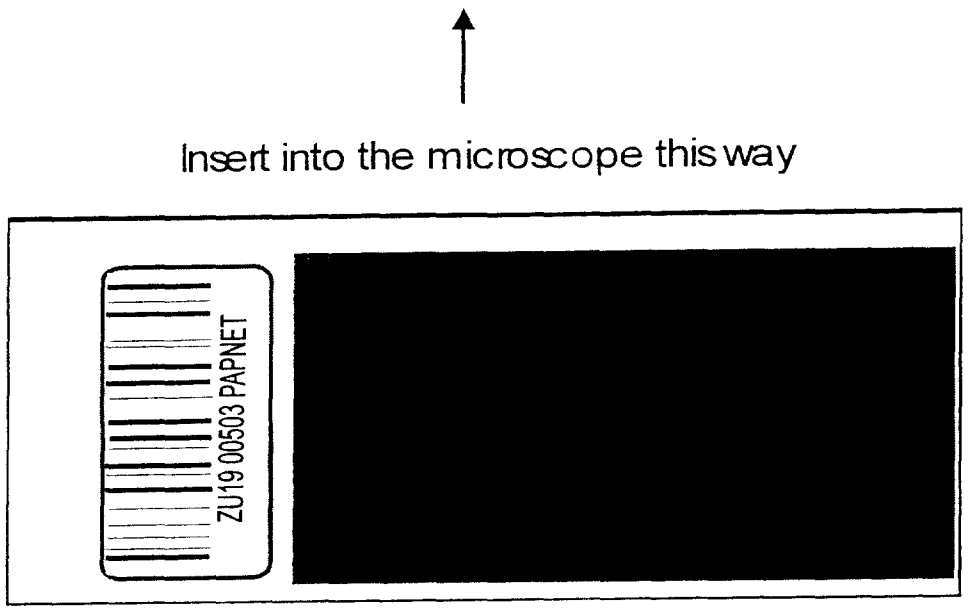
11.10.1 POSITIONING THE SLIDE

To locate a tagged cell under the microscope, obtain the slide with the slide ID corresponding to the Case being reviewed. Place the slide on the microscope so that the slide ID label on the slide is to the left as shown in the following diagram. When positioning the slide on the microscope stage, verify that the stage and the slide retaining mechanism are clean, and that the base and edges of the slide are in direct contact with the slide retaining mechanism.

NOTE: If the microscope has been moved, ensure that it is properly realigned before attempting to position the slide.

11.10.2 LOCATING A CELL

To locate a tagged Tile, read the X/Y coordinates displayed on the screen and move the microscope stage to the corresponding location. Move the width-side of the stage to the X coordinate and the length-side of the stage to the Y coordinate. The tagged cell or cells should now be located near the center of the microscope field.



11.11 SHUTDOWN

Before shutting the PAPNET Review Station down, ensure that the REVIEW STATION MENU screen (Figure 7) is displayed on the command monitor. Press the push-button power switches on both monitors and the computer, and turn the printer power switch to the OFF position. Verify that the indicator lights on both monitors, the computer, and the printer are off.

CAUTION
NEVER SHUT OFF THE POWER TO THE PAPNET REVIEW STATION WITHOUT EXITING IN THE MANNER DESCRIBED ABOVE. FAILURE TO FOLLOW CORRECT PROCEDURE MAY RESULT IN LOSS OF DATA.

11.12 ERASING CASES FROM HARD DISK DRIVE

Cases that have been completed must be periodically erased from the hard drive, to allow space for loading new cases. The procedure for erasing cases is described below.

Use the mouse or press [R] to select the **Review Cases** option on the REVIEW STATION MENU screen. When the message **"Enter Reviewer Name"** is displayed, type in your user ID and press [Enter]. The REVIEW screen is displayed on the monitor.

Highlight the UTILITIES option at the top of the screen by using the right arrow key. Press [Enter] after the UTILITIES option is highlighted. A submenu including the choice **Erase Run** is displayed. Select the desired option on the submenu by using the up or down arrow key and then press [Enter]. A list of the runs stored in the computer will be displayed.

Highlight the Run to be erased using the arrow keys, and then press [Enter]. If the Run selected has not been completed, a prompt is displayed to verify the erasing of the Run. The system will then display the prompt **"Erase Run xxxxx? OK/Cancel"**, with the **OK** choice highlighted. Verify that the Run Name displayed is correct, and press [Enter] to activate the O.K. option. If, for any reason, the Case or Run should not be erased, highlight the **CANCEL** option by pressing the right arrow key, and press [Enter]

A second prompt is displayed indicating that the data that were erased, and a message is displayed indicating to "**Hit any key to continue**". Repeat the procedure until all of the necessary runs are erased. When all of the desired runs have been erased, highlight the option "**Return to Main Menu**" from the Utilities menu and press [Enter] to display the Main Menu, or press [Esc].

11.13 MAINTENANCE

11.13.1 GENERAL CLEANING

The outside of the PAPNET Review Station components should be periodically cleaned with a paper towel or cloth. The area around the system components should be checked to ensure that air flow around the components is unrestricted and that materials such as papers are not interfering with the air flow.

Food and drinks should not be brought into the vicinity of the PAPNET Review Station.

The area where the mouse is used should be kept clear of lint and small particulate matter, as this may build up inside of the mouse housing and interfere with proper operation of the mouse.

11.13.2 HEAD CLEANING OF DDS DRIVES

A cleaning cartridge should be used to clean the head of the DDS drive after every 8 to 10 hours of tape motion. Generally, this is done weekly.

Per the manufacturer's instructions, insertion of the cleaning cartridge will cause the drive to initiate a cleaning cycle whereby the tape is in contact with the rotating drum of the head for 15 to 30 seconds. The status light will flash during the cleaning cycle. Upon completion, the cartridge will be ejected from the drive.

Once the cleaning procedure has been completed, sign and date the Maintenance Checklist form (NSI Form Number 750A0229) in the logbook that accompanies the Review Station.

After approximately 20 cleanings the end of the cleaning cartridge will be reached and the tape should be discarded.

11.13.3 REPLACEMENT OF CONSUMABLES

The only PAPNET Review Station consumables needing periodic replenishment are printer paper and the printer ink unit. Since different printer options are available, consult the labeling for the printer installed in your laboratory for information concerning replacement of the paper and printing unit.

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APPENDICES

APPENDIX A ADMINISTRATOR FUNCTIONS

A.1 MODIFYING SYSTEM SETUP

The PAPNET Review Station setup can be modified so that the laboratory name and the number and access names of PAPNET Review Station users can be changed. In addition, the alignment data for the microscope used in the laboratory can be modified, so that cell images selected during scanning can be viewed using different microscope. Finally, the current date and current time can be changed.

To access the Setup screen, with the Review Station's power turned off, insert the floppy diskette labeled "SETSITE BOOTABLE DISK" and turn on the power. A submenu including the choice **Initial Installation (full setup)** is displayed. Select the desired option on the submenu by using the up or down arrow key and pressing Enter. The SYSTEM SETUP screen (Figure 19) is displayed.

