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THE BLADDER CANCER COMPANY

Evaluation proposal to the Danish Health Technology Council regarding cystoscopy and transurethral resection of bladder tumours (TURBT) in patients with suspicions of bladder cancer

Date: 31/5-2023
Version 1

1 Background

In 2020 bladder cancer (BC) was identified as the fifth most prevalent cancer in Europe [1], causing an estimated 67,289 deaths every year. Bladder cancer is classified as either muscle invasive bladder cancer (MIBC), breaching the bladder lining, or non-muscle invasive bladder cancer (NMIBC). Approximately 75% patients present with NMIBC [2].

NMIBC is confined to the bladder mucosa and refers to the group of tumours staged as Ta (also referred to as carcinoma in situ (CIS)) or stage T1 (lamina propria/submucosa) [3] and is a heterogenous disease that can also be classified on the basis of disease risk progression, which is clearly linked to disease recurrence. NMIBC has a high recurrence rate (50-70% of patients), with 10-20% of NMIBCs and 54% of patients with CIS progressing to muscle-invasive disease (depending on stage and grade at diagnosis) [4-6].

Bladder cancer is a life-long disease which has a high burden to our healthcare system. Most of the time, there is a need for lifelong treatment and surveillance due to its high risk of recurrence and progression. The initial treatment for NMIBC is usually a transurethral resection of bladder tumour (TURBT), during which detected tumours in the bladder are surgically removed, and biopsies from suspect lesions are taken. Having visual enhanced cystoscopy techniques to aid the TURBT is essential, to improve initial detection and completeness of resection of bladder cancer tumours (and any recurring tumours), as well as taking biopsies for correct diagnosis (staging) and risk stratification: diagnosis depends on histological evaluation of suspect tissue obtained via TURBT or biopsies obtained during cystoscopy. High risk CIS tumours are particularly vulnerable to not being seen or to being misdiagnosed if not biopsied.

WLC is used for the visual detection of bladder tumours and to guide TURBT for complete resection of all visible bladder tumours. However, the use of WLC alone can lead to missed lesions [7] and identifying tumour boundaries can be challenging [8]. This is particularly true for identification of difficult-to-find flat, high-risk tumour lesions, e.g., carcinoma in situ (CIS), [7,9], papillary tumours, e.g., small, and/or multifocal Ta/T1-tumours. Early dysplasia can also be missed if using WLC alone [9-11].

Blue light cystoscopy (BLC) as an adjunct to WLC during TURBT, uses an intravesical photosynthesizing agent (fluorescence) such as hexaminolevulinate (Hexvix® - also referred to as HAL or HEX) [27] or the precursor 5-aminolaevulinic acid (5-ALA). The latter has no market authorization in Europe. BLC has been shown to provide superior detection and diagnostic accuracy compared to white light cystoscopy (WLC) alone. Regulatory approval of BLC as an adjunct to WLC was obtained in the EU in 2005. The photosynthesizing agent HAL is preferentially absorbed by rapidly proliferating cancer cells in the haem-biosynthetic pathway i.e., demonstrating tumour cell specificity. When illuminated under blue light, the accumulation of the photosynthesizing compounds (porphyrins) creates a clear and enhanced contrast that enables a clear distinction between dysplastic, cancerous tissue and surrounding normal tissue. The enhanced visualization and detection of difficult to find tumours and tumour borders during TURBT with BLC results in a more complete resection, a more accurate diagnosis and reduced risk of short- to long-term tumour recurrence [11,12], as confirmed by more than 20+ randomized controlled trials and 10+ systematic reviews [2,9], including a recent Cochrane review [13.14. In addition, there is also evidence that BLC might reduce the risk for long-term disease progression [13,15], and BLC use in real life clinical practice has been validated in several register studies with 5–10-year follow-up data cf. table 7 “Summary table of systematic reviews and meta-analysis.” For this reason, BLC as adjunct to WLC during TURBT was commonly used for improving bladder cancer detection, diagnostic and long-term management in Denmark from 2007 onwards [15]. There are 3 equipment manufacturers with BLC capable equipment that has been approved for use in the EU, and which are available in Denmark.

More recently, many Danish hospitals have migrated from BLC to the use of NBI which uses digital manipulation of the optical signal from WLC to enhance the visible contrast of vessels within the bladder wall. It does this by emitting two specific wavelengths of light known to be assimilated by haemoglobin and serves to enhance any area of the bladder which are markedly vascularised. Given the hypervascular nature of cancerous tissue, this indirectly improves the diagnostic yield versus WLC alone. There is only one manufacturer with equipment that can be utilised for this technique.

In contrast to NBI, BLC is tumour specific, because it preferentially accumulates in cancerous tissues and is a more direct marker of tumour tissue versus being based on image processing and indirectly a sign of tumours as in NBI. Such tumour cell specificity, and the resulting characteristic fluorescence signature with an enhanced contrast between cancer tissue and surrounding healthy tissue with BLC, is specifically important e.g., when identifying flat tumour lesions and dysplasia, which can be especially difficult to visualise macroscopically from normal tissue. Although NBI is broadly used in Denmark, the overall body of evidence is substantially smaller for NBI as compared to BLC, with a lack of long-term recurrence data, no progression data, and several studies failing to demonstrate superiority over WLC [14,7].

