# Digital Tools for Collecting Data from Cervigrams for Research and Training in Colposcopy

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■ **Abstract:** Colposcopy is a critical part of gynecologic practice but has documented deficiencies, including lack of correlation between the colposcopic appearance and the severity of underlying neoplasia, limited reproducibility, and difficulty in the optimal placement of colposcopically directed biopsies. In a collaborative effort to improve colposcopy, we are analyzing digitized cervigram images from National Cancer Institute-funded studies. Specifically, the National Cancer Institute has collected close to 100,000 cervigrams, digitized to create a database of images of the uterine cervix for research, training, and education. In addition to the cervigram images, this database contains clinical, cytologic, and molecular information at multiple examinations of 15,000 women, with password and ID labeling strategies to protect patient privacy. The National Library of Medicine has designed two web-accessible software tools. The Boundary Marking Tool allows experts on colposcopy to perform an evaluation of the pictures and to mark boundary regions of normal and abnormal regions of the uterine cervix; these evaluations are collected and saved in the database. The Multimedia Database Tool enables retrieval of test and image biomedical data according to specific queries, for example, all women with cervical intraepithelial neoplasia 3 whose cytologic results are atypical squamous cells of undetermined significance. The resource soon will be available as an open resource, via a teaching tool coordinated by a database manager, which will permit a variety of applications for teaching and research. In this article, we describe the perceived need for the resource and its components. ■

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Cervical cancer is the second most common cancer among women worldwide [1] and the first in many developing countries [2]. Cervical cancer is caused by persistent infection with one of approximately 15 carcinogenic types of human papillomavirus (HPV), which is sexually transmitted [3–5].

As soon as a woman becomes persistently infected with a carcinogenic form of HPV, she is at substantial risk of developing precancerous lesions (i.e., cervical intraepithelial neoplasia [CIN] 3) within 5 to 10 years [6], which typically lasts several years before turning into cancer. The success of cervical cancer screening is based on the capability of detecting and treating precancer during its prolonged natural history. The tests used for cervical cancer screening are able to detect women suspicious of having precancerous or cancerous lesions, but also detect HPV infection and its associated cytologic (low-grade squamous intraepithelial lesion [LSIL]) and histologic (CIN 1) lesions. Therefore, to avoid overtreatment, women with positive screening results are evaluated visually by colposcopy to evaluate any abnormal epithelium and to obtain directed biopsy samples with the goal of distinguishing precancerous or cancerous lesions from milder HPV-related changes.

Colposcopy and cervicography are both based on the property of the dysplastic epithelium to turn white when exposed to 5% acetic acid (vinegar), which is called *acetowhitening*. The observation of this phenomenon

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and other characteristics such as vascular patterns and borders of the lesion allow the evaluator to have a presumptive diagnosis and to identify the most suspicious area to direct biopsy sampling. However, visual assessments like colposcopy have some inherent problems that must be studied to reach the goal of a more reliable and reproducible evaluation. These issues include: poor correlation between colposcopic appearance and severity of disease, limited reproducibility of colposcopic impression, as well as suboptimal accuracy and reproducibility of biopsy placement.

Since the introduction of colposcopy by Hinselmann at the beginning of the last century [7], there have been many contradictory reports, some of them showing a clear correlation between visual appearance and severity of disease, and other reports showing a lack of correlation [8–11]. In 1985, Reid and Scalzi [9] reported an index based on scoring four characteristics of the acetowhite lesion (color, borders, vessels, and iodine staining), and in the experience of these authors with 72 patients, the index forecasted the histologic findings in most of the patients. In 1990, Carriero et al. [12] published their experience with the colposcopic evaluation of 134 patients; they used two grading methods, the international nomenclature for colposcopy and the index described by Reid and Scalzi. They reported 79% predictive accuracy for the international nomenclature for colposcopy and 86.6% for the Reid and Scalzi index. Similar results were reported by Baldauf et al. [13], who performed colposcopic evaluation of 567 women and found a concordance of 81% between colposcopy and the final histologic diagnosis.

However, several reports describe a lack of correlation between the colposcopic findings and severity of disease. Pretorius et al. [14] reported a study that took place in the Shanxi Province of China, where three gynecologist oncologists performed colposcopic evaluations of 3,063 women with positive screening results. Each quadrant of the cervix was evaluated separately, and a directed biopsy sample was obtained from detected abnormalities; but if there was no abnormal epithelium in one quadrant, a random biopsy was taken from the squamocolumnar junction of that quadrant. Interestingly, although random biopsies are not the current standard of care, only 57% of CIN 2 or worse cases were detected by colposcopically directed biopsy, and 37.4% of CIN 2 or worse cases were diagnosed by random biopsies taken from quadrants without colposcopic abnormality.