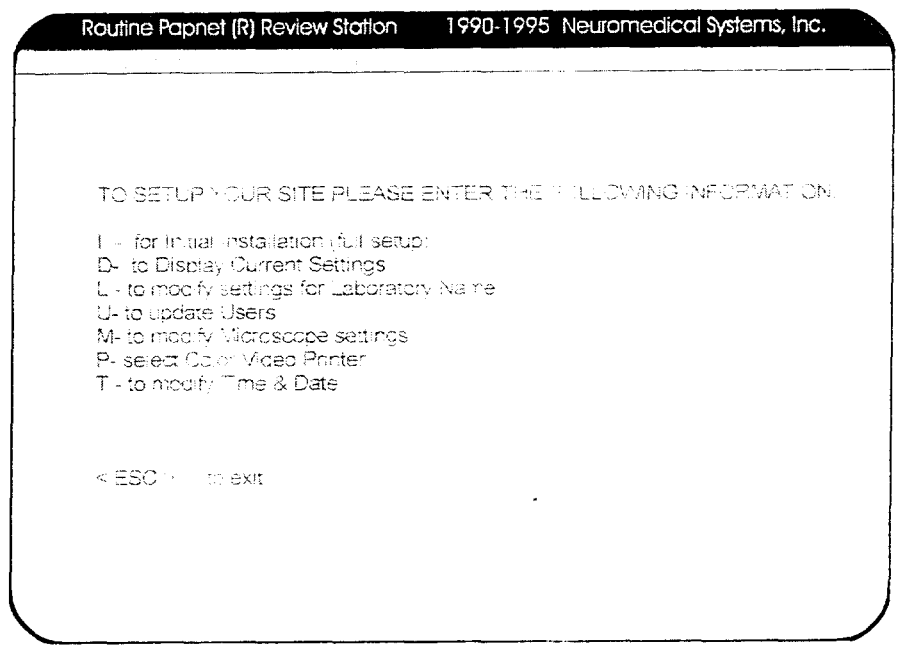

Figure 19 The SYSTEM SETUP Screen

If Esc is pressed, the Setup procedure is canceled and the operator receives a message instructing him/her to press any key and then reboot the computer.

A.1.1 MODIFYING SITE INFORMATION

After [L] is pressed, the SITE INFORMATION screen (Figure 20) is displayed. This screen contains the laboratory name that is currently entered into the system and a field that allows the user to enter a new laboratory name.

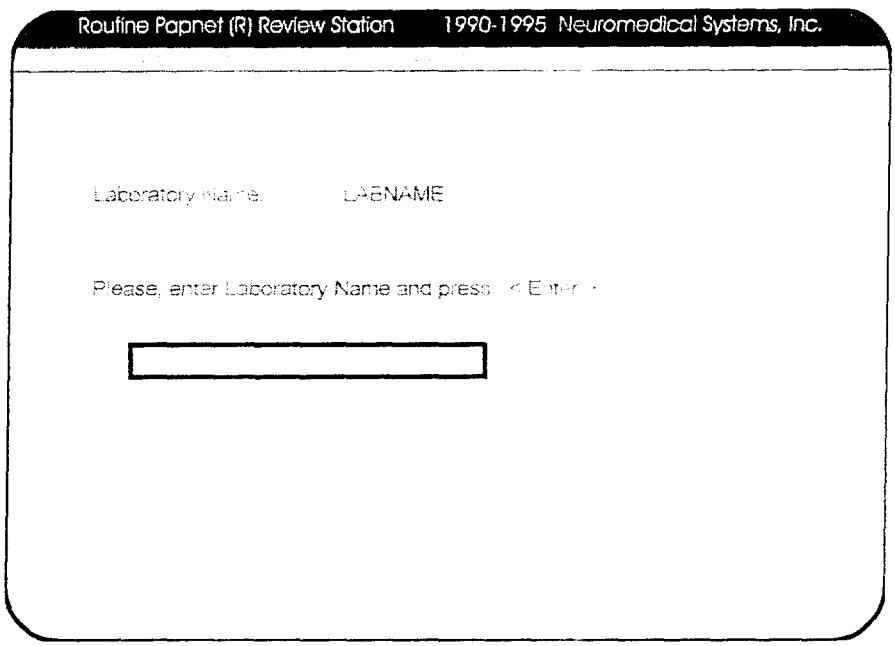

Figure 20 The SITE INFORMATION Screen

If the laboratory name is not to be changed, simply press [Enter]. If the laboratory name is to be changed, type the new laboratory name and press [Enter] to display the SITE INFORMATION CONFIRMATION screen (Figure 21). The confirmation screen lists the laboratory name and a field that allows the user to confirm the laboratory name (by pressing [Y]) or to reject the displayed laboratory name and return to the SITE INFORMATION screen (by pressing [C]).

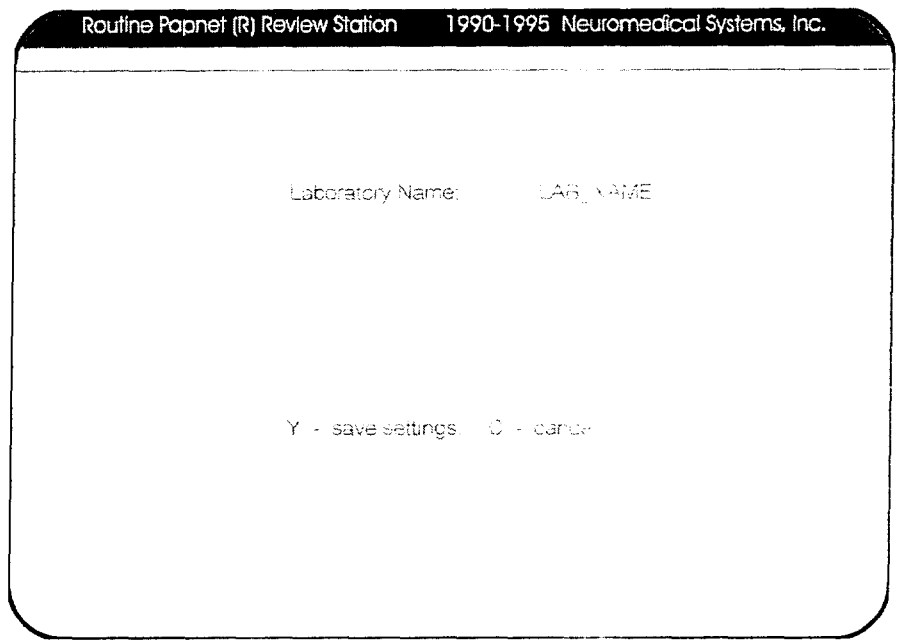

Figure 21 The SITE INFORMATION CONFIRMATION Screen

A.1.2 ALIGNMENT OF THE MICROSCOPE STAGE

The PAPNET Review Station does not in itself perform any measurements and therefore does not require alignment. However, the stage alignment of the microscope used in the laboratory must be measured and the alignment values that are obtained must be entered into the PAPNET Review Station so that cell images selected during scanning may be readily located during review. Refer to the *System Setup* section that follows for instructions on entering the alignment values.