Enhanced cystoscopy techniques like BLC and NBI have been shown to improve tumour visualisation and detection, leading to a more complete resection. BLC has also been shown to provide more accurate tumour staging and risk stratification through improved targeting of biopsies for more accurate histopathology. Subsequently, BLC leads to improved NMIBC management and reduced recurrence and progression rates. BLC and NBI utilisation is recommended in the European guidelines for NMIBC, if equipment is available. However, in case of suspicious of CISs, only BLC is strongly recommended based on its body of evidence for superior identification of high-risk bladder cancer, including carcinoma in situ (CIS). This is in line with various other European country specific guidelines [17,18]. In contrast, current Danish guidelines do not consider the differences in the strength of evidence between BLC and NBI, making general recommendations including both techniques to rule out high-risk bladder cancer [19].

In a systematic-review and meta-analysis of raw-data comparing detection rates in comparison between WL- and BL-TURBT, additional Ta or T1 tumours were identified in 25% of patients only by BLC. Importantly, 41% of CIS lesions were identified only by BLC alone [9] and relative risk reduction of recurrence for high-risk T1 and CIS was 31% [20]. Furthermore, the use of BLC during TURBT has been shown to reduce both recurrence and progression rates by around one-third compared to WLC alone (HR = 0.66 and 0.65 respectively). The absolute magnitude of this benefit is dependent on the patient's baseline risk stratification, with higher risk patients gaining most from BLC [13]. Risk stratification is determined by a range of metrics, including the tumour characteristics, such as number and size of tumours, assessed alongside their histological stage and grade, as well as the patients age as clinical parameter.

NBI has been shown in RCTs to have greater diagnostic sensitivity than WLC and has also shown a trend to improve 12-month recurrence rates, albeit without achieving statistical significance in three out of 6 RCT of the Cochrane review on NBI in NMIBC [13,14,21]. Unlike BLC, the greatest benefits of NBI are seen in low-risk patients, with little or no advantage being seen in those with intermediate or high-risk profiles [22]. This may manifest in terms of an inability to discriminate flat lesions, particularly carcinoma in situ (CIS) [23], where tumour margins may lie outside of the vascular bed, which is associated with an exceptionally high risk of recurrence and progression [24]. The differences in the strength of evidence for NBI as compared to BLC especially high-risk NMIBC, has been reflected in Health Technology Assessments, the EAU guidelines and Cochrane meta-analyses [7,13,14].

[redacted]

1.1 State the type of Health Technology

The health technology is a procedure.

Cystoscopy with transurethral resection of bladder tumour (TURBT) can be undertaken with white light cystoscopy (WLC), with tumor visualization enhanced using blue light cystoscopy (BLC) or narrow band imaging (NBI). Both BLC and NBI are used for enhanced cystoscopy in combination with white light.

This evaluation submission refers specifically to BLC, fluorescence-guided cystoscopy with blue light and Hexvix®/hexaminolevulinate (HEX), the fluorescence optical imaging agent, which is used as part of the diagnosis, treatment, and follow-up of bladder tumors in patients with known bladder tumors or in case of strong suspicion of bladder tumors.

Note: BLC is sometimes referred to as Photo Dynamic Diagnosis (PDD).

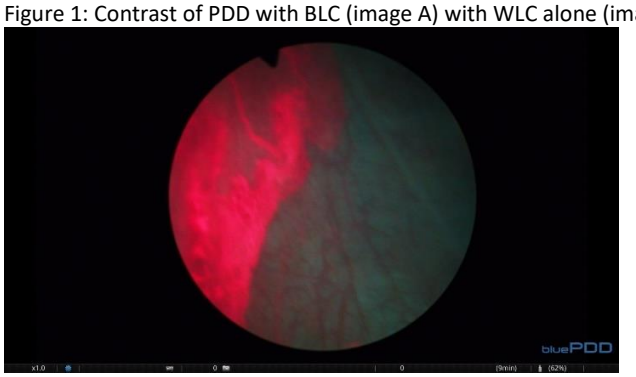
1.2 Briefly describe the technology and the current Danish clinical context in which the technology will be used.

Mode of Action

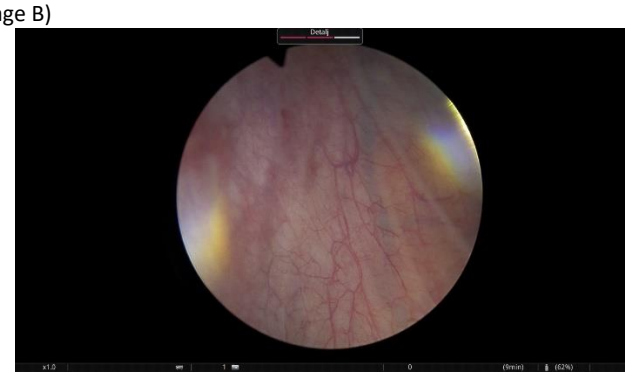
BLC uses the interaction of photoactive compounds and fluorescent light to increase the optical difference between normal and malignant tissue. After intravesical instillation of the optical imaging agent Hexvix (hexaminolevulinate (HAL)), porphyrins accumulate intracellularly in bladder wall lesions due to dysregulation in the activity of transport proteins in preferentially malignant cells [13]. As bladder cells become malignant, one of the molecular changes is a dysregulation in the activity of transport proteins, which leads to the accumulation of PPIX, a photoactive, fluorescing compound that emits red light upon blue light excitation. The presence of protoporphyrin IX (PPIX) is up to 16-fold higher in malignant cells than in healthy cells [25,26]. As a result, premalignant and malignant lesions in the bladder will glow red on a blue background, making them easier to visualize and remove [27,28].