Several aspects of colposcopic performance recently were evaluated by the NCI-funded ASCUS-LSIL Triage Study (ALTS), a randomized trial comparing three triage strategies for women with cytology of atypical squamous cells of undetermined significance or LSIL [15, 16]. Its size permits some important conclusions. In ALTS, 5,060 women with community-based cytologic results of atypical squamous cells of undetermined significance or LSIL were randomized to one of the three management arms: immediate colposcopy (all women referred to colposcopy), HPV DNA testing (colposcopy if the HPV DNA test results were positive or the enrollment liquid-based cytologic results were HSIL) and conservative follow-up (follow-up with cytologic examination and colposcopy if results are HSIL). One thousand eight hundred sixty-three women were included in the arm for immediate colposcopy; 199 of them had a final histologic diagnosis of CIN 3 during the 2-year follow-up. The colposcopic evaluation performed at enrollment detected 109 of them, yielding a sensitivity of only 54.8%. If we assume that most of the patients diagnosed with CIN 3 during the follow-up already had this result at the time of enrollment, we can say that colposcopy performed by a large and varied group of experienced colposcopists (comprised of nurse colposcopists, gynecologists, gynecologic oncology attending physicians, and fellows) was unable to detect almost half of the prevalent or incipient CIN 3 cases.

With regard to reproducibility of colposcopic impression, in 1995 Hopman et al. [17] reported their experience with 23 skilled colposcopists from the Netherlands using colposcopic slides. The images were shown to the experts twice in a 2- to 3-month interval, and the $\kappa$ value for intraobserver agreement was 0.54; the interobserver $\kappa$ values were 0.41 and 0.33 for the first and second session, respectively. In a similar study carried out by Etherington et al. [18] in the United Kingdom, the interobserver agreement was very poor ($\kappa$, 0.169), even when the cytologic status was revealed ($\kappa$, 0.212).

During the ALTS trial, digitized pictures were taken during all the colposcopic evaluations. These images then were used for quality control of colposcopy under a program where three expert colposcopists independently reviewed the digitized images. These reviewers were blinded from all clinical data but age of the patient. Ferris et al. [19] analyzed the data collected by this colposcopic quality control panel and found a $\kappa$ value of 0.36 (95% confidence interval, 0.33–0.39) for interobserver agreement between the expert colposcopists on diagnostic impression and $\kappa$ value between 0.23 and 0.28 for Reid index score.

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It is generally assumed that the level of training on colposcopy and the number of evaluations performed correlate with the skills of the evaluator [20]; however, there is a lack of data about this topic. Dexeus et al. [21] commented that when the diagnostic accuracy of colposcopy (correlation between the diagnosis at colposcopy and the histologic result) was evaluated throughout the years of fellowship, there was not improvement of the result for each additional year of training. Similarly, the ALTS data did not reveal a group of experts with exceptionally good accuracy, based on degree or years of experience (unpublished data).

## TOOLS FOR THE STUDY OF DIGITIZED CERVICAL PICTURES

The National Cancer Institute (NCI) and National Library of Medicine (NLM) have developed tools for the study of digitized cervical pictures, based (at present) on cervigrams taken during NCI-funded cohort studies. In the future, we hope to add images from other projects as collaborators join this inherently open, cooperative project. It is essential to stress that the confidentiality of subject images and data will be assured by a variety of strategies, including use of study IDs that are not linked to personal identifying information and deletion of any subject information that could be used to identity subjects. We have digitized images already from ALTS and a natural history study of HPV infection and cervical neoplasia. The Guanacaste Project, a population-based study developed in a rural area of Costa Rica with high incidence of cervical cancer, enrolled 10,000 women who were followed for up to 7 years. During this study, women were screened using visual (cervigrams), cytologic (Pap smear and liquid-based cytologic examination), and molecular tests to explore which factors influence HPV infection persistence and risk to develop CIN and cancer [22]. In ALTS [23], all women, regardless of randomization assignment, underwent cytologic analysis and cervigrams every 6 months for 2 years.

Some of the data collected during these projects are visual, such as cervicography, digital images taken at colposcopy (Denvu), cytologic analysis, and histologic analysis. Cervicography is a 35-mm photograph of the cervix taken using a specially designed camera [24] implemented with a 100-mm macro lens and ring flash.