The automatic microscope stages used at the PAPNET Slide Scanning Center are aligned in millimeters and are adjusted so that the position of the rear edge of the microscope slide body corresponds to an X coordinate reading of 0.0 millimeters, and that the position of the right hand edge of the slide body corresponds to a Y coordinate reading of 0.0 millimeters, when the slide is normally mounted on the microscope with the slide ID on the left.

Before measuring the alignment of the laboratory microscope, the stage of the microscope and the slide retaining mechanism should be cleaned so that the bottom face of the slide is in direct contact with the base of the stage and the edges are in direct contact with the slide retainer. A new, unused glass slide with no coverslip is placed on the stage of the microscope in the position shown in

Use the 10X microscope objective and the micrometer stage controls to determine the alignment values. To determine the X scale position (the slide width value), position the stage so that the rear edge of the slide is in focus at the center of the field. Read the value from the X scale to one decimal place (within 0.1 millimeter) on the micrometer. This is the X scale position value that is entered during System Setup.

Next, move the stage from the rear edge of the slide toward the center of the slide. Read the X scale value again on the micrometer. If the value increases, enter a Y (YES) on the System Setup screen. If the value decreases, enter an N (NO) in the System Setup screen.

To determine the Y scale position (the slide width value), position the stage so that the right edge of the slide is in focus at the center of the field. Read the value from the Y scale to one decimal place (within 0.1 millimeter) on the micrometer. This is the Y scale position value that is entered during System Setup.

Next, move the stage from the right edge of the slide toward the center of the slide. Read the Y scale value again on the micrometer. If the value increases, enter a Y (YES) on the System Setup screen. If the value decreases, enter an N (NO) in the System Setup screen.

After [M] is pressed, the MICROSCOPE SETUP screen (Figure 22) is displayed. There are five MICROSCOPE SETUP screens, which allow the user to enter the four stage alignment values for the laboratory microscope (see the *Alignment of Microscope Stage* section of this chapter). The first MICROSCOPE SETUP screen displays the current settings that are entered and prompts the user to enter a new slide width value. If the slide width is to be changed, type the new value and press [Enter] to display the next screen. If the slide width is not to be changed, simply press [Enter] to display the next screen.

The next MICROSCOPE SETUP screen prompts the user to enter a new slide length value. If the slide length is to be changed, type the new value and press [Enter] to display the next screen. If the slide length is not to be changed, simply press [Enter] to display the next screen.

The third and fourth MICROSCOPE SETUP screens prompt the user to change the direction of scale values for the slide width and length. The third screen prompts the user to enter Y (for yes) or N (for no) for scale values that increase as the field of view moves towards the center of the slide along the width axis, and to then press [Enter] to display the next screen.

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The fourth screen prompts the user to enter Y (for yes) or N (for no) for scale values that increase as the field of view moves towards the center of the slide along the length axis, and to then press [Enter] to display the next screen.

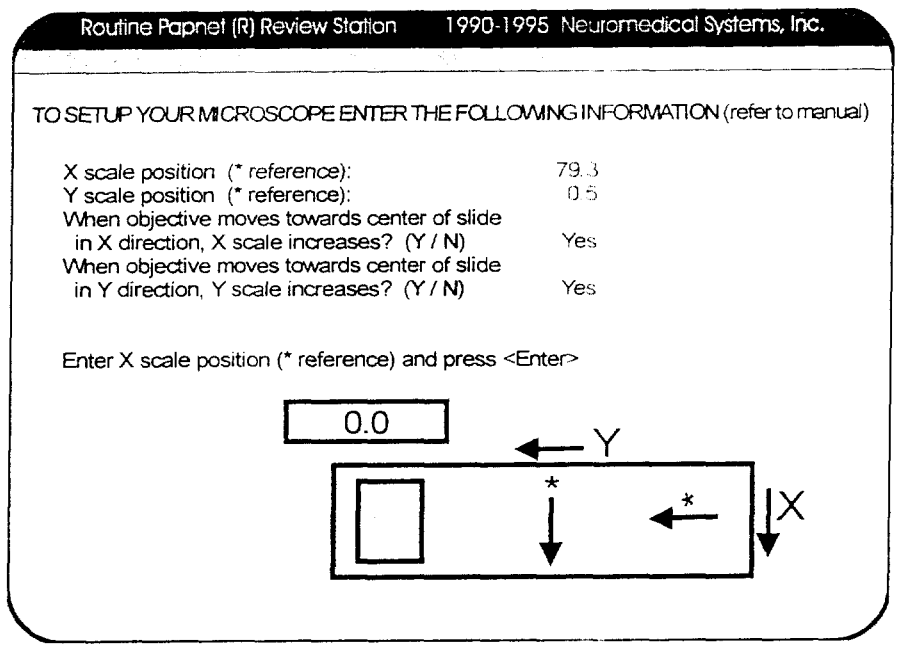

Figure 22 The MICROSCOPE SETUP Screen

The fifth MICROSCOPE SETUP screen is confirmed by pressing [Y] or canceled by pressing [C].

A.1.3 CHANGING THE SYSTEM DATE AND TIME

After [T] is pressed, the CURRENT DATE SETUP screen (Figure 23) is displayed. The CURRENT DATE SETUP screen displays the current date and prompts the user to enter a date. If the date is to be changed, type the new date and press [Enter] to display the next screen. If the date is not to be changed, simply press [Enter] to display the next screen.

The next screen is the CURRENT TIME SETUP screen. This screen is similar to the CURRENT DATE SETUP screen. The current time is displayed and edited in the same manner as the current date. After the current date is displayed and edited (if needed), press [Y] to confirm the current settings.

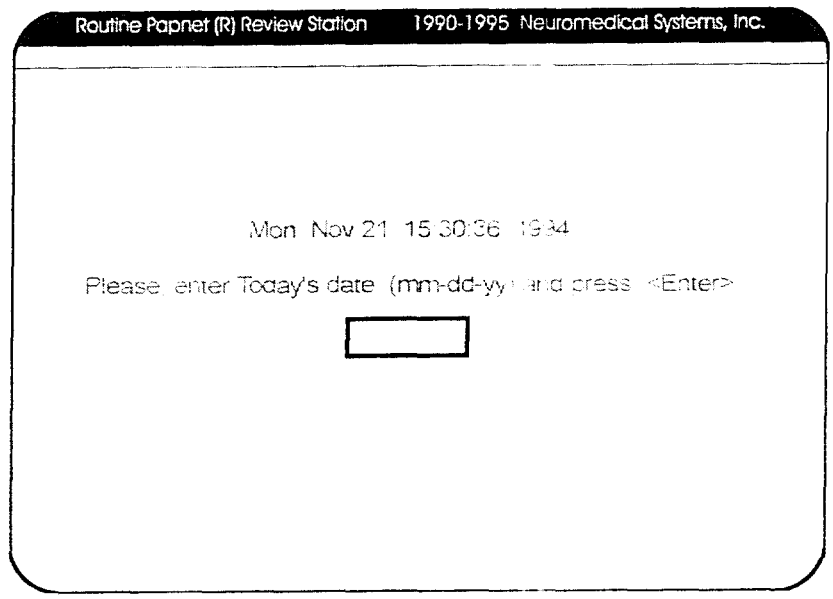

Figure 23 The CURRENT DATE SETUP Screen

A.1.4 ADDING, CHANGING, OR DELETING A USER ID

After [U] is pressed, the CURRENT USERS screen is displayed. The names of all users that have been entered are displayed, along with a prompt to add (by pressing [A]), to erase (by pressing [D]), or to modify (by pressing [M]) any of the currently displayed names. If the command to add, erase, or modify is entered, a screen is displayed that prompts for a user ID to be typed and modified.

