A novel urine cytology stain for the detection and monitoring of urothelial carcinoma

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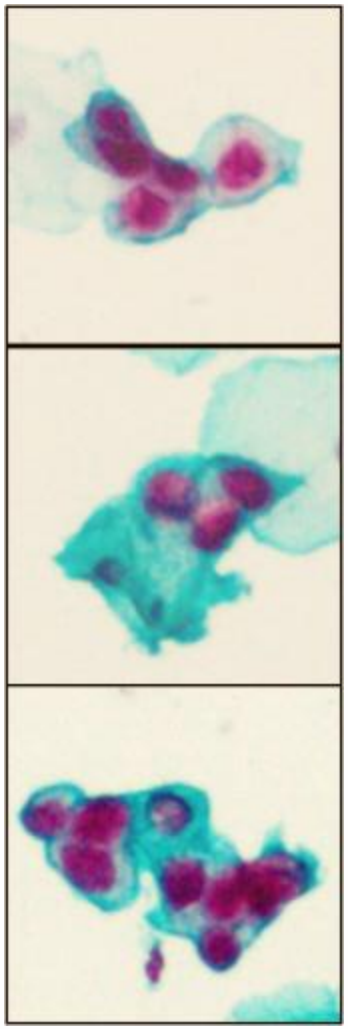
Introduction

CIN 2



- The CellDetect® stain provides a tinctorial distinction between normal to neoplastic cells
- The target of the stain is the cytoplasm : green → benign ---- purple-red → cancer
- The kit contains a plant extract and two histological dyes. The staining is based on a preferential attachment of the extract active component to cancer cells and differential pH affinity of the dyes to normal and cancer cells (irrespective of cell mitoses)
- The CellDetect® has been shown to identify malignant cells accurately in several solid tumors

Sagiv, J Carcinog 2009; Idelevich, J Histotechnol 2009; Idelevich , Diagn Pathol 2010; Idelevich, Diagn Cytopathol 2012

A Novel Urine Cytology Stain for the Detection and Monitoring of Bladder Cancer

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- Fifty eight archived bladder biopsies and 44 urine samples stained with CellDetect
- 100% concordance between H&E and CellDetect
- The sensitivity of detecting urothelial carcinoma in urine smears was 94% and the specificity 89%

Davis, J Urol 2014

Objective

- To further explore the performance of the CellDetect® staining technology in urine samples and compare to available non-invasive assays for detection of bladder cancer

Materials and Methods

- A multi-center study conducted at 9 medical centers in Israel between 04/2013 and 10/2014
- Study population :
  - subjects previously diagnosed with UC undergoing routine cystoscopic surveillance (voided urine samples collected before cystoscopy)
  - subjects diagnosed with urothelial carcinoma who were undergoing TURT/cystectomy (voided urine samples collected before surgery).
- Smaples tested for : Standard urine cytology, BTA stat, and NMP22 BladderChek.

Materials and Methods

- **CellDetect staining :**
  - a minimum of 50 ml of urine was required
  - Urine immediately fixated by a designated fixative and subsequently processed to cytospin smears
  - Smears were stained by CellDetect® and assessed by two independent cytology experts blinded to the final diagnosis
  - Four-scale reading was applied :
    - 1) Negative : Inflammatory/reactive cells
    - 2) Suspicious for malignancy
    - 3) Highly suspicious malignancy
    - 4) Urothelial carcinoma

Positive

Results

- Study population - 217 subjects : 121 negative (normal appearing bladder / negative biopsy) and 96 cancer cases (positive biopsy)

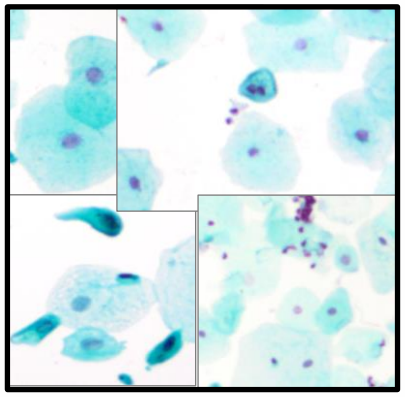
Cancer grade	No. (%)
LG	41
HG	54
Undetermined	1
Total	96

Cancer stage	No. (%)
Ta	50
T1 +/- CIS	21
Tis	1
≥T2	22
Undetermined	2
Total	96

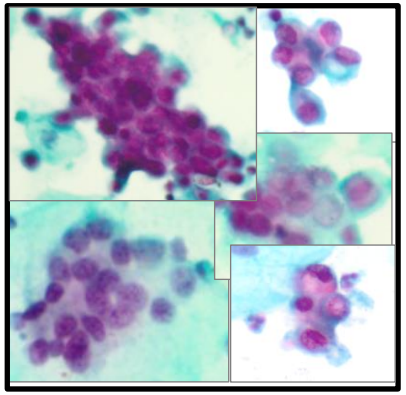
Results

	CellDetect (n=217)	BTA (n=216)	NMP22 (n=73)	Cytology (n=173)
Sensitivity	84.4%	68.8%	17%	50%
Specificity	82.7%	74.4%	97.2%	88%
NPV*	98.5%	96.7%	94.4%	96%
PPV*	28.1%	17.8%	30.3%	24.6%

* Adjusted to disease prevalence of 10% among monitoring population



Normal



Urothelial Cancer

CellDetect sensitivity stratified by tumor stage

Stage	Assay	Sensitivity
Ta	**CellDetect**	**80%**
	BTA	54%
	NMP22	Not enough data
	Cytology	25%
T1 +/- CIS	**CellDetect**	**84.7%**
	BTA	76.2%
	NMP22	16.7%
	Cytology	70%
≥ T2	**CellDetect**	**81.8%**
	BTA	90.9%
	NMP22	40.0%
	Cytology	76.9%

CellDetect sensitivity stratified by tumor grade

	Assay	Sensitivity
Low grade	**CellDetect**	**78.1%**
	BTA	53.7%
	NMP22	0.0%
	Cytology	33.4%
High grade	**CellDetect**	**88.9%**
	BTA	81.5%
	NMP22	30.8%
	Cytology	67.7%

Study limitations

- Study restricted to patients with history of urothelial carcinoma
- Technical limitations : very low cell count, severe obscuring inflammation, gross hematuria
- Short follow-up for patients with “false positive” staining – currently under investigation

Conclusions

- The CellDetect staining demonstrated an overall high sensitivity in identifying bladder tumors
- The performance characteristic of CellDetect appear to outperform the available non-invasive assays for detection of bladder tumors, particularly of low grade / low stage nature
- The clinical implications of CellDetect in serving as an efficient diagnostic tool in bladder cancer surveillance warrants further investigation