

# **Advances in Detection of Non Muscle- Invasive Bladder Cancer (NMIBC)**

**Cysview<sup>®</sup> Blue Light Cystoscopy<sup>™</sup>**

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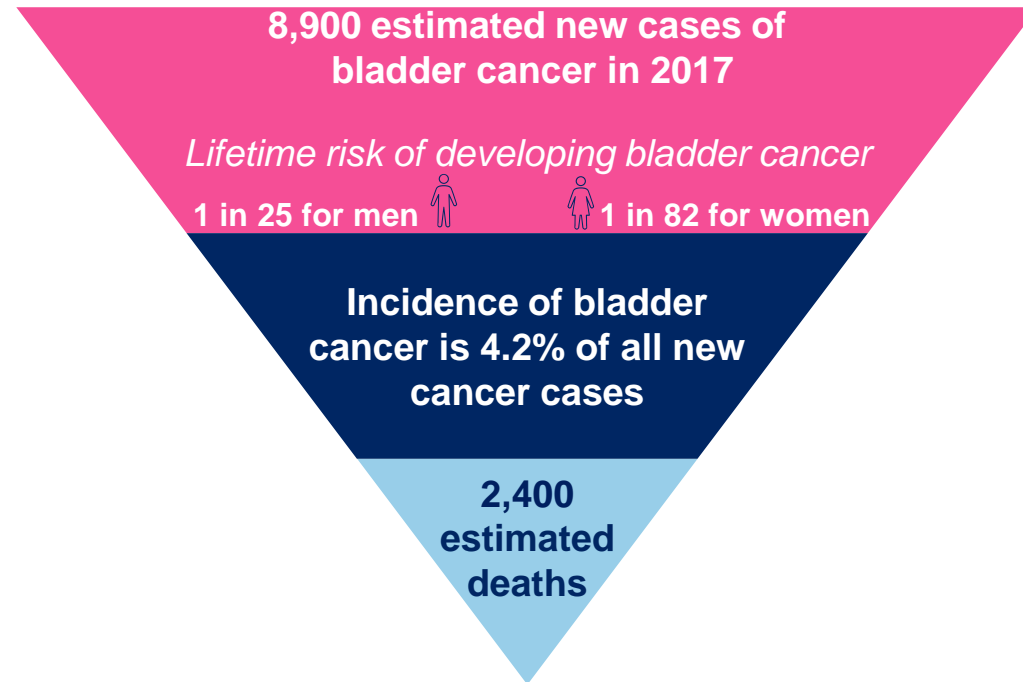
# Faculty/Presenter Disclosure

- **Faculty:** Dr. Jack Barkin md, fics, facs, dabu ,ccpe, mhm, frcs
- **Relationships with financial sponsors:**
  - **Grants/Research Support:** Astellas, NKVue, Pfizer, Biosyent, Lilly,Merck
  - **Speakers Bureau/Honoraria:** Storz, Biosyent, Cysview

# Bladder Cancer

## Disease Background

### Canadian Bladder Cancer Statistics – 2017\*



**>80,000** people are living with bladder cancer in Canada  
**5th** most commonly diagnosed malignancy in Canada  
**1st** in patient treatment costs

# Disease Background

## US Bladder Cancer Statistics

- 6<sup>th</sup> most common cancer<sup>4-USA</sup>
  - 4<sup>th</sup> most common in men, 12<sup>th</sup> in women (3:1 male to female ratio)
- Most expensive cancer - patient lifetime treatment costs<sup>5</sup>
- 81,190 estimated new cases of bladder cancer in the US in 2018<sup>2, 4</sup>
  - 1 in 27 men, 1 in 89 women
- 17,240 deaths related to Bladder Cancer in US<sup>4</sup>
- 90% of patients are over 55 years of age.

## Bladder Cancer Risk Factors

- Cigarettes
- Occupation: dyes, rubber, textile, diesel, exhaust
- Aromatic amines
- Older age