If the names of all users are correct, press [Esc] and then [Y] to confirm the settings.

A.2 QUALITY CONTROL

During the POWER ON procedure, satisfactory operation of the PAPNET Review Station computer is tested and verified electronically. If the results of any of these tests are unsatisfactory, a message is displayed, and the PAPNET Review Station cannot be operated.

Quality Control of each Case is intrinsic to the use of the PAPNET Review Station. During review of a Case on the PAPNET Review Station, all of the images are displayed on the high resolution monitor and viewed by the operator. Triage information cannot be entered for a Case until the operator has completed displaying each magnified quadrant for each of the two pages of the Case.

If one or more of the cells appear to be abnormal, the triage classification of **REVIEW** is selected, and the slide must be subsequently manually re-examined under the microscope. If all of the cells appear to be normal, the triage classification of **NEGATIVE** is selected.

The reviewer is alerted by the appearance of the **TECH** notation on the triage field of the command monitor that the scanning of this slide may have been affected by the presence of artifacts, or that other problems may have been detected during scanning of the slide. The particular problem that caused the **TECH** notation to be displayed is indicated by a numerical code that follows the notation. A listing of the various TECH codes is provided in Table 10.

APPENDIX B TROUBLESHOOTING

B.1 OVERVIEW

Operation of the PAPNET Review Station is designed to be intuitive and easy to use. However, there are times when problems may occur. This section describes some of the more common problems which may arise during use of the PAPNET Review Station and how to proceed if they occur.

General problems that may be encountered during startup or initial operation of the PAPNET Review Station are described in the following section titled *General Problems*. Specific problems that may be encountered during operation of the PAPNET Review Station that result in the generation of an error message are outlined in the section titled *Review Station Error Messages*.

For certain error messages, the message must be cleared before operation of the PAPNET Review Station can be continued by pressing Enter.

For technical assistance, please call the PAPNET® Testing System support line at 1-800-PAPNET4.

B.2 SYSTEM LOCKUP

Occasionally, the system may stop responding because of an internal error or other problem during operation. **If this occurs, exit the Review program by pressing Ctrl and C simultaneously.** At the prompt, select the **<Cancel>** option to exit the review program. Use of this keystroke combination to exit the program will allow data to be saved, however, this may not be possible, and, occasionally Review data will be lost and will need to be recreated.

B.3 GENERAL PROBLEMS

General problems that occur during startup or operation of the PAPNET Review Station are generally traceable to improper connection of components, the adjustment of the monitor controls, or to the failure to properly insert a tape or diskette into the proper drive. A listing of the common startup failures and general problems and their resolution is outlined in the general troubleshooting chart that follows. If, after consulting this chart, the failure is not resolved, contact your local NSI representative.

Symptom	Probable Cause	Action
The power indicator light on the computer does not illuminate after the power is switched ON.	Computer is not receiving electrical power.	1. Verify computer is plugged into correct electrical power source. 2. Verify power cord is properly attached at computer and outlet.
One or both monitor screens remain blank after power up.	Power cord is loose at electrical outlet or monitor. Signal cable is loose at monitor or computer connections.	1. Verify the monitor indicator lights are illuminated. If not, check power cable connections. 2. Remember, the high resolution monitor remains blank until beginning Review. 3. Check cable connections between monitor and computer.
Writing does not appear on the command monitor when typing on the keyboard.	NumLock has been pressed or the keyboard connection to computer is loose.	1. Verify the NumLock indicator light is not illuminated. If it is illuminated, press NumLock and verify the indicator light goes off. 2. Check cable connections between the keyboard and the computer.
Screen cursor on high resolution monitor does not move when mouse is moved.	A faulty connection exists between computer and plug at end of the mouse cable.	1. Remember, the mouse does not function until the Main menu appears. 2. Check mouse cable connection to computer. 3. Exit Review and reboot by simultaneously pressing Ctrl, Alt, and Del.

Symptom	Probable Cause	Action
The digital tape cannot be inserted into the tape drive.	There is currently a tape in the tape drive.	1. Verify the computer power is on. 2. Verify the tape is being inserted properly. 3. Verify that another tape is not present in the drive.
The desired Run does not appear in the list of Runs during the LOAD CASES or REVIEW procedure.	Incorrect tape is being used.	1. Verify the correct tape is being used. 2. Verify the Run was copied to the hard drive. 3. Call your NSI representative.
The image tiles appear to quiver or shake on the monitor.	Electrical interference exists between computer components.	1. Move the high resolution monitor further away from other computer components. 2. Verify the line voltage is stable. A professional electrician will be required for this check.
The image on a particular tile is distorted or colored bars appear in the tile.	Temporary data distortion.	1. Zoom in and out of the image. 2. Call your NSI representative.
Fewer than 128 images are present.	A low % cellularity value will result in less than 128 images.	Check the % CELLULARITY notation on the REVIEW screen. If the cellularity is low (< 30%), the reduction in number of images is expected.

Symptom	Probable Cause	Action
The system does not respond to commands on the keyboard or mouse.	The computer system has experienced an operational problem and is "locked-up".	Press Ctrl and C simultaneously. NOTE: This procedure will attempt to save data, but some data loss may occur.
Images on the high resolution monitor have a greenish tint around the edges.	This is a result of magnetic field interference and is not abnormal on large computer monitors.	Press the DEGAUSS button, on the front of the monitor, for 5 seconds. *WARNING: Do not have any computer diskettes or digital tapes near the monitor when performing this operation. Data loss may occur if magnetic media is located adjacent to or on top of the monitor.*
No printout is produced by the Epson color printer, and the "Paper out" light is red and the "Pause" light is amber (dark yellow).	The printer is out of paper.	Obtain paper, insert it into the paper slot in the printer, and press the Pause button on the printer.

B.4 PAPNET REVIEW STATION MESSAGES

During routine operation of the PAPNET Review Station, a number of different messages may be displayed on the command monitor. These messages may provide information concerning a choice that must be made during review of a Case, or they may indicate that a problem has occurred and that corrective action must be taken. **The various messages that may be displayed during operation of the review station and their meaning and/or the action that should be taken are alphabetically listed on the following pages.**

NOTE: If the message seems to indicate a problem, press [Print Scrn] . This action will result in a print-out of the message on the bubble-jet printer and may be useful to your NSI representative in resolving your problem.

