

Detection of Cervical Cancer and High Grade Neoplastic Lesions by a Combination of Liquid-Based Sampling Preparation and DNA Measurements Using Automated Image Cytometry

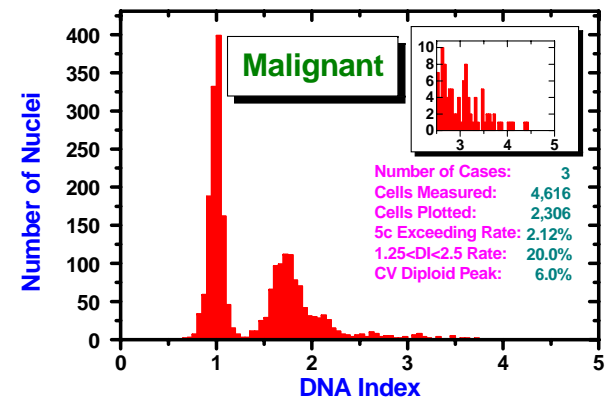
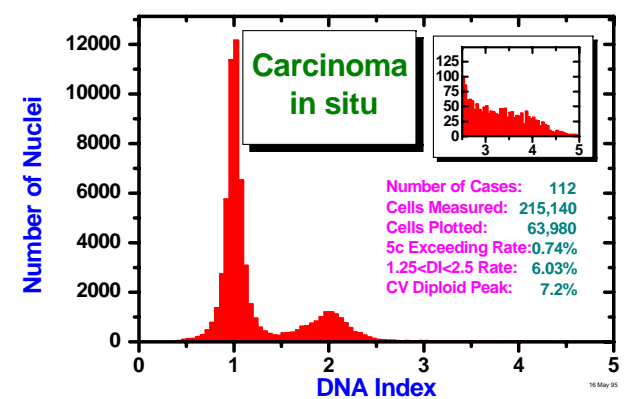