Cigarette Smoking



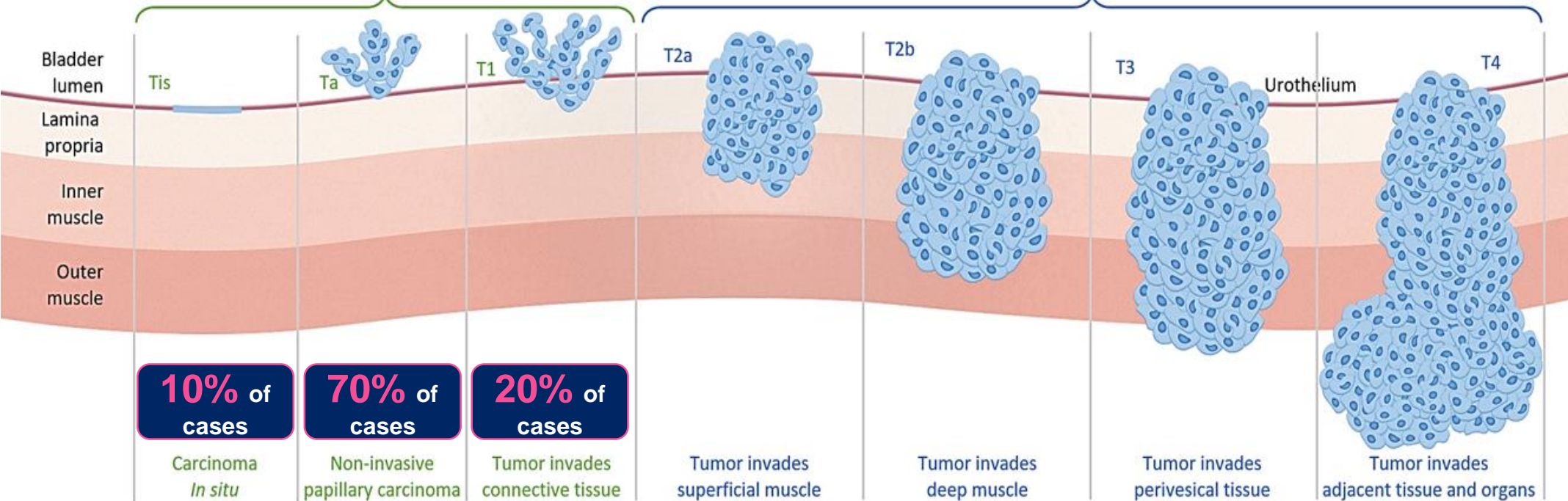
Chemical Exposure



# Non-Muscle Invasive Bladder Cancer

70% of newly diagnosed cases<sup>6,13</sup>  
Non muscle invasive (NMIBC)

30% of newly diagnosed cases<sup>6,13</sup>  
Muscle invasive (MIBC)



# Non-Muscle Invasive Bladder Cancer (NMIBC)

## Disease Background and Treatment

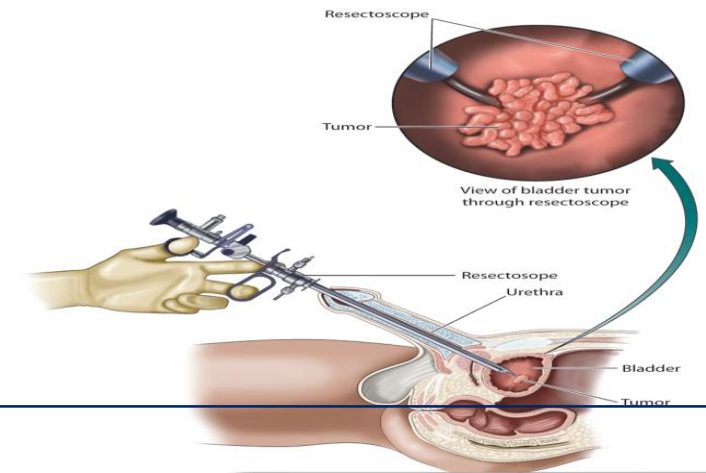
### Background<sup>14</sup>

- Patients with NMIBC represent 75-85% of all bladder cancer patients
- Increasing Stages of NMIBC
  - Ta : noninvasive papillary carcinoma
  - CIS : carcinoma in situ
  - T1 : tumor extends to the subepithelial connective tissue

### High rate of residual tumor after Transurethral Resection of Bladder Tumor (TURBT)

- |  |  |
|--|--|
| <ul style="list-style-type: none"><li>• Recurrence<sup>5</sup>:<ul style="list-style-type: none"><li>• Up to 61% after one year</li><li>• Up to 78% after five years</li></ul></li></ul> | <ul style="list-style-type: none"><li>• 34-76% of patients have evidence of tumor on repeat TURBT at 2–6 weeks<sup>8,9</sup></li></ul> |
|--|--|

### TURBT is first-line treatment for NMIBC<sup>36</sup>



Patients with incomplete initial resection are at high risk of recurrence<sup>11</sup>:

### Progression to muscle invasive disease<sup>6</sup>:

Up to 17% at 1 year  
Up to 45% at 5 years for NMIBC  
Common in patients with carcinoma in situ (CIS), which are often difficult to detect<sup>11</sup>

# Cysview ( HexaminoLevulinate Hydrochloride)

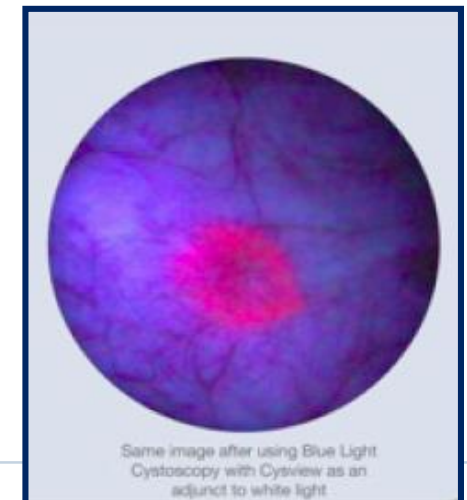
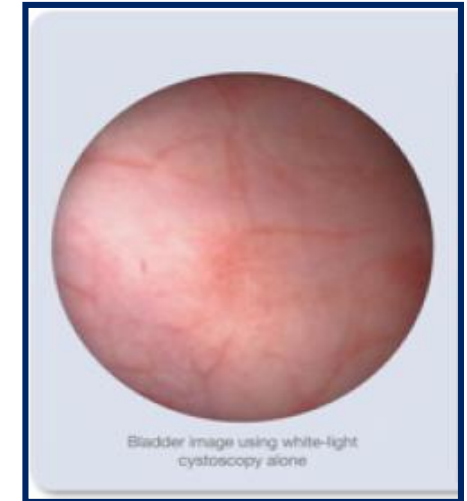
## Technology<sup>1</sup>