Hexvix is a pro-drug (synthesized derivative) of 5-ALA, which can also be used during BLC. However, the degree of penetration into tissues is limited with 5-aminolevulinacid (5-ALA). In contrast, Hexvix cell uptake is increased compared to 5-ALA [26,29].

Figure 1: Contrast of PDD with BLC (image A) with WLC alone (image B)



BLC = Blue-light cystoscopy; PDD = Photodynamic diagnosis



WLC = White-light cystoscopy.

The standard procedure in patients with suspected bladder cancer is transurethral resection of the bladder tumour (TURBT). It is utilised to identify and completely resect the tumour(s) within the bladder. As such, the procedure itself is not only a diagnostic procedure, but is also therapeutic - and potentially curative - at the same time. Depending on the histopathology of the resected specimen and biopsies, patients undergo different risk-based management pathways. Patients with NMIBC may undergo surveillance with/without adjuvant intravesical therapies (chemotherapy drug or immunotherapy) whereas patients with MIBC will undergo radical cystectomy and more aggressive therapies in the majority of cases. In patients with NMIBC, low risk patients will only undergo surveillance whereas patients with intermediate and high-risk bladder cancer will also undergo adjuvant intravesical instillation treatment in addition [7]. Incomplete resection or completely missed cancerous lesions may lead to inaccurate staging and follow-up management of the patients, adversely influencing their risk for bladder cancer recurrence and progression. In a study involving 362 patients, additional lesions were found in 35.2% of patients by HAL-BLC and consequently, the recurrence- and progression-risk categories of patients and subsequent treatment improved in 19% of the cases due to fluorescence cystoscopy [30].

Residual tumours after TURBT, when using WLC alone, has been reported in up to 67% and 71% for Ta and T1 tumours, respectively. The presence of difficult to detect CIS lesions were reported between 0 to 64% [31]. An analysis of seven large RCTs has shown that, using conventional white light cystoscopy (WLC), there is a high risk of disease recurrence (around 48%) and progressive disease (11%) after a median follow up of 3.9 years, with at least half of the observed recurrence occurring in the first 12 months [32].

Expected annual procedures & treatment management guidelines in Denmark.

Around 2,000 cases of bladder tumours are newly diagnosed each year in Denmark. Clinical data suggests that at the time of diagnosis, 75% will be NMIBC and 25% MIBC. According to the Danish Bladder Cancer guideline, which refers to the invasiveness of tumours at the time of diagnosis, about 50% of all bladder tumours will be invasive, and half of those muscle invasive. The guidelines state that these tumours should therefore be treated with particular attention for early radical surgical treatment [19].

The importance of various prognostic factors in recurrence and progression has been investigated in several studies. The main prognostic factor in bladder tumours has been shown to be T-stage, determined either histologically or clinically [19].

The cardinal symptom of bladder tumours is blood in the urine. Hematuria of varying degrees - most often intermittently - occurs in 80-90% of patients with bladder tumours [19]. Urological investigation in cases of

hematuria or suspected bladder tumour includes cystoscopy [19]. If a bladder tumour or other type of pathology is detected in the bladder, cystoscopy is performed under anesthesia with, as far as possible, transurethral resection of the bladder tumour, selected site biopsies and bimanual palpation of the bladder. In combination with the histological tissue examination, a relatively picture of the stage and degree of the tumour is obtained. In many cases, TURBT in addition to being a diagnostic, is also often the definitive, curative treatment of the bladder tumour [19].

The correct investigation, including visual identification of the bladder tumour and complete resection and histopathology, is essential for the patient to receive the right treatment [33]. The quality of the cystoscopy performed is therefore central to the correct investigation and quality of NMIBC care. Correct and early diagnosis is important for long term outcomes in NMIBC, as under-staging of the tumours is seen in 15-40% of patients, which can lead to under-treatment. Long-term monitoring of treatment response e.g., with intravesical adjuvant mitomycin (MMC) and Bacillus Calmette Guërin (BCG) instillations, and in the future other novel emerging treatments, all contribute to a preferred bladder sparing approach in NMIBC management.

1.3 Describe the expected patient population.

Around 3,100 patients in Denmark are referred annually for investigation for suspected Bladder cancer [34], cf. Table 1 below. The correct diagnosis, including pathology, histology, and diagnostics, is crucial for the patient to receive the right treatment [19].

Table 1 Data extract from the National Patient Registry (Landspatientregisteret (LPR) [34]

Urinblæren, prevalens* og incidens**									
DaBlaCa registrering af diagnosekoder (ICD10) i Landspatientregistret (LPR)	Kode	2019		2020		2021		2022	
		Number of patients registered for the first time	Number of patients registered at least 1 time	Number of patients registered for the first time	Number of patients registered at least 1 time	Number of patients registered for the first time	Number of patients registered at least 1 time	Number of patients registered for the first time	Number of patients registered at least 1 time
Obervation pga mistanke om kræft i urinblæren	DZ031H2		4.038	3423	3.937	3.286	3.882	3038	3.709
Obervation pga mistanke om recidiv af kræft i urinblæren	DZ031H2R		192	128	155	153	173	131	154
Kræft i urinblæren	DC679		2.004	1.156	2.095	1.089	2.110	1.038	2.207
Carcinoma in situ (Tis) i urinblæren	DD090		520	298	596	209	573	210	576
Non-invasiv papilar tumor (Ta) i urinblæren	DD095		2.524	1.519	2.971	1.382	3.237	1.269	3.336
Godartet tumor i urinblæren (fraset uroteliale Ta-tumorer) inkl. inverteret papillom	DD303		942	271	1.839	177	724	118	588

* Prevalens antal patienter, som er registret med diagnosen mindst 1 gang i løbet af det pågældende år.
**Incidens 2022 patientregistreret første gang med diagnosen, defineret ved ikke at være registreret året før, dvs. for 2022 er patienten ikke registreret med en kontakt i 2021.