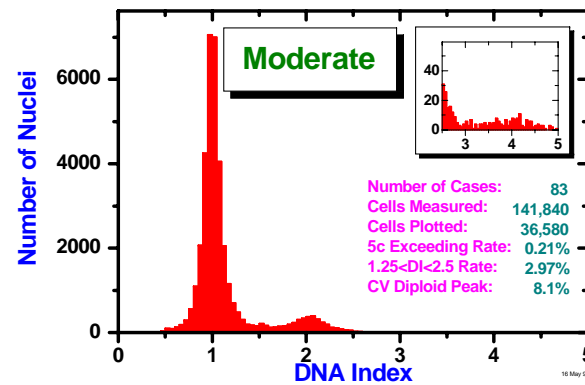
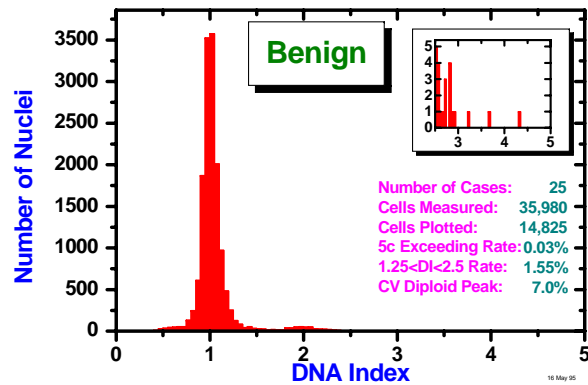
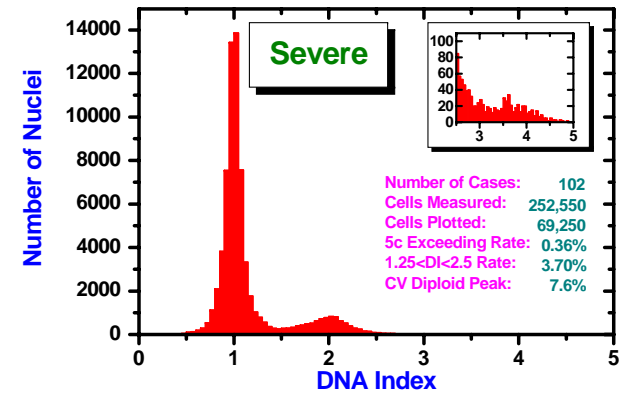
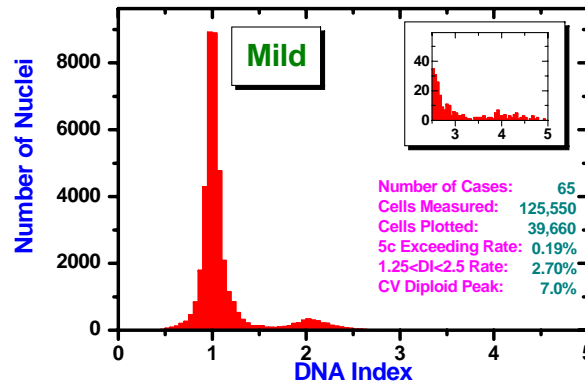
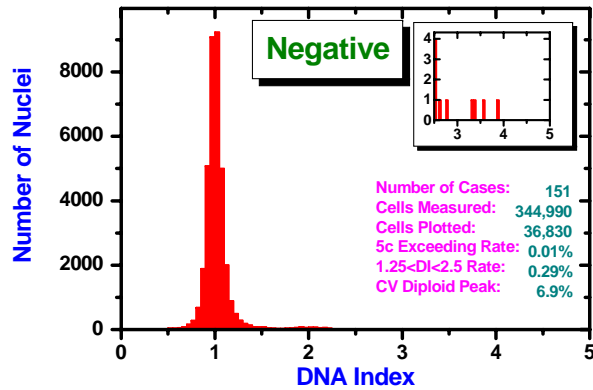
Xiao Rong Sun¹, Jian Wang¹, David Garner^{2,3}, Branko Palcic³