- **Involves instilling a photosensitizing agent into the bladder with a catheter**
  - Agent penetrates the tumour's cellular membrane
  - Interferes with the heme biosynthetic pathway
  - Leads to preferential intracellular accumulation of **photoactive porphyrins (PAPs)**
- PAPs selectively accumulate in rapidly proliferating cells
- After one hour, sufficient PAPs have been generated
- **Under subsequent blue light illumination, neoplastic cells fluoresce red, enabling detection of the tumour(s)**



# About Cysview®

- **Bioavailability:** 7%
- **Half-life:**
  - Initial elimination half-life of 39 minutes,
  - Followed by a terminal half-life of approximately 76 hours.
  - Whole blood analysis showed no evidence of significant binding of Cysview® to RBCs.
- **Dosage and administration:** Intravesical administration, at concentration of 8 mmol/L, in 50 mL, retained for 1 hour
- **Mechanism of Action:**
  - After cellular uptake, Cysview® enters the hem biosynthetic pathway, where it is metabolised into the photoactive intermediate compound protoporphyrin IX. (Photoactive Porphyrins- PAP)
  - Cancer cells exhibit abnormal hem metabolism, resulting in increased intracellular concentrations of protoporphyrin IX (PPIX) after topical or systemic application of hem precursors
  - **The excitation of PPIX by blue light (360–450 nm) induces a pinkish red (640 nm) fluorescence in cancer cells**
  - The background normal tissue appears dark blue.

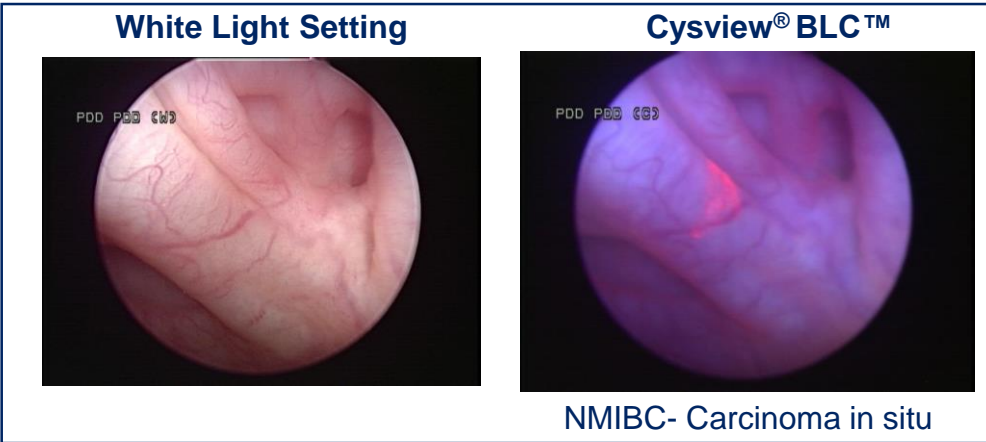
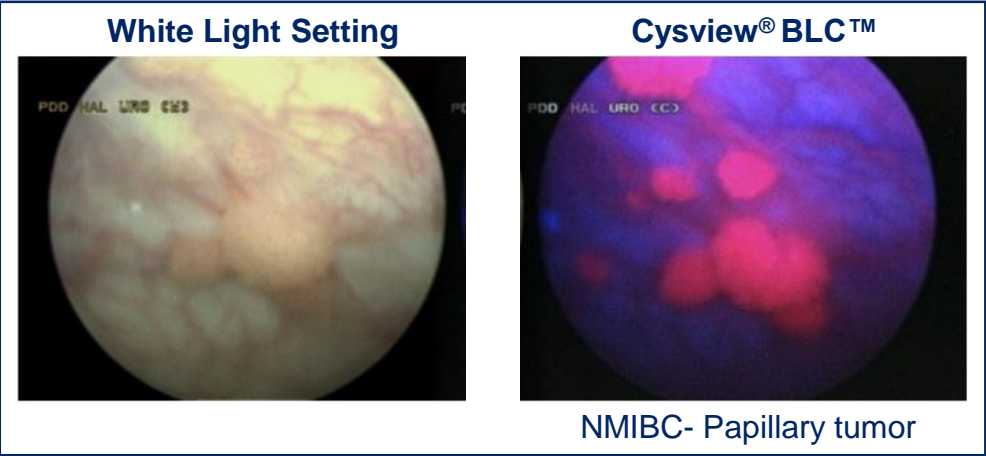




# Cysview<sup>®</sup> Indication<sup>1</sup>

- An adjunct to white light cystoscopy in the detection of non-muscle invasive papillary bladder cancer in patients with known or suspicion of bladder cancer.
- Only approved cystoscopic equipment should be used, equipped with necessary filters to allow both white light (WL) cystoscopy and blue light (BL) (**wavelength 360–450nm**) fluorescence cystoscopy.
- Training in blue light cystoscopy with an approved Photodynamic Diagnosis (PDD) System is essential prior to the use of Cysview<sup>®</sup>.