When patients are diagnosed, they are treated in line with the Danish guidelines for the specific histology, the 4 guidelines below:

- Behandling og opfølgning af ikke-invasive blæretumorer (Ta tumorer og CIS) [35]
- Behandling og opfølgning af muskelinvasiv blærekræft [36]
- Behandlingsstrategi og opfølgning af T1-tumorer [37]
- Behandling og opfølgning af T4b og metastatisk blærekræft [38]

According to the Danish treatment guidelines mentioned above, PDD (BLC) is relevant for CIS and high-risk patients, which are registered with the diagnosis codes: “DD090 Carcinoma in situ (Tis) i urinblæren”, “DD095 Non-invasive papilar tumor (Ta) i urinblæren”. [19]. In total, approximately 3.900 (576+3.336) patients were registered with one of these diagnoses yearly.

Patients with high-risk bladder cancer have a 5-year risk of recurrence and progression of up to 78% (according to EORTC risk calculator) and 44% (EA Guideline), respectively. Notably, CIS will progress to

muscle invasive disease in 54% without any treatment [39] and is per definition categorised as high-risk bladder cancer. If NMIBC progresses to muscle-invasive disease, in the absence of metastases, the standard treatment is radical cystectomy in the absence [7]. Radical cystectomy is associated with a high morbidity and mortality rate [40] and furthermore, has a major adverse impact on the patient's quality of life and well-being [41].

1.4 Describe the current status for use in Denmark and abroad.

BLC has been recommended in the Danish guidelines for diagnoses of bladder cancer since 2007 and was broadly used in all five regions until 2018. The recently revised guidelines (2023) recommend BLC and NBI interchangeably regardless of diagnosis or procedure [19,35-38]. In this regards the Danish NMIBC guidelines differ from the majority of other international guidelines on the use of visual enhancement like BLC and NBI. The difference in level of evidence and performance between BLC and NBI, regarding high-risk tumours where only the use of BLC has a strong recommendation and is considered best practice, is not reflected in the Danish guidelines [19,7,18]. The number of BLC procedure have decreased continuously during the last years in Denmark and the status is, that patients only have access to BLC in two regions compared to NBI in all five regions.

According to the newly updated Danish guidelines the indication for the use of PDD or NBI with evidence level B are [19]:

"Indikationer for anvendelse af PDD eller NBI: (B)

- *Førstegangs blæretumor mhp komplet resektion og som alternativ til selected site biopsier mhp påvisning af CIS*
- *Første kontrol efter Bacillus Calmette Guërin (BCG) pga. CIS.*
- *Urotelceller suspekt for høj malignitetsgrad (Paris Kategori IV) eller urotelceller med høj malignitetsgrad (Paris Kategori V) celler i urinen ved normale fund ved cystoskopi og CT-urografi"*

1.5 State completed or ongoing health technology evaluations performed by health technology assessment (HTA) organizations.

Table 2. Overview of HTA studies

Country	HTA Organisation	Review type & Date	Research question	Reference	Status
Canada	CADTH (Canadian Agency for Drugs and Technologies in Health)	Health Technology Review (Rapid Review) Feb 2017	Blue Light Cystoscopy in Patients with Suspected Non-Muscle Invasive Bladder Carcinoma: A Review of Clinical Utility	CADTH Rapid Review - BLC Clinical Utilities	Completed
Canada (Ontario)	Ontario Health	Health Technology Assessment	Enhanced visualisation methods for first trans-urethral resection of bladder tumour in suspected non-muscle invasive bladder cancer: a health technology assessment (assesses BLC and NBI)	Ontario Health HTA	Completed
Australia	MSAC (Medical Services Advisory Committee)	Health Technology Assessment	Blue-light cystoscopy with hexaminolevulinate as an adjunct to standard white light cystoscopy, for the diagnosis, treatment and management of non-muscle invasive bladder cancer (NMIBC)	MSAC HTA	Completed
France	(HAS) Haute Authorite de Sante	Reimbursement renewal decision (Dec 2015)	Hexvix compared to white light cystoscopy alone in the management of malignant bladder tissue in patients with aa history or strong suspicion of bladder cancer. NB The original and subsequent reviews are not published in English	HAS - Hexvix - English Summary	Completed

1.6 State Danish or international clinical guidelines on use of the technology.

Clinical guidelines for NMIBC consistently state there is a need to improve the detection, diagnosis, and quality (completeness) of surgery, TURBT, to positively influence the long-term clinical results (benefit) and minimize the risks and side effects of surgical resection and post-operative management in care of NMIBC.

Europe

The European Association of Urology (EAU) clinical guidelines for the diagnosis and treatment of bladder cancer (2023) [7] includes the following:

1. Diagnosis: All patients with suspected bladder cancer should undergo a cystoscopy and biopsy to confirm the diagnosis. Imaging studies, such as CT scans or MRI, may also be used to help stage the cancer. The use of urine cytology, a test that examines the urine for cancer cells, in certain circumstances, is recommended.