Message or Symptom	Probable Cause	Action
About to print quadrant 1 to the color video printer [3]	[F5] was pressed, which causes Quadrant 1 of the current page to be printed on the color printer.	If color printer (optional equipment) is installed, press [Enter]. If color printer is not installed, select <CANCEL> to continue.
About to print Quadrant 2 to the color video printer *	[F6] was pressed, which causes Quadrant 2 of the current page to be printed on the color printer.	Same as above.
About to print Quadrant 3 to the color video printer *	[F7] was pressed, which causes Quadrant 3 of the current page to be printed on the color printer.	Same as above.

[3] The color video printer is an option for the PAPNET Review Station. It is not included as standard equipment.

Message or Symptom	Probable Cause	Action
About to print Quadrant 4 to the color video printer *	F8 was pressed, which causes Quadrant 4 of the current page to be printed on the color printer	Same as above.
About to save 64 tiles in the ARCHIVE directory.	F3 was pressed.	If the keystroke was intentionally executed, press Enter. The 64 tiles in the current page will be saved in the ARCHIVE directory. If key was pressed erroneously, select <CANCEL> to continue.
Cannot delete slide #s from RUNNAME. Probable Reason:	A problem was encountered in the deletion of slide ID number(s).	1. Press Enter to continue. 2. Contact your NSI representative at your convenience.
Cannot open image file. Probable Reason:	A problem was encountered while attempting to open a file.	1. Press Enter to continue.(Program may automatically exit.) 2. Contact your NSI representative immediately.
Could not copy image to temp.cmp	A problem was encountered while attempting to copy an image.	1. Press Enter. 2. Reboot computer by simultaneously pressing Ctrl + Alt + Del 3. If the previous steps did not correct the problem, contact your NSI representative immediately.

Message or Symptom	Probable Cause	Action
Could not find STAGE driver!	The image display program has encountered a problem.	1. Press [Enter] 2. Reboot computer by simultaneously pressing [Ctrl] + [Alt] + [Del] 3. If the previous steps did not correct the problem, contact your NSI representative immediately.
Could not open file:___ for reading. Probable Reason:	An error was encountered while opening a file.	1. Press [Enter] to continue.(Program may automatically exit.) 2. Contact your NSI representative immediately.
Could not open file:___ for writing. Probable Reason:	An error was encountered while opening a file.	1. Press [Enter] to continue.(Program may automatically exit.) 2. Contact your NSI representative immediately.
Could not read dot file:__ Review will continue without previous dotting record.	The dot file (previously tagged slides) could not be read.	Press [Enter] to continue.
DAT tape is a Non-PAPNET tape.	The digital tape may be damaged.	1. Retension the tape. 2. Reattempt to Load Cases.
Due to inadequate preparation, the scanning of this slide may be incomplete. Please examine further if indicated.	Problems traceable to the preparation of the slide were encountered during scanning of the slide	See Table 7 for a complete explanation.

Message or Symptom	Probable Cause	Action
Due to physical problems with the slide, the scanning of this slide cannot be performed.	The slide could not be automatically scanned for the reason shown in Table 7.	See Table 7 for a complete explanation.
Due to technical difficulties, the processing of this slide on the PAPNET Testing System is incomplete. Please examine further if indicated.	Problems, such as focus failure, were encountered during the scanning of the slide.	See Table 7 for a complete explanation.
ERROR COPYING	An error was encountered while copying a file.	Press [Enter] to continue.(Program may automatically exit.) Contact your NSI representative immediately.
ERROR CREATING ARCHIVE DIRECTORY	An error was encountered while creating a directory. [F3] or [F4] was pressed, but an ARCHIVE directory was not created.	Press [Enter] to continue. Contact NSI Customer Service Representative (CSR).
ERROR CREATING DLG DIRECTORY.	An error was encountered while creating a directory.	Press [Enter] to continue. Contact NSI Customer Service Representative (CSR).
ERROR CREATING DOT LOG FILE.	An error was encountered while creating a file.	Press [Enter] to continue. Contact NSI Customer Service Representative (CSR).

Message or Symptom	Probable Cause	Action
ERROR CREATING TEMP DIRECTORY.	A problem was encountered while attempting to store an image.	1. Press Enter 2. Reboot computer by simultaneously pressing Ctrl + Alt + Del 3. If the previous steps did not correct the problem, contact your NSI representative immediately.
Error determining free disk space.	An error was encountered while measuring the space remaining on the hard drive.	Press Enter to continue.
ERROR IN OLD DLG FILE. REVIEW WILL CONTINUE WITHOUT PREVIOUS DOTTING INFO.	The dot file (tagged slides) could not be read.	Press Enter to continue.
Error opening Log File. OK to continue anyway?	An error was encountered while opening a file.	Press Enter to continue.
Error opening the ____ file for saving.	A problem was encountered while attempting to save a file.	Press Enter to continue.
ERROR READING ____.	An error was encountered while reading a file.	Press Enter to continue.
ERROR READING .CMP HEADER INFO! FILE MAY BE CORRUPTED.	A problem was encountered while attempting to read a file.	Contact your NSI representative immediately.
ERROR READING .CMP POINTER ARRAY INFO! FILE MAY BE CORRUPTED.	A problem was encountered while attempting to read a file.	Contact your NSI representative immediately.

Message or Symptom	Probable Cause	Action
ERROR READING .CMP SLIDELOG INFO! FILE MAY BE CORRUPTED.	A problem was encountered while attempting to read a file.	Contact your NSI representative immediately.
ERROR READING DLG FILE. REVIEW WILL CONTINUE WITHOUT PREVIOUS DOTTING INFO	The dot file (tagged slides) could not be read.	Press [Enter] to continue. Contact your NSI representative.
ERROR READING EXISTING DOT FILE	The dot file (tagged slides) could not be read.	Contact your NSI representative immediately.
ERROR READING IMAGE FILE!!! FILE MAY BE CORRUPTED	A problem was encountered while attempting copy the image file.	Contact your NSI representative immediately.
ERROR READING SLG FILE	A problem was encountered while attempting to read a file.	Contact your NSI representative immediately.
ERROR READING SLIDE LOG FILE	A problem was encountered while attempting to read a file.	Contact your NSI representative immediately.
ERROR SEEKING IN SLIDE LOG FILE	A problem was encountered while attempting to locate a file.	Contact your NSI representative immediately.
ERROR WRITING ___.	An error was encountered while writing a file.	Contact your NSI representative immediately.
ERROR WRITING TEMP.SLG.	A problem was encountered while writing a file.	Reboot computer by simultaneously pressing [Ctrl] + [Alt] + [Del] If the previous steps did not correct the problem, contact your NSI representative immediately.
ERROR WRITING TO DOT LOG FILE	An error was encountered while creating a file.	Contact your NSI representative immediately.