¹Landing Early Cancer Detection Centre, Wuhan, Hubei, China,
²Perceptronix Medical Inc., ³BC Cancer Agency, Vancouver, Canada

Presented at the 22nd International Papillomavirus Conference and Clinical Workshop in Vancouver, British Columbia, 30 April - 6 May, 2005

OBJECTIVE:

- **To establish if measurements of DNA ploidy could support population based cervical cancer screening programs in countries where manually reading slides is impossible due to the inadequate number of skilled cytotechnologists.**

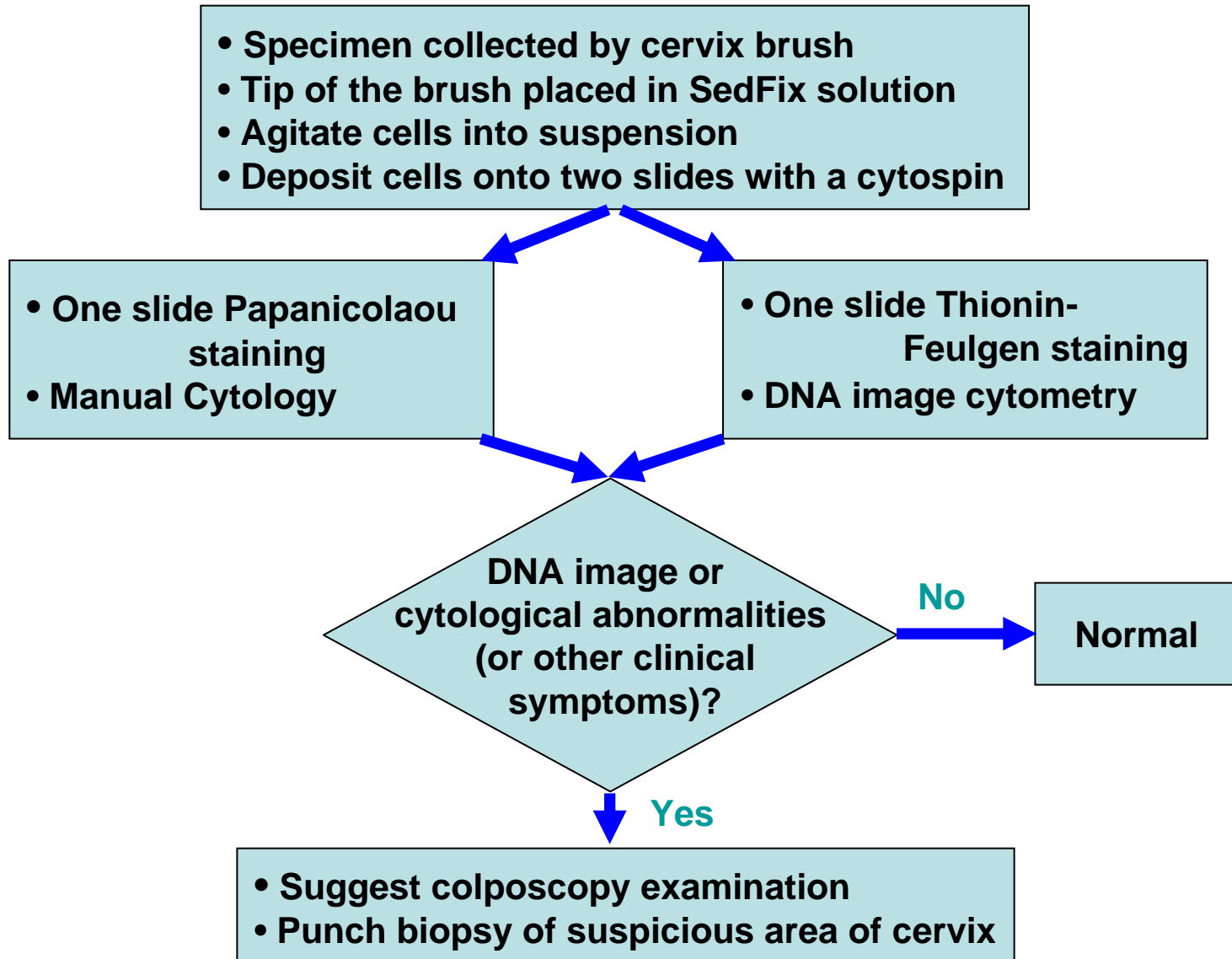


- **Background Information:**
 Historical cumulative DNA ploidy histograms of multiple cases of various grades of dysplasia leading to the study objective

STUDY DESIGN:

- **Cervical samples were taken from 9,905 women by cervix brush, placed into fixative and the cells were separated from mucous by mechanical and chemical treatment**
- **Two slides were prepared from each case:**
 - **one slide was stained by Papanicolaou stain for manual cytology examination**
 - **the other slide was stained by Feulgen stain for DNA ploidy measurement**