2. Staging: Bladder cancer is staged based on how deeply it has invaded the bladder wall and whether it has spread to nearby lymph nodes or other organs. Staging is important for determining treatment options and predicting outcomes. The guideline recommends the use of imaging, such as CT scans or MRI, to stage the cancer.

3. Treatment: Treatment options for bladder cancer depend on the stage and grade of the cancer, as well as the patient's overall health. The guideline recommends the following treatments:
    - Non-muscle-invasive bladder cancer (NMIBC): For low-risk NMIBC, the guideline recommends transurethral resection of the bladder tumour (TURBT) followed by intravesical therapy with a chemotherapy drug or immunotherapy drug. For intermediate- or high-risk NMIBC, the guideline recommends a more aggressive approach, such as repeat TURBT and intravesical therapy, or radical cystectomy (removal of the bladder).
    - Muscle-invasive bladder cancer (MIBC): The guideline recommends radical cystectomy as the standard treatment for MIBC. In certain cases, chemotherapy or radiation therapy may be used in combination with surgery.
    - Metastatic bladder cancer: For patients with metastatic bladder cancer, the guideline recommends chemotherapy as the standard treatment. Immunotherapy may also be used in certain cases.

4. Follow-up: Patients with bladder cancer should undergo regular follow-up exams to monitor for recurrence or progression of the cancer. The EAU guideline recommends follow-up cystoscopy and imaging studies, as well as urine cytology, at regular intervals based on the stage and grade of the cancer.

The EAU guidelines include a meta-analysis of 17 RCT and non-RCTs for PDD and NBI guided TURBT, [7]

"A systematic review and meta-analysis by Russo et al., (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy [200], while another one (including 5,217 patients) showed improved RFS with either enhancement technique [201*] (LE: 1a). Conversely, a systematic review and network meta-analysis that took into account the use of single postoperative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURBT (with or without single instillation) <u>but not</u> with NBI-guided surgery [202*] (LE: 1a)."* [7].

**The references in the citate ref. 200 = ref. 7, ref. 201 = ref. 42 and ref. 202 = ref. 43*

Denmark

The Danish guidelines for bladder cancer are developed by the Danish Bladder Cancer Group, which is a part of the Danish Urological Society. The guidelines provide recommendations for the diagnosis, treatment, and follow-up of patients with bladder cancer and includes the following:

1. Diagnosis: Bladder cancer is typically diagnosed through cystoscopy and urinary cytology. Imaging studies like CT scans or MRI may also be used to evaluate the extent of the disease [19].
2. Staging: Bladder cancer is staged using the TNM system, which considers the size and location of the tumour, the involvement of lymph nodes, and the presence of distant metastases [19].
3. Treatment: Treatment options for bladder cancer depend on the stage of the disease. For non-muscle invasive bladder cancer (NMIBC), transurethral resection of the bladder tumour (TURBT) is the standard treatment [35]. Additional treatments like intravesical chemotherapy or immunotherapy may be used to prevent recurrence. For muscle invasive bladder cancer (MIBC), radical cystectomy (removal of the bladder) is the standard treatment. In some cases, chemotherapy or radiation therapy may be used before or after surgery [36].
4. Follow-up: Patients with bladder cancer should be monitored closely after treatment to detect any recurrence or progression of the disease. Follow-up may involve cystoscopy, urinary cytology, imaging studies, and other tests [19,36-38].

5. Cystoscopy, TUR-B and Cytology [19]
   Tumour is described in terms of: [B]
   a. Number
   b. Size
   c. Characteristics (papillary, solid, ulcerating, or necrotic).

Fluorescence-guided cystoscopy (PDD), or BLC, and Narrow Band Imaging (NBI) detect more CIS changes and provide a more complete tumour resection compared to white light. Indikations for use of PDD or NBI: [B]

"Indikationer for anvendelse af PDD eller NBI: (B)
a. Førstegangs blæretumor mhp komplet resektion og som alternativ til selected site biopsier mhp påvisning af CIS
b. Første kontrol efter BCG pga. CIS
c. Urotelceller suspekt for høj malignitetsgrad (Paris Kategori IV) eller urotelceller med høj malignitetsgrad (Paris Kategori V) celler i urinen ved normale fund ved cystoskopi og CT-urografi" [19]

The Danish guidelines are broadly like EAU guidelines with some notable difference in the recommendation of PDD/BLC and NBI. Unlike the EAU and other international NMIBC guidelines, the Danish guidelines equate recommendations for BLC with NBI, and do not distinguish between the differences in strength of evidence or differences in diagnostic performance. The specific value of BLC when ensuring sufficient resection margins of flat e.g., CIS lesions, or when there is multi focal small tumors noted in many studies, is not being considered in the Danish guidelines, but is noted in many international guidelines.

Differences between evidence of clinical outcomes of BLC vs NBI in 2023 EAU guidelines
The EAU guidelines recommendations do indicate differences in the evidence regarding the two visual enhancement technologies BLC and NBI. In comparison to BLC, the studies on NBI have greater uncertainties in the RCT design, robustness of results, limited follow-up, limited data on sensitivity for detection of CIS and outcomes, minimal data on recurrence beyond 1 year, no long-term data on progression, and no specific strong recommendation regarding e.g., use for targeted biopsies.

From the 2023 EAU guidelines on BLC, chapter 5.12.1.2 Impact on bladder cancer recurrence:
"The beneficial effect of ALA or HAL fluorescence cystoscopy on recurrence rate in patients with TURBT was evaluated.