Message or Symptom	Probable Cause	Action
Excessive bubbles (*nn*% of cellular areas of the slide) prevented a complete scan of this slide. Please examine further if indicated.	The slide contained a large number of bubbles.	See Table 7 for a more complete explanation.
Excessive bubbles (>30% of cellular areas of the slide) prevented a complete scan of this slide. Please examine further if indicated.	The slide contained a large number of bubbles.	See Table 7 for a more complete explanation.
Exit Review?	The exit option was selected.	Press [Enter] to exit or select <CANCEL> to remain in the Review program.
FAILED SAVING TG	[F3] or [F4] was pressed, but the tiles were not archived.	Press [Enter] to continue.
File corrupted.	The file in use has been damaged.	Contact your NSI representative.
Image must be in 16 tile mode before using the [Tab] key. Hit [Z] to toggle between 64 and 16 mode.	[Tab] was pressed while in full-page mode.	If key was pressed in error, ignore the message and continue. If tabbing is desired, press [Z] to switch from 64 to 16 tile mode.
Image must be reviewed completely before comment can be made. Use [Pg Dn] key to review second page.	A comment was attempted to be entered before reviewing both pages	View each of the two pages of images before entering a comment.
Image must be reviewed completely before triage can be made. Use [Pg Dn] key to review second page.	Triage was attempted before reviewing both pages of images.	View each of the two pages of images prior to triage.

Message or Symptom	Probable Cause	Action
INCORRECT INFORMATION IN OLD DLG FILE. REVIEW WILL CONTINUE WITHOUT PREVIOUS DOTTING FILE.	The dot file (tagged slides) could not be read.	Press Enter to continue.
INVALID >CMP DESCRIPTOR SIZE:	A problem was encountered while attempting read a file header.	Contact your NSI representative immediately.
INVALID >CMP FILETYPE:	A problem was encountered while attempting read a file header.	Contact your NSI representative immediately.
INVALID DLG DESCRIPTOR SIZE: Should be ___. REVIEW WILL CONTINUE WITHOUT PREVIOUS DOTTING INFO	The dot file (tagged slides) could not be read.	Press Enter to continue.
Magnification not available for present Case.	Magnified images were unable to be obtained during scanning of this slide.	Press Enter to continue.
Magnified tiles are unavailable for this slide	Magnified images were unable to be obtained during scanning of this slide.	Press Enter to continue.
Not enough memory.	Additional computer memory is needed to complete the operation	Contact your NSI representative immediately.

Message or Symptom	Probable Cause	Action
OK to print ___ quarter of screen (max. __ tiles) to color video printer.	The system is ready to print a quadrant of images on the color printer.	If you have a color printer installed, press [Enter] to continue. If you do not have the color printer installed, select <CANCEL>.
OK to delete RUNNAME: Cancel to abort this operation.	A request has been made to erase a RUNNAME.	Press [Enter] to continue with erasing. Select <CANCEL> to stop erasing and continue.
OK to return to main menu?	A request was made to return to the Main Menu.	If you want to go back to the main menu, press the [Enter]. If the request was made in error, select <CANCEL> to remain at your current program location.
Only 64 or less tagged tiles per Case can be displayed.	SUMMARY was selected and more than 64 tiles were tagged.	Untag some of the tiles by using the mouse and then press [Enter]. (The program will display only the first 64 tiles tagged if the message is ignored and the operator elects to continue.)
Only Page 1 is available for the current Case.	[Pg Dn] was pressed and no images exist for Page 2.	Press [Enter] to continue.

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Message or Symptom	Probable Cause	Action
Only registered users can erase runs.	A database change was requested and you are currently in the 'Demo mode (changes are not permitted in the Demo mode).	Start the Review program with your user ID. If you do not have a user ID and are required to be a registered user, your supervisor must assist. See the *System Setup* section of this manual for instructions on adding additional users.
Out of memory!	An insufficient amount of system memory is available to proceed.	Contact your NSI representative.
OUT OF MEMORY FOR DIAGNOSIS MENU!	An error has occurred in the computer's memory.	Contact your NSI representative immediately.
OUT OF MEMORY FOR FILE MENU!	There was not enough memory to continue	Contact your NSI representative immediately.
OUT OF MEMORY FOR SUMMARY WINDOW!	An insufficient amount of system memory is available to proceed.	Contact your NSI representative immediately.
OUT OF MEMORY FOR UTILITIES MENU!	An insufficient amount of system memory is available to proceed.	Contact your NSI representative immediately.
Possible TECH difficulty - scan again if indicated	A problem was encountered while attempting to scan the slide. The reason is indicated by the numerical code that follows the message.	See Table 10.
Printer is busy. Please wait another __ seconds before attempting to print	You attempted to print while the printer was completing a previous print request.	Retry to print after waiting the indicated number of seconds.

Message or Symptom	Probable Cause	Action
PRINTER TIMEOUT ERROR	Data were not properly transferred to the printer.	Press [Enter] to continue.(Program may automatically exit.) Contact your NSI representative immediately.
Slide not Triaged! Please triage this Case before going on to the next Case.	Triage must be completed for this Case before proceeding to the next Case.	Press [Enter] to proceed with the slide triage.
Slide not Triaged! Please triage this Case before returning to the Main Menu.	Triage must be completed for this Case before returning to the Main Menu.	Press the [Enter] to proceed with the slide triage.
Tape not ready.	[Enter] was pressed too soon.	Make certain that the tape drive light is illuminated before pressing [Enter].
The F3 (64 Tile) Save Tiles Feature is used without zooming. Use the [Z] key to go back to the 64 tile mode. F4 provides the 16 tile save feature.	[F3] was pressed while a quadrant was displayed. A full page of 64 tiles must be displayed for F3 to operate.	Press [Enter] to continue.
The F4 (16 Tile) Save Tiles Feature is used after zooming. Use the [Z] and [Tab] keys to select the quadrant you would like to save. [F3] provides the 64 tile save feature.	[F4] was pressed while a full page of 64 tiles was displayed. A quadrant of 16 tiles must be displayed for F4 to operate.	Press [Enter] to continue.
There are no tagged tiles to display.	"Summary" was selected, but no tiles were tagged.	Press [Enter] to continue.

Message or Symptom	Probable Cause	Action
There has been __ tile(s) dotted (highlighted).	A triage classification of NEGATIVE was selected while one or more tiles were tagged.	Press Enter to confirm the NEGATIVE classification, or select the <Cancel> option to reconsider.
This exit is used ONLY for emergency purposes.	Ctrl + C were pressed simultaneously. This will exit the Review program and attempt to save data, if possible.	If erroneously selected, select <CANCEL> to return to the program.
This slide contains a significant number of artifacts. Please examine further if indicated.	The slide contained a large number of artifacts.	See Table 6 for a more complete explanation.
To continue viewing this slide, hit Enter and then type Z in the Triage Menu. Use the Tab key to move from quadrant to quadrant.	An attempt was made to proceed to the next Case or to triage the current Case without viewing each quadrant.	Press Enter to continue.
You are NOT a registered user. Unregistered users can enter DEMO to Run REVIEW WITHOUT recording data.	You have attempted to log on the Review program with an incorrect user ID; you have probably mistyped your user ID	Press Enter and then select <CANCEL> to exit the program. Reenter your user ID or 'Demo'. If you do not have a user ID and are required to be a registered user, your supervisor must assist. See the *System Setup* section of this manual for instructions on adding additional users.
Warning: Log file entry failure. Check available disk space on the drive.	There was not enough space on the hard drive to continue.	Press Enter to continue.