# Detection of NMIBC: Case Study Images



# Body of Clinical Evidence

## Extensive Body of Evidence

- Cysview® Blue Light Cystoscopy™ has been extensively studied to investigate improvement in detection of bladder tumors versus white-light cystoscopy
  - **6 multi-center phase III trials** in the USA, Canada and Europe
  - **> 2,100 patients** with known or suspected bladder cancer

## Significantly Improves Detection

- Significantly improves detection of papillary (Ta/T1) tumors in up to **29% of patients**
  - **Leads to improved tumor resection**
  - Leads to more appropriate treatments compared to white-light cystoscopy alone

# Study: Stenzl AS et al. J Urol. 2010<sup>22</sup>

## Study Design: North America and Europe

### Randomization Process

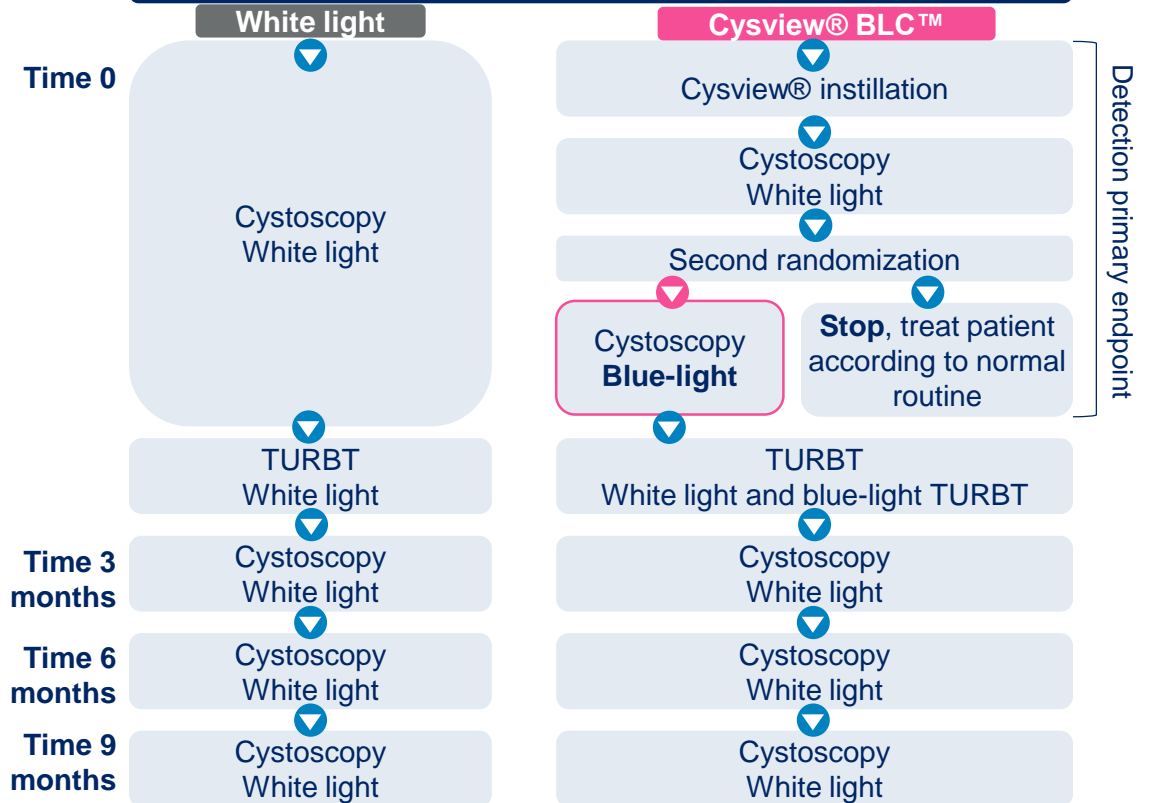
#### Study Design

- Multicenter (Total: 28 centers: 19 US/Canada, 9 Europe)
- Randomization performed centrally
- **Second randomization** performed with Cysview<sup>®</sup> BLC<sup>™</sup> group immediately following white light inspection to ensure thorough inspection with white light

### Study Design

Inclusion

#### Randomization and stratification



*Residual*

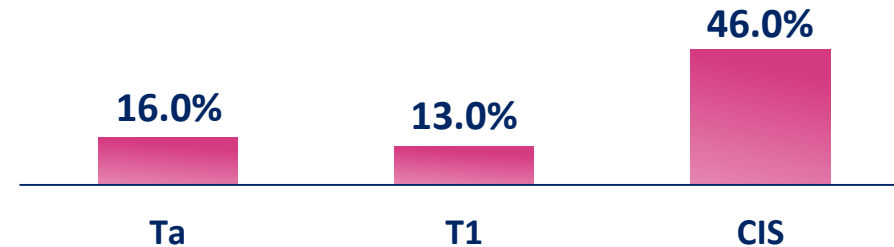
# Study: Stenzl AS et al. J Urol. 2010<sup>22</sup>