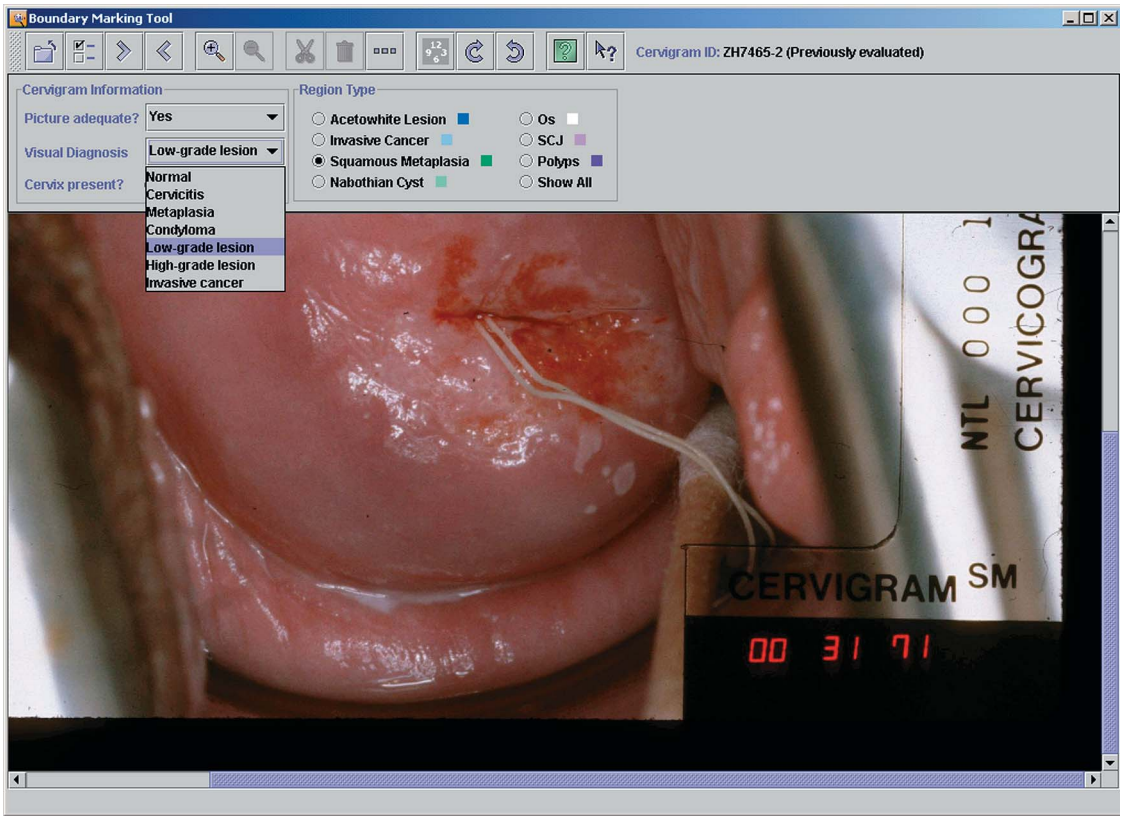


**Figure 1.** Boundary marking tool: the evaluation starts with general questions about the picture.

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The focus of the camera is fixed to preserve a constant distance between the lens and the cervix; therefore, we can make measurement of areas of the cervix [25] and compare the pictures from different patients.

During the ALTS and Guanacaste projects, close to 100,000 cervigrams were obtained from 50,000 patient-visits and included patients with invasive cancer or CIN, women without CIN at enrollment but in whom disease developed at follow-up, healthy women in whom pathologic changes in the cervix never developed, and so forth. This enormous visual database gives us a unique opportunity to study the normal and abnormal uterine cervix, changes related or not related to HPV infection, and its evolution to clearance of HPV or the development of precancer. To manage, evaluate, and collect information from the pictures, we decided to translate the conventional 35-mm pictures into digital files.

We carefully researched the optimal parameters for scanning to permit compression and web-based transmission (see article in this issue). The scanning of the slides was performed under standard high-resolution features to preserve all the anatomic details; however, the files obtained are large (16 MB), impractical for evaluation and difficult to be shared through the Internet. Engineers from Texas Tech University created software for compression of pictures that permitted compression of the 16-MB pictures into 300 KB images (ratio, 50:1).

To access, evaluate, and collect information from these thousands of cervigrams, we developed two digital tools to work with them: the boundary marking tool (BMT) for marking areas of particular importance in the images and the multimedia database tool (MDT) for Internet dissemination of the images and to relate them with text data and information collected with the BMT. We are now designing a teaching tool and virtual microscope to complete the system, which is scheduled for release to collaborating members of American Society for Colposcopy and Cervical Pathology (ASCCP) and other collaborators late in 2006.

## THE BOUNDARY MARKING TOOL

The BMT is a web-accessed tool created by NLM and NCI to permit pictorial evaluation of uterine cervix images by expert evaluators. The BMT is a cross-platform Java application tha runs on the desktop of the evaluator and works with digitized cervigrams from local storage such as CD or DVD.