Experimental Protocol



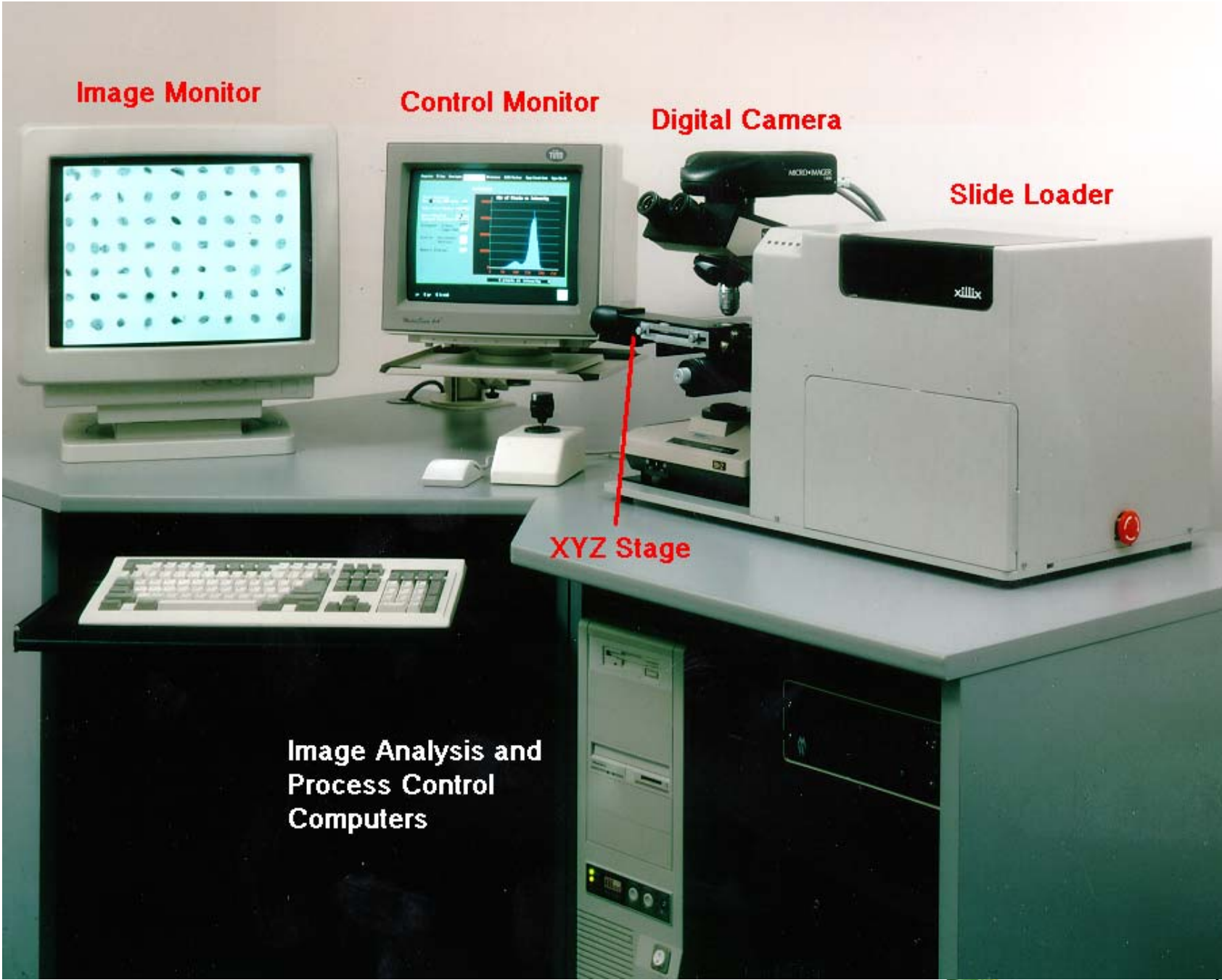


Image Monitor

Control Monitor

Digital Camera

Slide Loader

XYZ Stage

Image Analysis and
Process Control
Computers

RESULTS:

- 876 women underwent colposcopy examination
- Histopathology diagnosed 459 normal or benign cases, 325 CIN1, 36 CIN2, 25 CIN3/CIS, and 31 invasive cancers
- Manual cytology called 655 normal or ASCUS, 197 LSIL, 16 cases HSIL, and 8 cancers
- DNA measurements found 704 cases having no cells with 5c exceeding DNA amount, 98 cases with 1 or 2 cells having 5c exceeding DNA amount, and 74 cases where there were 3 or more cells having 5c exceeding DNA amount
- Manual cytology called for 23 severe lesions to be removed (2 CIN2, 11 CIN3/CIS, and 10 cancers), for a sensitivity* of $(25.0 \pm 5.2)\%$ at specificity* of $(99.9 \pm 0.1)\%$
- DNA ploidy assisted cytology with positivity defined as 3 or more cells with 5c exceeding DNA amount, discovered 50 severe lesions (10 CIN2, 15 CIN3/CIS and 25 cancers) for a sensitivity* of $(54.3 \pm 6.2)\%$ at specificity* of $(96.9 \pm 0.6)\%$