## Detection Results – Cysview<sup>®</sup> BLC<sup>™</sup>

Randomized, Multicenter within Patient Comparison

**16.4%** of patients with  $\geq 1$  additional Ta/T1 tumor detected with Cysview<sup>®</sup> BLC<sup>™</sup>

Patient with  $\geq 1$  Ta or T1 tumor detected with Cysview<sup>®</sup> BLC<sup>™</sup> only (%)



- Provided basis for the US and Canadian regulatory approval of Cysview<sup>®</sup> BLC<sup>™</sup>
- Of the **286 patients** with confirmed Ta or T1 bladder cancer, **16.4% had one or more Ta or T1 detected with Cysview<sup>®</sup>**
- The additional tumors identified using Cysview<sup>®</sup> were high grade or **T1 in 43% of the patients**
- **No significant difference in number of false-positive results** (12% with Cysview<sup>®</sup> BLC<sup>™</sup>; 10-11% with WL)

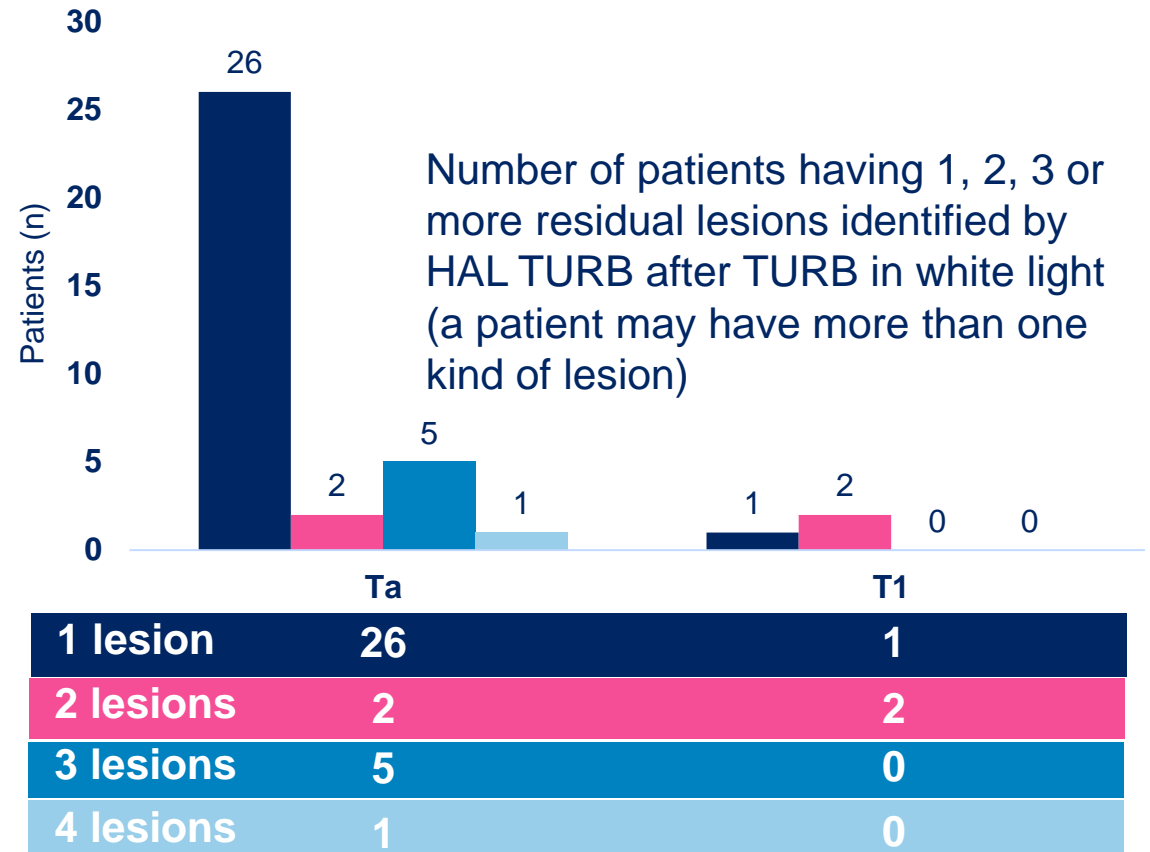
# Study: Hermann et al. BJUI 2011<sup>29</sup>

## Detection Results

### Study Results

- This study investigated whether Cysview<sup>®</sup> BLC<sup>™</sup> could detect residual tumors after white-light guided resection
- 90 patients were confirmed to have bladder cancer on biopsy after white-light resection
  - In 49% of these, residual lesions were found with Cysview<sup>®</sup> BLC<sup>™</sup> after initial TURBT
- These results emphasize that multiple tumors may be missed under white light but can be visualized with Cysview<sup>®</sup> BLC<sup>™</sup>
- The rate of false positives was 25% with Cysview<sup>®</sup> BLC<sup>™</sup> and 16% with white light