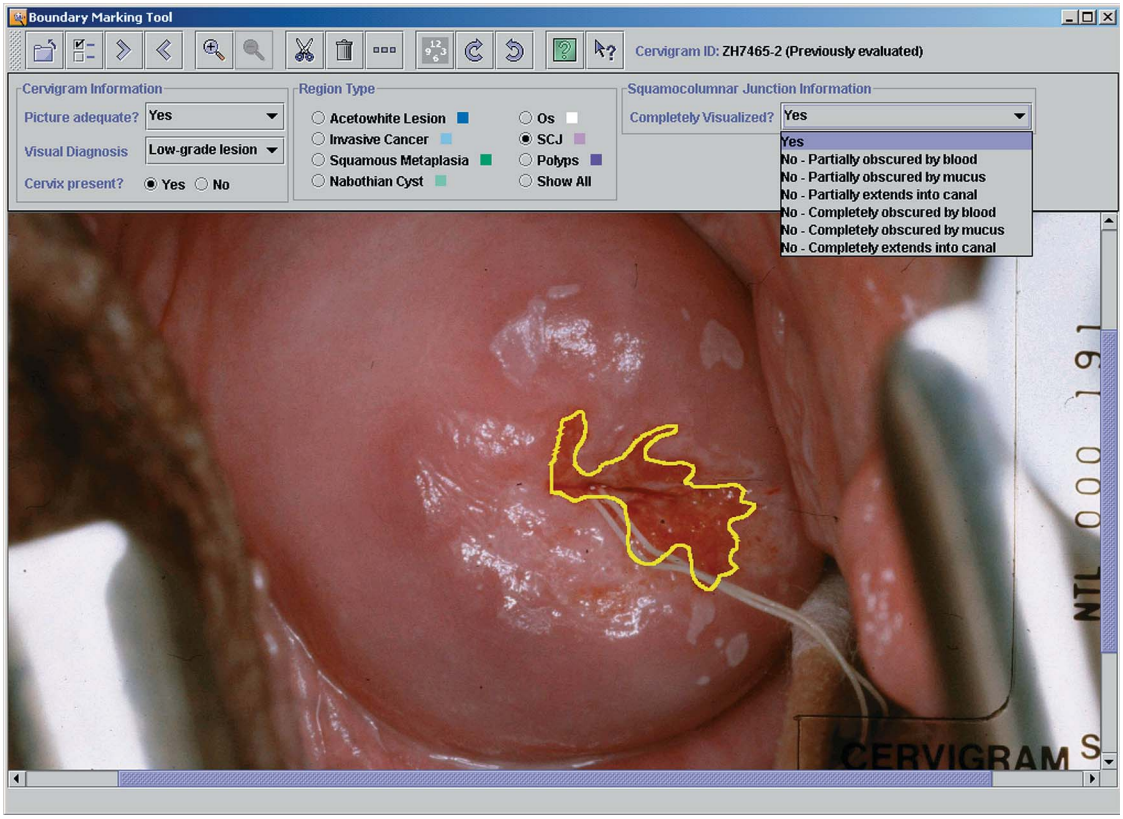


**Figure 2.** Boundary marking tool: the evaluator is asked to draw boundaries around anatomic areas of the uterine cervix.

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Two pictures for each patient visit are presented to the evaluator, who chooses the best one to be displayed. The evaluation starts with a set of general questions about quality and adequacy of the image, the presence of the cervix, and the colposcopic impression (Figure 1). Using the mouse or a special screen pen, the expert then marks boundaries around anatomical regions corresponding to cervical os, squamocolumnar junction, acetowhite epithelium, invasive cancer, squamous metaplasia, cysts, and polyps (Figure 2).

Each anatomic area has a color-coded form and a pull-down menu of questions to be answered by the expert drawing the boundaries. The evaluator can indicate that a boundary is partially visualized or obscured, with special line characteristics of the boundaries where it is not completely visible. The tool permits zooming in for a magnified view of particular regions (Figure 3); additionally, for acetowhite regions, after the boundary of the lesion is drawn, it can be expanded to mark subboundaries of special features such as mosaicism, punctuation, or internal borders. Each acetowhite lesion is scored using an index similar, but not equal, to the Reid index [9].

All the information collected with the BMT (Figure 4) is saved as records in a central MySQL database at the NLM. The spatial boundary data are recorded as a set of (x,y) pixel coordinates in a standard image coordinate system. Later, we can translate that information into pixel measurements to be used for epidemiologic studies. Additionally, the data collected can be retrieved by the MDT detailed below.

In collaboration with colleagues in the ASCCP and elsewhere, the NCI will use the BMT in longitudinal research studies of HPV infection and cervical cancer to explore and understand in a topographical, lesion-by-lesion manner, the cervical changes that take place after infection with HPV, leading to clearance or neoplastic progression. Also, we will explore the differences in visual manifestations of the several kinds of HPV. Additionally, studies on visual characteristics of normal cervices will allow us to obtain information about physiological changes in healthy women.