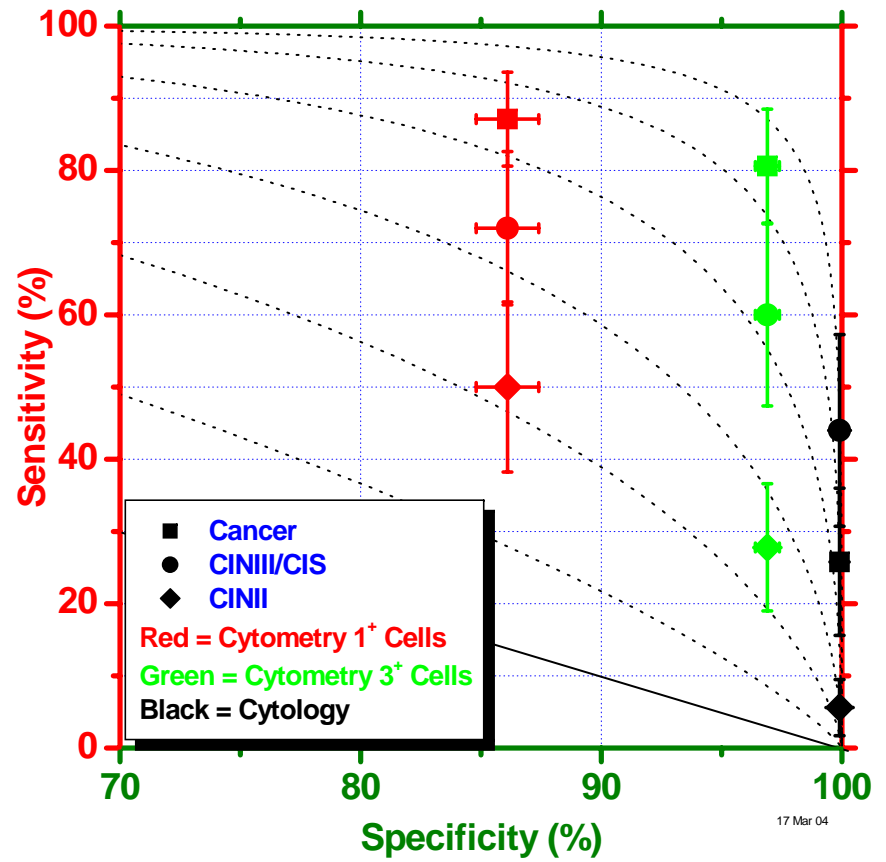
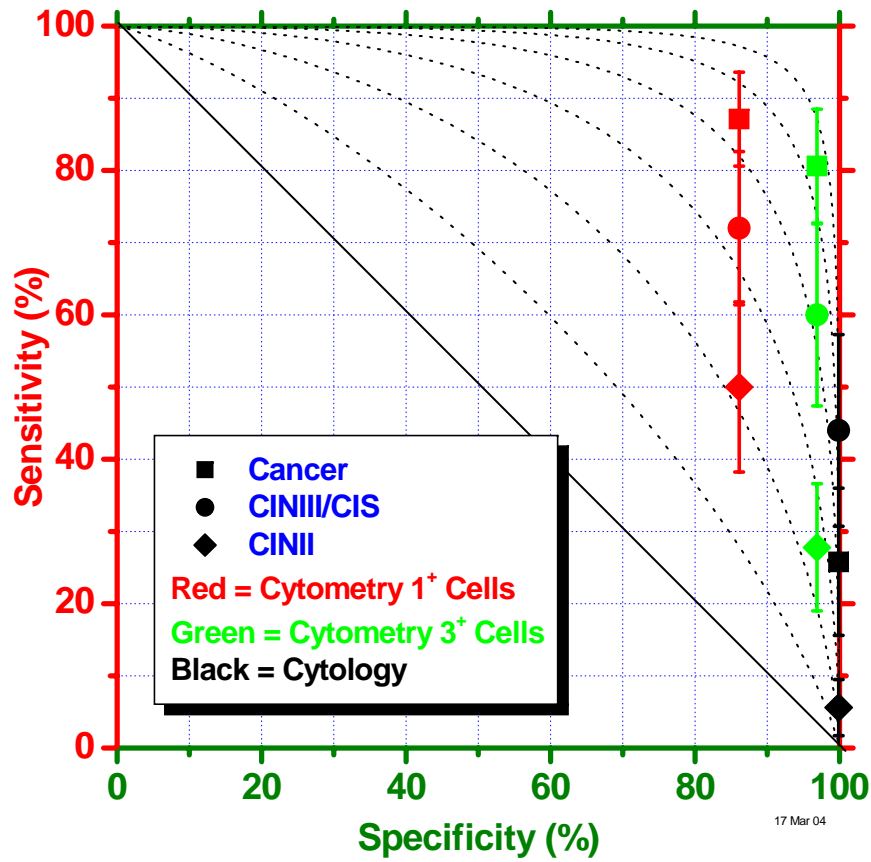
* sensitivity and specificity are defined here with respect to the 876 biopsy cases only (see next panel)