### Lesions Identified with Cysview<sup>®</sup> BLC<sup>™</sup>



***Recurrence***



# Cysview® BLC™ bladder cancer recurrence impact

	Burger M et al. Eur Urol. 2013	Geavlete B et al. BJUI 2012		Mariappan P et al. Urol. 2015	Gallagher M et al. World J Urol. 2017	
Patients	2212	362		808	808	
Time to follow-up	1-year	3-month	1-year	First follow-up Cystoscopy	1-year	3-year
Recurrence rate Blue-light	34.5%	7.2%	31.2%	13.6%	21.5%	39.0%
Recurrence rate White-light	45.4%	15.8%	45.6%	30.9%	38.9%	53.3%
p-value	0.006	0.003	0.001	<0.001	<0.001	0.02

**Cysview® BLC™ improves tumor detection vs. WLC alone, leading to reduction of recurrence rates**

# *Additional Tumours*

# Cysview<sup>®</sup> Blue Light Cystoscopy™ 27

## Results of meta-analysis in nine studies with 2,212 total patients

Detection of additional tumors in patients with at least one Ta or T1 tumor and additional carcinoma in situ (CIS) lesions in patients with at least one CIS lesion

Tumor Type	Patients in who at least one Ta or T1 tumor was detected only by BL, n (%)	Meta-Analysis Event Rate	Patients in whom at least one CIS lesion was detected only by BL, n (%)	Meta-Analysis Event Rate
<b>Total</b>	188/831 (22.6%)	24.9%; p < 0.001 (0.184-0.328)	68/268 (25.4%)	26.7%; p < 0.001 (0.183-0.371)
Primary cancer	66/360 (18.3%)	20.7%; p < 0.001 (0.131-0.312)	31/111 (27.9%)	28.0%; p < 0.001 (0.193-0.388)
Recurrent cancer	122/471 (25.9%)	27.7%; p < 0.001 (0.218-0.343)	37/157 (23.6%)	25.0%; p < 0.001 (0.168-0.354)
High risk	97/397 (24.4%)	27.0%; p < 0.001 (0.168-0.402)	-	-
Intermediate risk	84/350 (33.6%)	35.7%; p = 0.004 (0.271-0.453)	-	-
Low risk	7/183 (3.8%)	5.4%; p < 0.001 (0.026-0.106)	-	-

At least one additional Ta/T1 was found in 24.9% of the patients (p<0.001), along with, 26.7% of the CIS patients were diagnosed with Cysview<sup>®</sup> BLC™ only p<0.001

# Cysview® Blue Light Cystoscopy™

## Time to recurrence and recurrence-free survival



- Cysview® BLC™ results in a 7-month increase in time to recurrence of bladder cancer<sup>33</sup>
- Cysview® BLC™ results in a 10.5-month increase in mean recurrence-free survival<sup>32</sup>

**Cysview® BLC™ improves time to recurrence and mean recurrence-free survival relative to WLC**



# Cysview<sup>®</sup> Blue Light Cystoscopy<sup>™</sup>

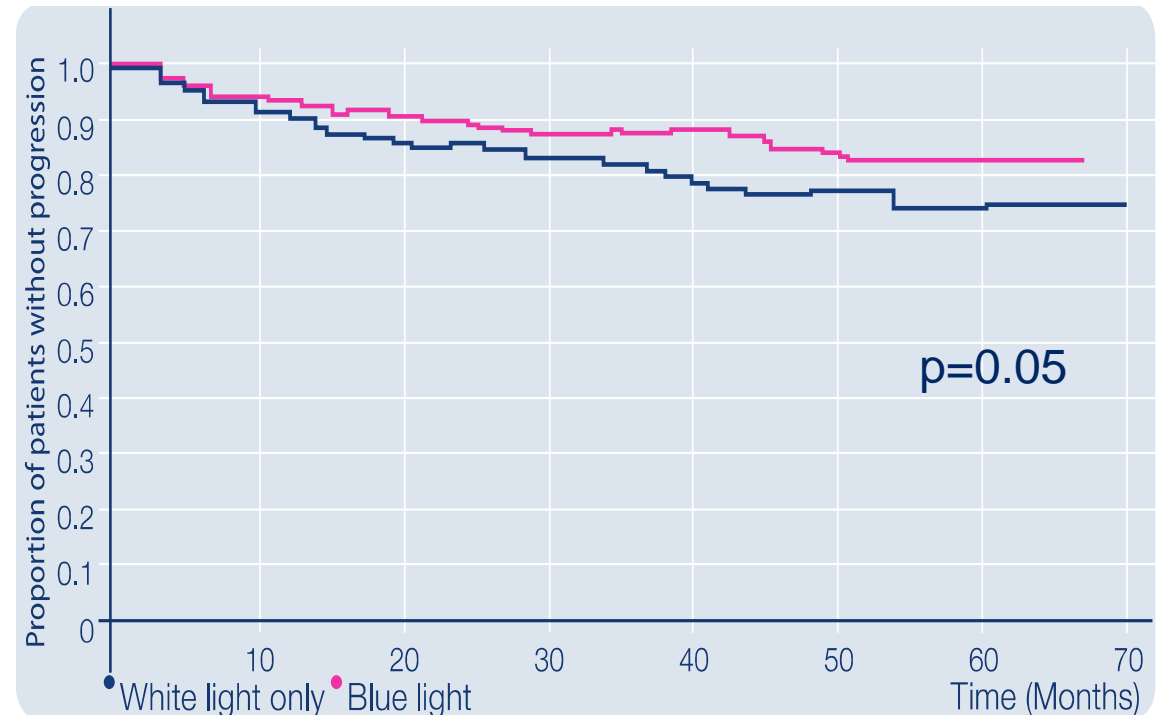
## Cysview<sup>®</sup> BLC<sup>™</sup> impacts bladder cancer progression