Message or Symptom	Probable Cause	Action
Warning: reviewing __ had not been finished by users:	This warning appears whenever a Run is erased.	Press Enter to continue.
Warning: Run __ has been restored multiple times. The Run Name and slide numbers will therefore be displayed in green, even though you may have previously reviewed some of these images.	The order of cases stored on the hard disk has changed from that saved during copying of data from the digital tape.	1. Press Enter to continue and exit the Review program. 2. Execute Load Cases to reload the data from the tape to the computer's hard disk.
OK to erase the run	A request has been made to erase Review data for a Run Name.	Press Enter to continue with erasing. Select <CANCEL> to stop erasing and continue.
OK to erase image files you printed.	A request has been made to erase Quadrant images	Press Enter to continue erasing. Select <CANCEL> to stop erasing and continue.
No Runs found in _____ directory.	No Review data.	None.
Cannot open printer: make sure printer is on-line.	Printer is not on-line.	Press "ONLINE" button on printer.
Please wait. Printing image _____.	----	Press Esc to stop printing.
More than 100 files found in directory _____. Only first 100 files will be processed.	Can only print up to 100 files.	Proceed to print first 100 Quadrant images; print the rest at a later time.
File _____ is too big.	Review data is too large	Exit program.
Error creating _____ directory. Probable reason: _____.	An error was encountered while creating a directory.	Press Enter to continue. Contact NSI Customer Service Representative (CSR).

Message or Symptom	Probable Cause	Action
Error saving _____ directory. Probable reason: _____.	An error was encountered while saving a directory.	Press [Enter] to continue. Contact NSI Customer Service Representative (CSR).
Error erasing _____ directory. Probable reason: _____.	An error was encountered while erasing a directory.	Press [Enter] to continue. Contact NSI Customer Service Representative (CSR).
About to print images... Ensure there is adequate supply of paper in the printer. OK to print.	----	Press [Enter].
Display the images in Quadrant mode first, then press [F2] or [F9] to save the Quadrant image for print.	Images are in page mode.	Press [Enter]. Go into page mode and press [F2] or [F9] to print desired Quadrant.

APPENDIX C SPECIMEN PREPARATION

C.1 SLIDE PREPARATION

Any conventionally prepared Pap smear slide can be submitted for scanning. No changes in the specimen preparation procedure are required for analysis of the slides on the PAPNET Testing System.

A sufficient number of the various cells to allow conventional microscopic examination of the Pap smear must be present on the slide. The stained smears should be protected with either a glass or plastic coverslip. The slides should be examined for damage, and any slides that are cracked or broken should be excluded.

Slides should be prepared so that artifacts such as dirt, fibers, air or water bubbles, etc. are minimized, since large numbers of these artifacts in a slide may affect the scanning results, as well as conventional examination of the slide under the microscope.

Portions of a slide that contain large numbers of air bubbles cannot be scanned. If a slide contains a large number of air bubbles, the number of tiles for that Case may be reduced and a TECH code of 61 assigned (see Table 10).

C.2 LABELING OF SLIDES

Each slide, and the laboratory record corresponding to that slide, must be labeled with special slide ID labels. Two identical slide ID labels, containing a slide ID and human readable number, are provided by NSI for each slide. One label is attached to the slide, and the other is attached to the slide record retained at the pathology laboratory. The slide ID labels are provided by NSI in rolls of label pairs in ascending numerical order.

To label slides, clear the work area of all materials except the slides that are to be labeled, the laboratory records for the slides, and the roll of labels. Place the first slide and its corresponding laboratory record on the workspace. Examine the first pair of slide ID labels and verify that the human readable numbers are identical. Peel off one of these two labels from its backing on the roll and affix it to the laboratory record. Peel off the second label, and affix it to the slide. The slide ID label should be attached to the slide so that the slide ID is adjacent to the coverslip, and so that the number printed below the slide ID is positioned towards

the slide edge, as shown in Figure 24. Slides should be labeled in ascending numerical order.

C.3 PACKING

After the slides have been labeled, they can be packed in the PAPNET Slide Shipping Container, provided by NSI, for shipment to the PAPNET Slide Scanning Center. The shipping box contains a Styrofoam liner with pre-cut slits to accommodate the edges of each slide.

Place the slides to be shipped and the PAPNET Slide Shipping Container on the work area. Arrange the slides so that they are in numerical order according to their slide ID labels. Open the shipping container and place the lowest numbered slide in the slot at the upper left hand corner of the internal nest in the shipping container. Place the next slide in the slot below, and continue packing additional slides in ascending numerical order until the row of slots on the left side of the container is filled. Continue filling the container, beginning at the top of the next row and packing slides in ascending numerical order until that row is also filled. Continue filling the container until all of the slides have been packed.

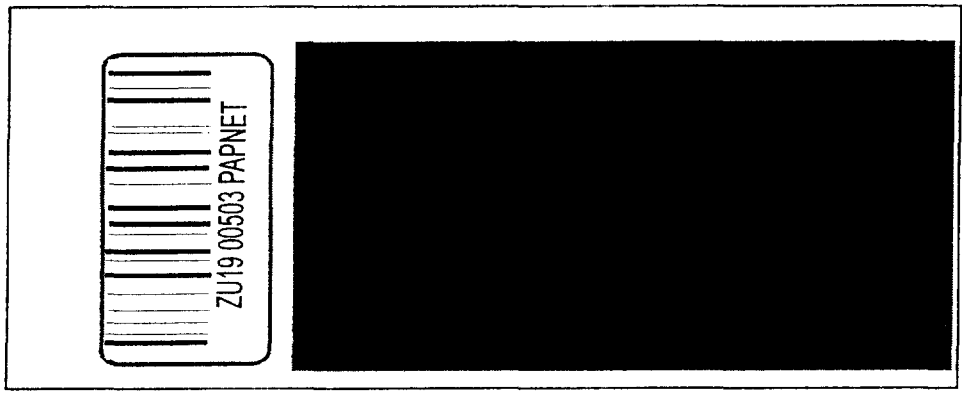

Figure 24 Slide ID Label Position on Slide

C.4 SHIPMENT TRACKING TAG

A Shipment Tracking Tag (Figure 25), provided by NSI, must be filled out for each slide shipment. Enter the participating laboratory account number, the date the slides are shipped, the shipment number, and the number of slides in the shipment. Remove the protective backing from the Shipment Tracking Tag and attach the tag to the top inside cover of the PAPNET Slide Shipping Container.

Close the cover of the shipping container and seal it with adhesive shipping tape. The filled PAPNET Slide Shipping Container can now be shipped to the PAPNET Slide Scanning Center.

NSI®

NEUROMEDICAL SYSTEMS, INC.