- A systematic review and analysis of 14 RCTs including 2,906 patients, 6 using 5-ALA and 9 HAL, demonstrated a decreased risk of BC recurrence in the short and long term. There were, however, no differences in progression and mortality rates. The analysis demonstrated inconsistency between trials and potential susceptibility to performance and publication bias [44] (LE: 1a)."
- "A recent systematic review and meta-analysis of 12 RCTs (n = 2,288) revealed lower risk of recurrence and improved time to recurrence (at least in the first 2 years and possibly up to 5 years) with PDD [2] (LE: 1a), the most recent Cochrane systematic review and meta-analysis of 16 RCTs (n = 4,325) demonstrated that PDD-assisted TURBT may prolong not only recurrence over time but also risk of progression, albeit supported only by low certainty evidence [13]."
- "Carcinoma in situ can present as a velvet-like, reddish area, indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from suspicious urothelium should be taken [7]. If equipment is available, photodynamic diagnosis is a useful tool to target the biopsy in case of suspicious urothelium."

From the 2023 EAU guidelines, chapter 5.12.2 Narrow-band imaging (NBI):
"Improved cancer detection has been demonstrated by NBI flexible cystoscopy and NBI-guided biopsies and resection (LE: 3b). Two RCTs assessed the reduction of recurrence rates if NBI is used during TURBT. Although the overall results were negative, a benefit after 3 and 12 months was observed for low-risk tumours (pTa LG, < 30 mm, no CIS). A systematic review and meta-analysis by Russo et al (17 RCTs and non-RCTs) demonstrated improved detection (diagnostic accuracy) of bladder tumours with either PDD or NBI over WL cystoscopy, while another one (including 5,217 patients) showed improved RFS with either enhancement technique (LE: 1a) [45]. Conversely, a systematic review and network meta-analysis that considered the use of single post-operative instillation of chemotherapy, concluded that there was a lower likelihood of recurrence at one year only following PDD-guided TURBT (with or without single instillation) but not with NBI-guided surgery (LE: 1a)."

1.7 Describe the best existing, widely implemented alternative(s) to the technology.

The most widely implemented alternative is transurethral resection of the bladder tumour (TURBT) with an endoscope using white light (WLC), noting that enhanced cystoscopy techniques are recommended to use, if available.

In Denmark, WLC is mostly used in conjunction with narrow-band imaging (NBI), which only can be used with equipment from one manufacturer. In contrast to the evidence on BLC, the long-term impact of the use of NBI has not been robustly evaluated for e.g., risk of tumour progression.

2 Clinical outcome and safety

2.1 Briefly describe the most significant clinical outcomes from the health technology compared with the alternative.

BLC has been evaluated compared with WLC in 8 randomized clinical sponsor trials, including 2200 NMIBC patients, numerous independent controlled trials, and several long-term RWE registries of up to 10-years. In terms of clinical outcome, compared to WLC alone BLC improves the sensitivity of tumour detection,

improves the ability to visualize tumours margins more clearly & enables the surgeon to make a more complete resection thus reducing the risk of residual tumours and tumour recurrence. In addition, BLC targeted biopsies allow for a greater proportion of 'hits' from suspect lesions which facilitate a more correct staging and risk stratification during the first TURBT. Post operative management is risk based e.g., using the EORTC or EAU risk tables.

The quality of TURBT is increasingly considered of importance to the oncological outcome, and a number of initiatives have been emphasized to improve the quality, including the use of BLC, e.g., *Getting It Right First Time (GIRFT), and* Mariappan P et al [45]. Consequently, the implementation of BLC can result in a change and improved staging and risk classification, which allows for a more optimal risk-based post-operative follow-up, and treatment strategy which can reduce the risk of under staging and under treatment, reduce the total number of surgical resection procedures for recurrence (re-TURBT) over time, prolong the time to resection of recurrence, and ultimately may impact the time to progression of disease [47].

The majority of trials evaluating the outcomes of BLC focus on differences in detection rates for various tumours as primary outcome, with follow-up of between 3 months up to 1-3 years. The sponsor RCTs provide the basis of the SmPC and are of high, regulatory grade quality. However, since approval in 2005 there have been numerous independent trails conducted to evaluate the benefits of BLC. The outcomes of such trials are represented in the included more recent meta-analyses e.g. Cochrane in 2021 including 16 RCTs in 4.325 patients.

There is also substantial real-world evidence (RWE) available on the use of BLC in clinical practice, in a wide variety of patients, from different countries, regions. The Cysview BLC registry in more than 2200 NMIBC patients, which was initiated 1997 in the US, and from research collaborations with academic institutions on two Nordic registries. Follow-up 2- and 5-years data from more than 8000 NMIBC patients in the Danish National population registry was recently presented at NUF, Helsinki 2021 [48]. The RWE on BLC brings additional validity to the clinical trial results regarding the clinical outcomes in a broader population.

BLC has not been compared directly to NBI in robust multi-centre clinical studies, however Photocure has conducted a Network Meta-Analysis comparing BLC with NBI. [redacted]

Cochrane has conducted meta-analysis for both BLC vs WLC, and NBI vs WLC. There were some differences between BLC and NBI on long-term outcomes between the Cochrane meta-analysis between the BLC and NBI Cochrane review, reflecting the differences in the available evidence.

When comparing the two Cochrane reviews for BLC vs NBI, the more extensive data with BLC is stronger in the high-risk, CIS populations and on long-term oncological outcomes (recurrence and progression).

2.2 Briefly describe the most important risks associated with use of the health technology compared with the alternative.