### Rate of progression reduced

- **Prospective study in 808 patients<sup>32</sup>:**
  - Cysview<sup>®</sup> BLC: 8/146 patients (5.5%)
  - WLC: 18/135 patients (13.3%)
- **Meta analysis in 5 studies and 1301 patients<sup>34</sup>:**
  - Cysview<sup>®</sup> BLC: 44/644 patients (6.8%)
  - WLC: 70/657 patients (10.7%),  $p=0.01$

*“This meta-analysis supports the assumption that the detection of NMIBC with Cysview<sup>®</sup> BLC<sup>™</sup> reduces the risk of progression. Therefore patients should receive Cysview<sup>®</sup> BLC<sup>™</sup> at their first resection as this might allow more patients at risk of progression to be treated timely and adequately”<sup>30</sup>*

### Time to progression is prolonged<sup>28</sup>



# Cysview® Blue Light Cystoscopy™ 47

## Post-Marketing Real World Data

### White light cystoscopy versus Cysview® Blue Light Cystoscopy™

- **25% patients (133/533) were detected exclusively with the addition of Cysview® BLC™**
- The false-positive rate of **white light cystoscopy (30%)** was similar to that of **Cysview® BLC™ (25%)** although there was **significant variability among the surgeons** most likely **attributable to user experience**

### Cysview® Blue Light Cystoscopy™ resulted in a change in patient management

- **6% of patients (33/533) were found to have a higher AUA/SUO risk category with Cysview® BLC™**
- **The addition of Cysview® BLC™ to standard white light cystoscopy increased the detection rate by 12% for any papillary lesions and 43% for CIS**
- **9% of cystectomies were performed due to lesions detected exclusively by Cysview® BLC™**

**Cysview® BLC™ significantly increases the detection rates of CIS and papillary lesions relative to WLC alone and can result in upstaging ~14% of all patients**

# Patient Types <sup>40</sup>

- **Patient(s) identified as Cysview<sup>®</sup> BLC<sup>™</sup> cases**
  - At Initial TURBT on suspicion of NMIBC
  - Following BCG instillation
  - In patients with multiple low grade tumors
  - In patients with recurrent bladder tumors
  - Cysview<sup>®</sup> BLC<sup>™</sup> is recommended for use during re-evaluation 4-6 weeks post TURBT
  - In patients with positive cytology and negative White Light Cystoscopy



# HRH: Pilot Study (J.B.)



Name	Primary/Rep	Tumor (WL)	Bx/ with(BL)	Cysto Report
BB	Rep	Low Grade N/I	Pap 2/3-HG	No CIS/no 2 <sup>nd</sup> Tumour
GD	REP	NEG	Low grade dysplasia	2 <sup>nd</sup> - ? susp
JF	PRIM	HG/NI	Bx-NEG	Susp- BL
MH	REP	Not seen	1-CIS 2-CIS-prev Inflammation	Bad recurrent cancer- nothing on WI
CI	REP	Low Grade	BT- BL- HG	Not seen before
GJ	PRIM	A-Atypia B-low grade	C- NEG	Susp- BL
HL	REP	BT- 2/3- pap	Bx- CIS	Not seen WL
LM	REP	BX- NEG	BX- CIS	Not Seen WL
JM	PRIM	BX x2 NEG	BX- ? CIS	Not Seen WL
KP	PRIM	BX- atypia	BX-CIS	Susp- WL
SD'S	PRIM	BT- Low Grade	BX-CIS	Not Seen WL



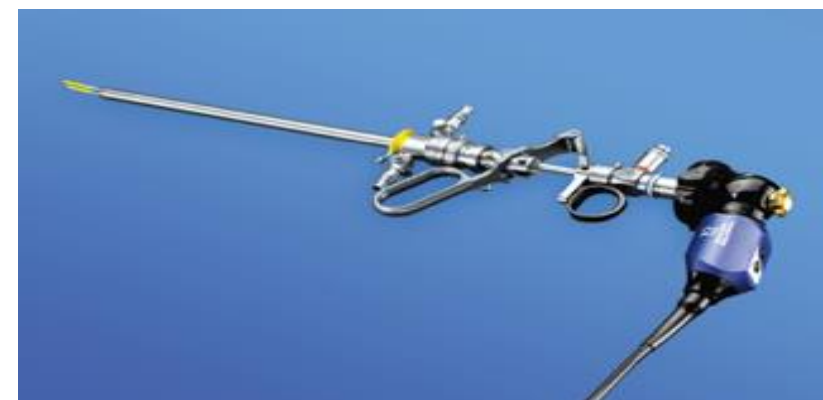
# HRH Summary Results

- 5/11 cases found **CIS-** not seen on White Light >> 45%
- 2/11 **additional Transitional lesions** or low grade to High Grade >> 27%