## MULTIMEDIA DATABASE TOOL

The NLM first obtained experience in the development of a Web-based Medical Information Retrieval

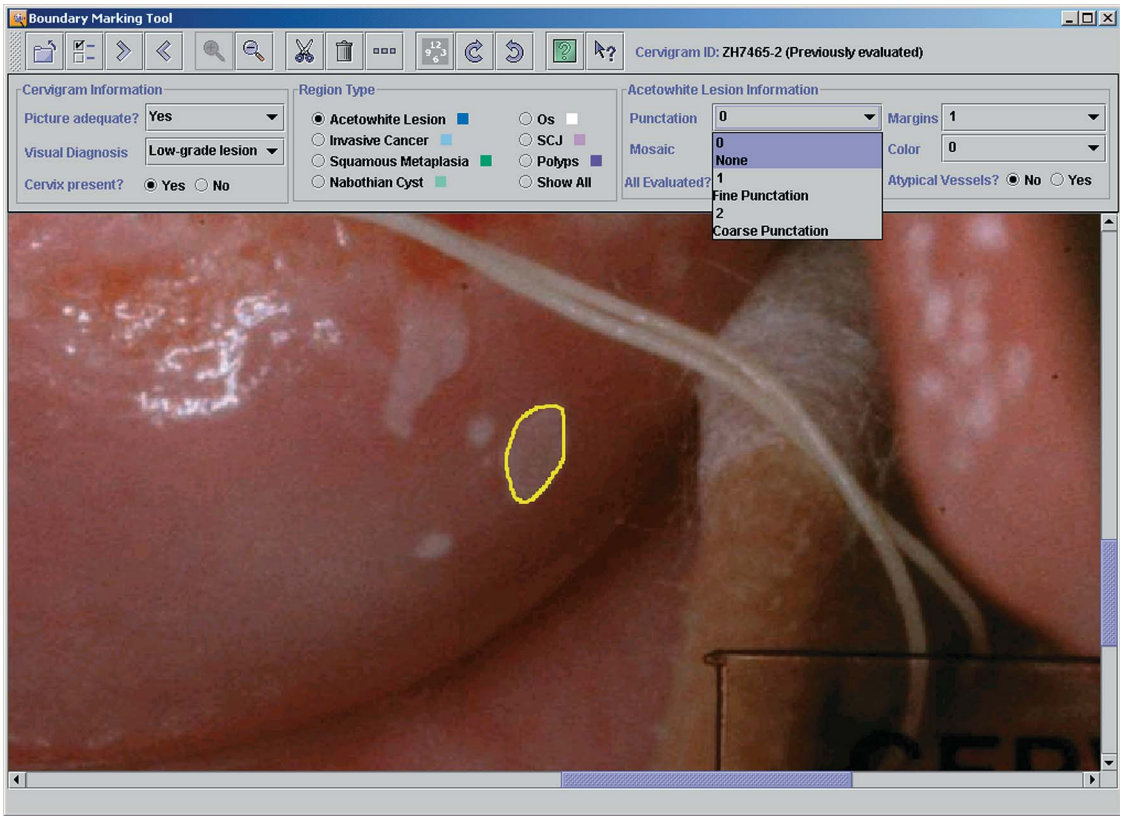


**Figure 3.** Boundary marking tool: the evaluator is able to zoom in to have a better view of the lesions.

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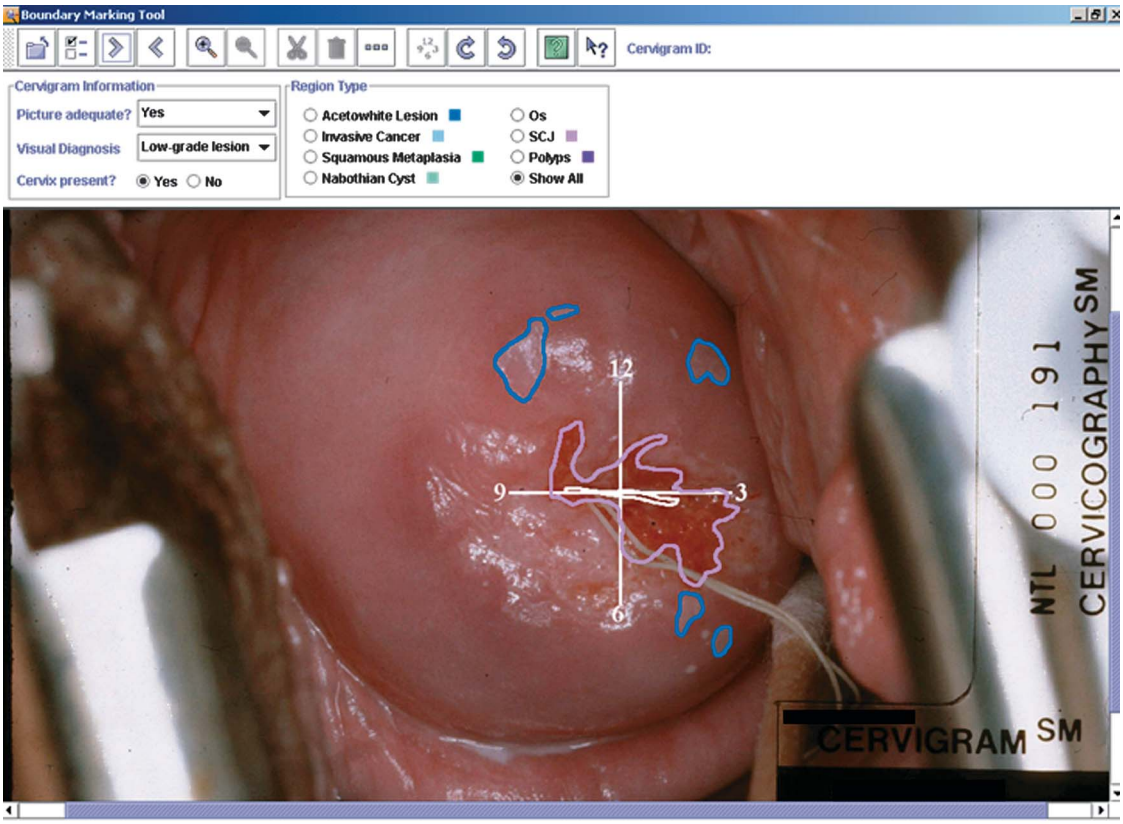


**Figure 4.** Boundary marking tool: all the answers and areas drawn by the evaluator are saved in the database.

System (WebMIRS) to provide access to text and visual data regarding cervical spine radiographs collected during the National Health and Nutrition Examination Survey (NHANES) II and NHANES III surveys [26]. After this experience, they wished to build a system architecture capable of deploying color images and related information on the Web with minimal reprogramming. This prototype system is the MDT that has the flexibility to accept new datasets with the required customization performed at the level of a database administrator, rather than a programmer.

The first dataset incorporated into the MDT is the text data and images collected by the NCI during the Guanacaste and ALTS projects. The MDT has the capability of querying a database of text and images over the Web, of showing the results of the query displaying multiple images and text data, and of exporting these results for statistical analysis (Figures 5 and 6). Additionally, the MDT is designed for data collection from remote users; given adequate password protection and anonymizing data to assure patient privacy, experts working all over around the world will be able to access the data resource. Through the Internet, they will evaluate images and test data, perform analysis of the information, and record their evaluations in a central database. Additionally, because of its architecture, the MDT system can support a broad class of text and image databases. Therefore, the MDT is designed to grow if we can help additional groups that may wish to merge their data on cervical cancer or to use it to manage their own multimedia data collections.

The MDT should be considered as an exploratory tool for retrieving visual and textual data according to specific characteristics such as age, parity, Pap smear results, HPV status, contraceptive methods, and so forth. The MDT identifies patients matching the query and retrieves and displays their image and text data. Researchers, educators, and students can retrieve pertinent records with or without images and can study correlations between the text and image data.

Of particular interest in the MDT design is the incorporation of capability for retrieval and display of spatial data. The boundaries of spatial regions collected with the BMT are being incorporated in the MDT to allow the query, retrieval, and display of these regions, superimposed on the uterine cervix images. The MDT is able to support a broad class of image types such as digitized cervigrams, colposcopy images, cytologic results, and