False positive detection of bladder cancer tumours may be a cause for concern because of consequent unnecessary biopsy of healthy bladder tissue. Tumour detection with WLC or BLC carries a risk of false positives. It is thought that false positives are attributable to inflammation following recent TURBT or

during the first 2-3 months after BCG instillations. In studies where false-positive rates of the technologies have been compared directly, many studies have failed to find a significant difference in false-positive detection rates between WLC and BLC [11,30,49], however, other studies have found BLC to produce statistically significantly higher false positive rates [6,50,20]. A somewhat higher false-positive rate with enhanced visualisation techniques is considered acceptable in the context of the higher likelihood of suitable treatment given superiority of detection (high sensitivity), little information on false positive detection has been found for NBI or Chroma.

2.3 State ongoing and/or completed clinical studies of the technology in the table.

BLC compared to WLC:

Table 3. Summary of sponsor BLC studies forming basis of SmPC

Reference (Study ID)	Study design	n	FU	Study objectives	Key inclusion criteria	Key endpoints	Key results	Summary
Jichlinski, 2003 (PC B201/00) [51]	Prospective, comparative within patient, single-arm, open label, multicenter study	52	3mo	Sensitivity and specificity of HAL BLC in comparison to WLC	Suspected superficial bladder cancer	Sensitivity and specificity of BLC in patients with superficial bladder cancer	- Sensitivity was 96% for BLC and 73% for WLC on a patient level. - BLC detected CIS in all cases except for one	BLC showed improved sensitivity for detection of bladder tumors, in particular CIS when compared to WLC alone.
Schmidbauer, 2004 (PC B301/01) [52]	Prospective, comparative within patient, single-arm, open label, multicenter, phase III study	286	NA	Detection of CIS comparing BLC and WLC with a 7 days safety follow-up	Suspected high risk bladder cancer	Proportion of patients with additional CIS detected by BLC compared to WLC	- BLC identified 28% more patients with CIS than WLC. - Lesion detection rates for dysplasia, CIS and Ta tumors were significantly higher with BLC	BLC was superior in detecting CIS compared with standard WLC.
Jocham, 2005 (PC B303/01) [53]	Prospective, comparative within patient, single-arm, open label, multicenter, phase III study	146	NA	To determine if improved tumor detection by BLC could lead to improved treatment in patients with bladder cancer	Suspected or known bladder cancer	Treatment plan comparison	- BLC improved overall tumor detection (96% vs. 77%) - 17% of patients received more appropriate treatment following BLC	BLC was more effective for detection of bladder tumors and lesions compared with WLC which led to an improved treatment in a significant number of patients.

Table 4. Outcomes (detection rates) from sponsor BLC reg studies

Study ID	Sample size	Additional Ta/T1 using BLC	Additional CIS using BLC	Publication
PHO 201	52		58.3%	Jichlinski 2003 J Urol [51]
PHO 301	279	26.6%	21.3%	Schmidbauer J 2004 J Urol [52]
PHO 302	298	28.9%	17%	Fradet 2007 J Urol [54]
PHO 303	162	18.7%	13.8%	Jocham D 2005 J Urol [53]
PHO 304	112	42%		Herrman 2011 BJU Int [55]
PHO 305	814	16.4%	41%	Stenzl 2010 J Urol [11]
RCT 308	304	35%	31%	Daneshmand 2018 J Urol [56]
Total	**1,628**	**27.9% (16-42%)**	**30.4% (14-58%)**	

Table 5. Outcomes (recurrence rates) from sponsor BLC reg studies

Study ID	Sample Size	Follow-up	Recurrence BLC	Recurrence WLC	Difference	Publication
PHO 304	112	12 months	30.5%	47.3%	16.8%	Hermann 2011 BJU [55]
PHO 305	551	9 months	47%	56%	9%	Stenzl 2010 J Urol [11]
PHO 305E	551	54 months	31.8%	38%	6.2%	Grossmann 2012 J Urol [12]
Total	**663**		**36.4%**	**47.1%**	**10.7%**	

Table 6. Diagnostic accuracy of BLC for various tumours based on randomized controlled trials.

	BLC sensitivity %, Median (range)	WLC sensitivity %, Median (range)	No. of patients (biopsies)	No. of studies
Low risk				
Patient based detection	92 (20-95)	95 (8-100)	266	3
Biopsy based detection	98 (88-100)	88 (74-100)	1206 (5777)	7
Intermediate-high risk, incl CIS				
Patient based detection	89 (6-100)	56 (0-100)	563	6
Biopsy based detection	99 (54-100)	67 (0-100)	1756 (7506)	13
CIS				
Patient based detection	83 (41-100)	32 (0-83)	563	6
Biopsy based detection	86 (54-100)	50 (0-68)	1756 (7506)	13

Summary of BLC studies enrolling 2949 patients, presented at EAU congress 2023.