Two Executive Boulevard
Suffern, New York 10901-4114 USA
914-368-3600
Fax 914 368-3896

Laboratory: Please complete top part and adhere to inside cover of shipping container.

SHIPMENT TRACKING TAG

Two Digit Account Number	*Date Sent (DD/MM/YY)*	*Shipment Number (Consecutive)*	*Number of Slides Sent*
For NSI Use Only			
Date Received (DD/MM/YY)	Date Returned (DD/MM/YY)	Number of Slides Returned	
Federal Express Air Waybill Number			

Figure 25 Shipment Tracking Tag

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APPENDIX D COMPUTER OPERATION TERMINOLOGY

The PAPNET Review Station is a **DOS** (Disk Operating System) based desktop computer system utilizing standard computer components, nomenclature and operation. Several fundamental operations and terms are outlined below to assist in the familiarization of operations for users who have never utilized a desktop computer.

The actual components of the computer system, such as the keyboard, the computer itself, the printer and the mouse are referred to as **hardware**. The various specified routines that the computer performs are referred to as **programs** or **software**. The programs are operated by entering instructions (**commands**) by using the keyboard or the **mouse,** which is a two-key pointer control used to select options on the video display, or **monitor**. The computer may request that an instruction is entered before carrying out a task. The request, referred to as a **prompt**, is displayed in printed letters on the monitor with a rectangle of contrasting color behind the letters (it is **highlighted**), or it is displayed within a rectangle, or **box**.

The programs and the data that are utilized are stored on the **hard disk,** which is a sealed unit inside the computer which can magnetically store a large amount of information. The information is organized in **files,** and a number of related files are stored in a **directory**. Each file is given a name (a **filename**) so that it can be easily identified. Information can be erased **(deleted)** from the hard disk when it is desirable to do so in order to make room for other information. Information should only be erased one file at a time, in order to prevent the accidental erasing of programs or other data not intended to be erased.

Information can also be stored on **diskettes** or **digital tape**. Unlike the hard disk, the diskette and tape are portable and can be carried or mailed to other locations to transfer large amounts of information. The information is transferred (**loaded** or **copied**) to and from the computer to the diskette or tape using a **tape drive** or **diskette drive**.

The tape is sometimes referred to as **DAT** (Digital Audio Tape), and the diskette is sometimes referred to as a **floppy diskette** or a **floppy**. During start up of the computer, various routines are automatically started, or **loaded**, so that the computer is ready to receive commands (**initialized**). These routines are permanently stored in the computer memory. The process of loading the various routines to initialize the computer is referred to as **booting** or **boot-up**.

The filename for each Case contained in the PAPNET Review Station is the slide ID number for that Case. The filenames and the image data are loaded during the RESTORE procedure outlined in 11.0 REVIEW STATION OPERATION on page 29. All of the cases for a Run are stored in a directory which is named with the RUNNAME.

All of the programs that are needed to operate the PAPNET Review Station are present in the computer. Each of these programs is named, and the name is displayed on the monitor at certain times while that program is beginning to operate. For example, the name of the program that loads the image data from the digital tape to the PAPNET Review Station is **DRESTORE**. This name is displayed during the loading procedure.

The conventions and terminology used in this manual are similar to those used in other computer applications. Whenever a key on the keyboard is identified, the name of the key is boxed. For example, [Enter] is identified as shown. Menus and screens are identified In standard capitalized text. For example, the Main Menu is described as shown. Prompts that require a command or action are printed in bold text.

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APPENDIX E REVIEW STATION SPECIFICATIONS AND ELECTRICAL REQUIREMENTS

E.1 Specifications

Specifications for the PAPNET Review Station are outlined in Table 13 below:

Microprocessor	Intel I486® minimum
Random Access Memory	8 MB minimum
Video Memory	1 MB minimum
Command Monitor	VGA color display, 14" screen minimum
High Resolution Monitor	RGB color display, 20" screen minimum
Hard Disk	1.2 GB minimum
Tape Drive	4mm, 1.2 GB minimum
Diskette Drive	3 1/2 inch, 1.44 MB
Mouse	2-button minimum
Printer	Ink Jet or Bubble Jet (Parallel interface)

Table 13 PAPNET® REVIEW STATION Hardware Specifications

E.2 Electrical Requirements

Provided with the Review Station is an Uninterruptible Power Source (UPS). The UPS provides a battery back-up that enables Review Station Operators to prevent the loss of data in the event of a utility failure.

The UPS requires connection to an electrical outlet. For customers connecting to a 120 Vac power source, the UPS must be connected into a 2 pole, 3 wire grounding receptacle. For customers connecting to a 220-240 Vac power source, the UPS must be connected into the plug connector as required by the local electrical service provider.

The computer, the printer, and both monitors all connect to the UPS using input cords supplied with the Review Station. The electrical requirements for the individual components of the Review Station are provided in the following table.

	Computer	High-Resolution Monitor	Command Monitor	Printer	UPS
Type	Personal Computer	RGB Color Display Monitor	VGA Color Display Monitor	Color Inkjet Printer	Uninterruptible Power Source
Input Voltage	100-127 Vac 200-240 Vac (self-sensing/switchable)	100-120 Vac(± 10%) 220-240 Vac(± 10%) (self-sensing)	120 Vac 220-240 Vac (self-sensing)	103.5-132 Vac 198-264 Vac	120 Vac 220-240 Vac
Frequency	50-60 Hz	50-60 Hz	50-60 Hz	50-60 Hz	50-60 Hz (± 5%)
Power Consumption	40-50 w (typical) 170 w (maximum)	140 w (maximum)	80 w	20 w	400 w
Complies with Standard(s)	FCC Part 15 Class B UL 1950	FCC Part 15 Class B UL 1950	FCC Part 15 Class B UL 1950	FCC Part 15 Class B UL 1950	UL 1950
Physical Dimensions:					
max. width	45 cm	50 cm	37 cm	47 cm	12 cm
max. height	20 cm	50 cm	38 cm	20 cm	17 cm
max. depth	45 cm	55 cm	39 cm	53 cm	36 cm
max. weight	16 kg	32 kg	12 kg	7.5 kg	12 kg
# of Sockets	0	0	0	0	4 (all grounded)
Fuse Protection	None	250 Vac; 3.5 A	None	None	None
Circuit Breakers	None	None	None	None	1

Notes:

1. Three-prong (grounded) power cords are used for all components.
2. The UPS contains a Site Wiring Fault indicator which warns the Review Station Operator about the possibility of reversed hot and neutral wires, missing ground wiring, and neutral wiring overload in the building's electricity.
3. The UPS contains a Circuit Breaker that protects the Review Station Operator and components from electronic overcurrent and short circuits. If either of these failures are present, the UPS will prevent the Review Station from operating, thus preventing harm to the operator and damage to the equipment.
4. For information regarding harmful ingress of water, refer to Section 8.14.1, "Spills".
5. The Review Station does not require the use of inverters.
6. In the event of a utility failure (blackout, brownout, or power sag), the UPS will transfer the Review Station equipment to a battery source within the UPS. This provides the Operator ample time to save files and properly shut down the system, preventing data loss.