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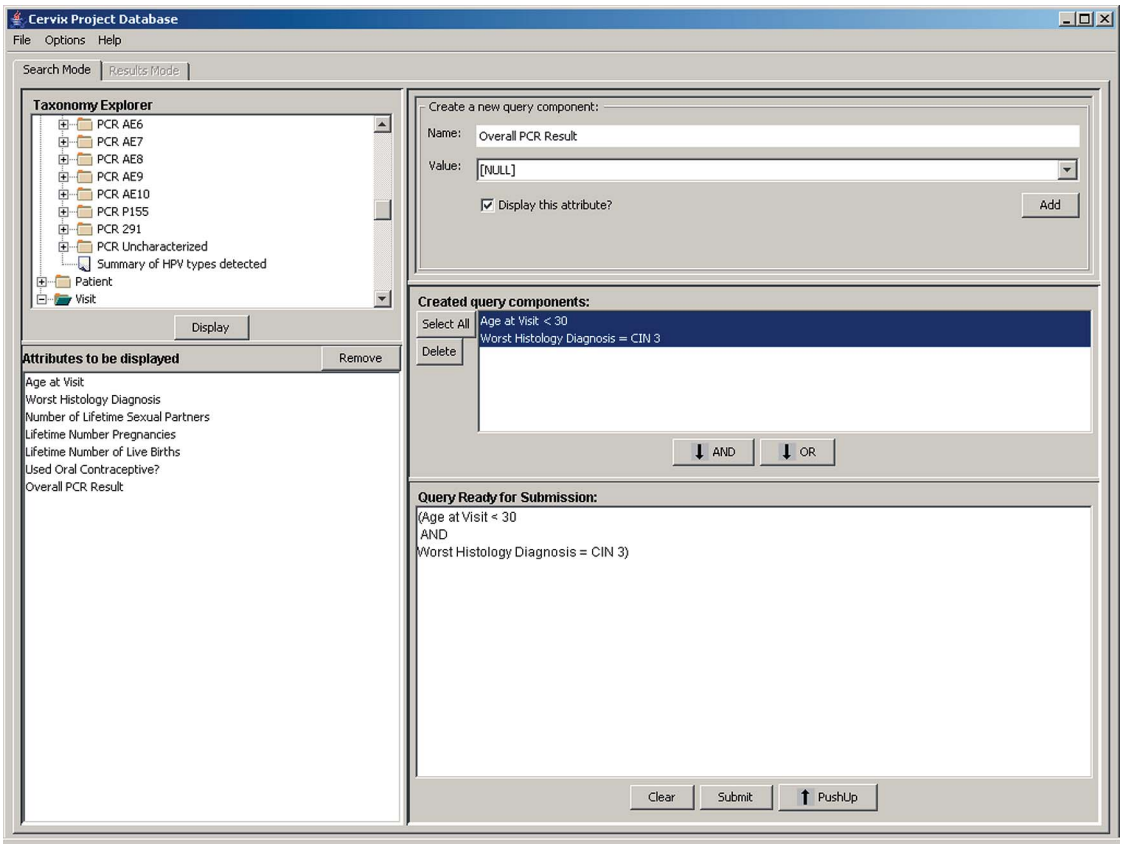


**Figure 5.** Multimedia database tool. Main menu: in this example, we are querying for information about all 30-year-old women with a histologic diagnosis of CIN 3.

histologic results. The user may want to see only the histologic results for a particular patient initially, but then switch to a view the picture taken at colposcopy, of cytologic results, or all the images displayed side by side.

The NLM currently is developing the possibility of switching to a patient-centric view within query results that were returned for a general query. This means that the user may start with a query and, after the data are retrieved, then browse through all data on that subject within the limits imposed by privacy restrictions. For example, we will not permit any combination of data that conceivably could unmask the identity of the patient, for example, age, date of appointment, or clinic. Apart from these constraints, a patient of interest may be identified and the evaluator would be able to focus on that particular patient.

## VIRTUAL MICROSCOPE

As described above, cervigrams are not the only source of visual data collected during the NCI studies on cervical cancer. For example, histologic samples were obtained during those studies. Microscopic evaluation of a sample from the tumor (biopsy) or the surgical specimen continues to be the cornerstone of diagnosis for almost all malignant diseases. Traditionally, glass slides and conventional microscopes have been used for cancer education, diagnosis, and research, but there are some inherent problems: slides glasses are fragile and can be broken easily; stains can fade over time, especially for some techniques such as immunofluorescence; and slides are difficult to share among experts around the world.

Digital images are replacing conventional photographs and technology for image capturing and management. In addition to improved capture and informatics systems, the decreasing cost of digital memory makes it possible to have small and cheap devices for storage of the huge amounts of information represented by slides at high resolution.

*Virtual microscope* is a name that is becoming popular in medical literature. The development of digital