## Ciccolini Gala- March 31, 2016

- **Dr. Jack Barkin**, MD, FICS, FACS, DABU, FRCS(C)
- **Featured Speaker:**
- *The evening's*
- *proceeds will benefit*
- *the Department of*
- *Urology at Humber*
- *River Hospital*
- *in recognition of the*
- *pioneering work of*
- *Dr. Jack Barkin.*
- *\$1,000,000.00 Raised*
- **January 23, 2017:**
- Sam Ciccolini and Dr. Jack Barkin
- **DEDICATED:**
- The **First in Canada:**
- ***Blue Light Cystoscopy Program with Cysview***
- Humber River Hospital

# KARL STORZ D-Light PDD System



# Cysview<sup>®</sup> Components

## Each Cysview<sup>®</sup> Kit Includes:

- One 100 mg vial of Cysview<sup>®</sup> powder (hexaminolevulinate HCL)
- One 50 mL diluent for Cysview<sup>®</sup>



# BLCC ( Blue Light Cysview Cancer) Patient Types @HRH

- Primary detection if huge, multiple and suspect CIS and/or significant NMIBC
- Repeat TURB for tumor recurrence (secondary detection) within 6 months
- Repeat TURB for stage T1 cancer
- Patients with high grade Ta, T1 or CIS at 3-month re-staging
- Evaluation on basis of positive or suspicious cytology (occult detection)
- BCG failures
- **Play It Forward- Pt. directed foundation donation to Cysview fund**

# Existing Guidelines on the use of Cysview®™

Setting	AUA 2016 <sup>19</sup>	NCCN 2018 <sup>43</sup>	EAU 2015 <sup>44</sup>	ICUD 2012 <sup>45</sup>	NICE 2015 <sup>46</sup>
To guide initial bladder cancer resection and biopsy	✓	✓	✓		✓
In patients with positive urine cytology but negative WLC	✓		✓	✓	
To aid diagnosis of CIS		✓		✓	
To assess suspected recurrence	✓		✓	✓	✓
During follow-up of patients with high risk recurrence (e.g., HG T1, CIS or multifocal lesions)			✓		✓

**Cysview® BLC™ is recommended by numerous expert groups in both national and international NMIBC guidelines**

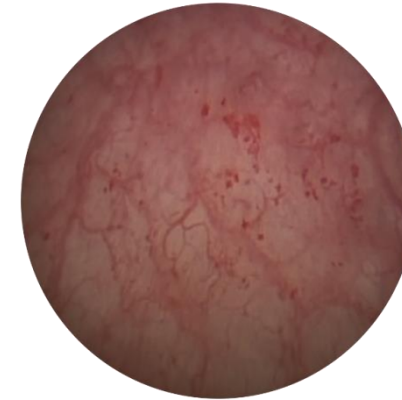
# Improving Tumor Detection

## Overall Impact of Cysview<sup>®</sup> BLC<sup>™</sup>

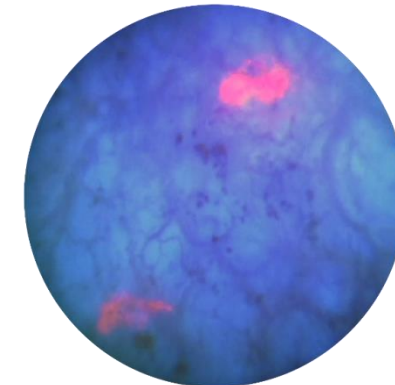
### Importance of TURBT

- TURBT is the first and critically important diagnostic and staging tool in the management of bladder cancer
- A thorough high quality TURBT is a critical component of managing NMIBC. **An incomplete TURBT can lead to understaging, misdiagnosis and incomplete resection<sup>39</sup>**
- Over reliance on intravesical therapy may lead to less optimal treatment, worse outcomes and increased cost for patients
- **TURBT procedures with Cysview<sup>®</sup> BLC<sup>™</sup> has been shown to increase diagnostic accuracy<sup>39</sup>**

White Light Setting



Blue Light setting  
with Cysview<sup>®</sup>



# Patient Management with BLC Makes A Difference In Outcome!<sup>1</sup>

- Patients undergoing **Cysview® BL-TURBT** vs WL-TURBT:
  - Higher number of TURBs before RC (1.7 vs. 2.9;  $p < 0.001$ ) (RC- Rad Cystectomy)
  - Higher number of repeat-TURBs (32.6% vs. 54.5%;  $p = 0.015$ )
  - Longer time between first TURB and RC (71 vs 45 months;  $p = 0.044$ )
  - Lower rate of postoperative systemic chemotherapy use (6.5% vs. 14.1%;  $p = 0.007$ )
- No further significant differences between groups in other clinical and pathologic characteristics



# Questions