Comparative detection yields of manual cytology versus DNA assisted cytology for various colposcopy referral rules

| Criterion for Colposcopy Referral | Number of Slides examined by Cyto-technologists | Number of Colposcopies Required | Number of CIN II+ That Would be Detected - rate per 10,000 cases (%) | Sensitivity [†] for CIN II+ Detection (%) | Specificity [†] for CIN I- Detection (%) |
|-----------------------------------|---|---------------------------------|--|--|---|
| Cytology HSIL+ | 9905 | 24 | 23 (23.2) | 25.0 ± 5.2 | 99.9 ± 0.1 |
| Cytology LSIL+ | 9905 | 221 | 59 (59.6) | 64.1 ± 6.2 | 79.3 ± 1.6 |
| DNA Ploidy 3 or more >5c cells | 700 | 74 | 50 (50.5) | 54.3 ± 7.0 | 96.9 ± 0.6 |
| DNA Ploidy 1 or more >5c cells | 700 | 172 | 63 (63.6) | 68.5 ± 5.9 | 86.1 ± 1.3 |

- HSIL+ means high grade SIL, CIS or cancer
- LSIL+ means low grade SIL, high grade SIL, CIS or cancer
- CIN II+ means cervical intraepithelial neoplasm grade II, grade III, CIS or cancer
- CIN I- means cervical intraepithelial neoplasm grade I, normal or benign atypia

[†] sensitivity and specificity are defined here for detection of CIN II+ based only on the 876 cases subjected to biopsy. *This is a highly biased selection of cases comprised only of those cases suspicious for disease. Presumably, the majority of the remaining 9029 cases were correctly called negative by both cytology and DNA ploidy, so the true test specificity is expected to be much higher than indicated. Similarly, the experimental design will not discover all CIN II+ cases in the 9905 subjects, so the sensitivity indicated is an upper limit.*



Receiver Operator Characteristics (ROC) of automated DNA cytometry *versus* manual cytology of the 876 cases submitted to biopsy (left) and with specificity scale expansion (right).

Dotted contours are parameterizations based on unit Gaussian distributions, separated in 0.5σ steps ranging from 0.5 to 3.0σ .

CONCLUSIONS:

The study suggests that screening for high grade cervical neoplastic lesions and cervical cancer by DNA ploidy assisted cytology could be implemented with *minimal* use of skilled cytotechnologists in those countries where it would be difficult to introduce population based screening for cervical cancer due to the lack of availability of such skilled cytotechnologists