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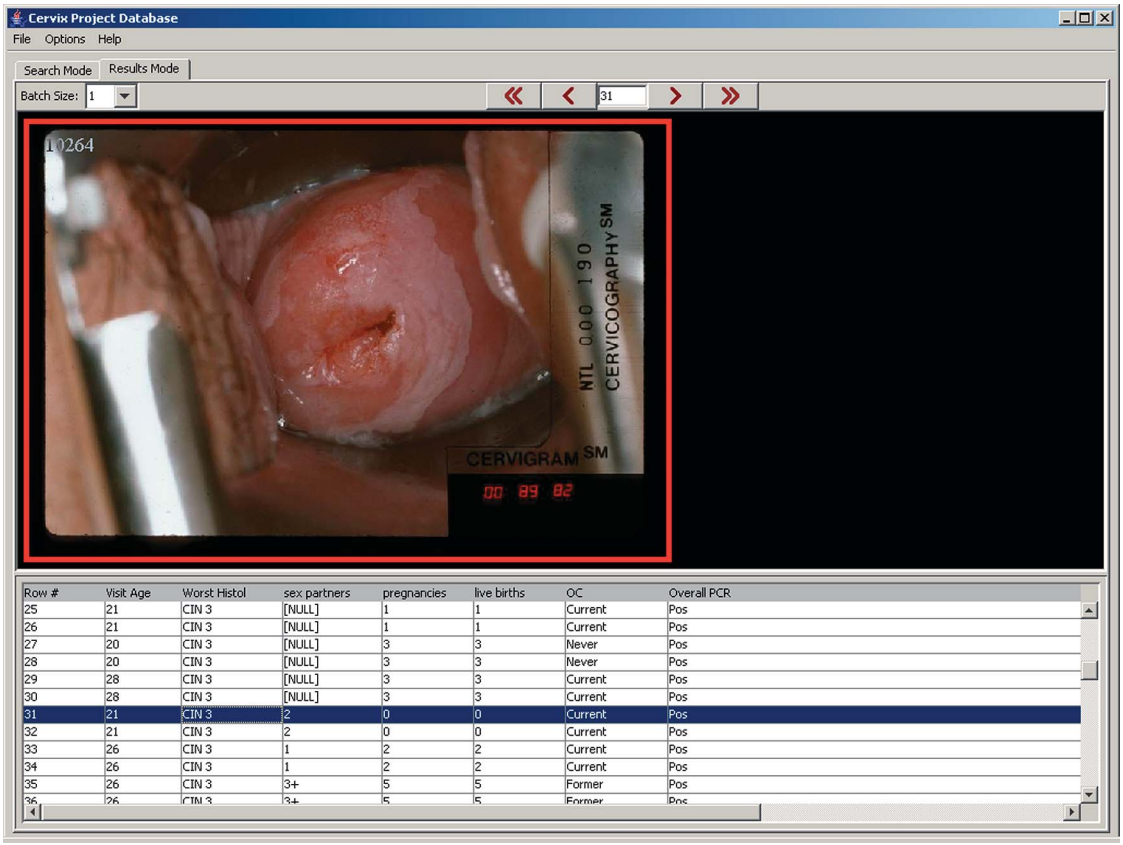


**Figure 6.** Multimedia database tool: visual and text information of women matching the query (30-year-old women with a histologic diagnosis of CIN 3) is retrieved.

images of histologic samples has evolved in recent years, going from manual capture of static low-magnification views of some parts of a biopsy to automatic scanning of an entire specimen at high magnification. Now, virtual microscopes are being used for storage of slides [27], telepathology [28, 29], and training [30].

Currently, the NCI and NLM are developing software for displaying, through the Internet, digitized histologic specimens. Similar to the design of the MDT, the virtual microscope will have the flexibility to accept new datasets with the required customization carried out at the level of a database administrator, rather than the programmer. The main goal is to collaborate with expert pathologists worldwide, and these selected evaluators will be granted access, with a user name and password, to the server where the digitized ID-labeled slides are stored. With the virtual microscope, we expect to collect evaluations from experts working in their own offices, eliminating the need to move the samples or to convene long working meetings of research pathologists.

## TEACHING TOOL

A major goal of colposcopy research at the NCI is to use the data collected using the MDT from the evaluation of the expert colposcopists to advance the expertise of health workers at all levels regarding cervical cancer and evaluation of the uterine cervix. We are collaborating with NLM and a group of volunteer colposcopists (mainly from the ASCCP) to fulfill this goal. To advance the educational objectives while we study the natural history of cervical cancer, we are developing software that will permit users of the MDT to record their impressions of what they see. Expert opinions will increase our certainty of what images show and will help to guide our natural history studies. Opinions from trainees will be educational.

Specifically, we will compose sets of images designed to teach trainees about the characteristics of the healthy uterine cervix and precancerous changes. Also, students will be able to take tests and show their proficiency. We hope that the educational opportunities afforded by the system will be managed by the ASCCP, but

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whichever group uses the resource, it will be open and nonprofit.

## CONCLUSIONS

We hope that the NCI/NLM system, including the BMT, MDT, virtual microscope, and teaching tool, will be valuable digital resources for colposcopic research, training, and teaching purposes. They allow the evaluators to manage, evaluate, and collect data from high number of images of uterine cervix. In addition, they organize the visual and text data for retrieving information according to specific queries. Currently, the NCI, assisted by the ASCCP, is compiling a list of studies to be developed with gynecologist experts in cervical cancer working at geographically dispersed sites in the United States. New partnerships or collaborative studies can be developed with researchers for working on our current data or with those interested in using these digital tools in their own database.

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