Table 7. Summary table of systematic reviews and meta-analysis

Reference	Design of included studies	Studies included	n	Aim	Inclusion criteria	Primary and secondary endpoints	Results	Summary
Maisch, 2021 [13]	RCTs	16	4,325	To assess the effects of BL-TURBT compared to WL-TURBT in the treatment of NMIBC.	- RCTs comparing WL-TURBT versus BL-TURBT - BLC with 5-ALA or HAL - Patients with high level of suspicion for primary or recurrent bladder cancer.	- Time to disease recurrence - Time to disease progression - Serious surgical complications - Time to death from bladder cancer - Any adverse events - Non-serious surgical complications.	- BL-TURBT may reduce risk of recurrence over time by 34% - The impact of BL-TURBT was comparable between primary vs. recurrent NMIBC and solitary vs. multifocal disease.	BL-TURBT has a favorable impact on the risk of disease recurrence.
Motlagh, 2021 [43]	RCTs	22	4,519	To assess whether SIIC still adds value to bladder tumor management in combination with BLC.	- BL-TURBT ± SIIC - NIB-TURBT ± SIIC - WL-TURBT ± SIIC - Comparator: WLC alone	- 12-months recurrence rate	- BLC with and without were associated with lower recurrence rates at 12 months compared with WLC. - The addition of SIIC was superior compared to BLC alone.	Compared to WLC, BL-TURBT with and without SIIC reduced recurrence rates.
Ontario Health, 2021 [57]	RCTs and cost-related analyses	8 RCTs 5 analyses	2,402	To evaluate effectiveness, safety and cost-effectiveness of first BL-TURBT and NBI-TURBT.	- First BL-TURBT or NBI-TURBT for suspected NMIBC.	- Recurrence rate at 3, 6, 9, 12 months and up to 10 years - Recurrence-free survival - Overall survival - Tumor progression rate - Diagnostic outcomes - Adverse events - Costs - Health outcomes - Incremental costs - Incremental effectiveness - Incremental cost-effectiveness ratios	- BL-TURBT reduced the risk for recurrence. - Progression-free survival was significantly better in patients who received BL-TURBT. - 3 studies found that BLC is more cost-effective in comparison with WLC.	BL-TURBT likely reduces recurrence at 12 months, increases progression-free survival and likely is cost-effective compared to WL-TURBT.
Veeratterapillay, 2021 [2]	RCTs	12	2.288	To assess the effects of BL-TURBT compared to WL-TURBT on recurrence rates in NMIBC	- BL-TURBT with 5-ALA or HAL - Reported recurrence-free survival rates for at least 12 months. - Patients with suspected new NMIBC or recurrent NMIBC with a recurrence-free interval of at least 3 months.	- Recurrence rates at 12 and 24 months - Adverse events	- Recurrence rate at 12 and 24 months showed a reduction after BL-TURBT - Recurrence-free survival was increased after BL-TurbT	BL-TURBT is likely to increase recurrence-free survival and reduce recurrence rates for at least 2 years in comparison with WL-TURBT.
Sun, 2021 [58]	RCTs	18	3,618	To assess the effects of BLC with WLC on the rate of residual Ta, T1, and CIS, RFS and PFS.	- Suspected or proven NMIBC - BLC with 5-ALA or HAL - RCTs without intravesical therapy	- Residual tumor rate - Recurrence-free survival - Progression-free survival - Adverse events	- Residual tumor rates for Ta, T1 and CIS were significantly lower in the BL groups. - Recurrence-free survival at 12 and 24 months was significantly prolonged.	BLC reduced the rate of residual tumor and prolonged recurrence-free survival compared with WLC.
Chen, 2019 [59]	Observa-tional studies	26	3,979	To assess the diagnostic performance of BL-TURBT and NBI-TURBT compared with WL-TURBT.	- Primary and recurrent NMIBC - WLC was used as reference standard. - NMIBC was confirmed by histopathology.	- SSY - SPY - DOR - AUROC	- NBI showed significant superiority compared with WLC. - DOR and AUROC values of HAL, 5-ALA and NBI indicated excellent diagnostic performance.	For diagnostic performance BLC and NBI were superior over conventional WLC.

Table 7 Summery table of systematic reviews and meta-analysis - continued

Reference	Design of included studies	Studies included	n	Aim	Inclusion criteria	Primary and secondary endpoints	Results	Summary
Konecki 2019 [60]	RCTs and diagnostic accuracy studies	9 RCTs 21 single-arm studies	4,105	To assess the effect of BLC using HAL on diagnostic and therapeutic outcomes.	-Known or suspected NMIBC -Histopathology of lesion as reference test -Within patient comparison	-Diagnostic accuracy: Sensitivity, specificity and additional detection rate -Clinical efficacy: Recurrence rate	- BLC identified additional tumors in 25% of all patients and in 35% of CIS patients. - Specificity was comparable between BLC and WLC, but for CIS it was higher in the BL group. - Rates for recurrence-free survival were 6-14% lower in the BL groups at 3 months follow-up and 4-27% lower at 12 months.	HAL-BLC in addition to WLC detected significantly more tumors compared to WLC alone. BLC led to significantly reduced recurrence rates in a short-term follow-up period.
Di Stasi, 2015 [61]	RCTs, within-patient comparisons, observational comparative controlled trial.	16	3,895	To compare detection and recurrence rates after BL-TURBT and WL-TURBT	- Patients treated for NMIBC. - BL-TURBT using HAL in comparison with WL-TURBT.	- Tumor detection at a patient and lesion level, and discrimination between Ta, T1 and CIS - Recurrence rates at 3,6 and 12 months - False positive detection.	- HAL-BLC increased overall detection rates with being particularly significant in CIS (proportion difference 15.7%) - In 15% of patients at least 1 additional tumor was seen with BLC.	HAL-BLC increased tumor detection, in particular CIS.
Lee, 2015 [62]	RCTs	15	2,775	To assess the therapeutic outcome of BL- or NBI-TURBT in patients with NMIBC	- Measurement of clinical efficacy of HAL- or 5-ALA-TURBT or NBI-TURBT in comparison with WL-TURBT - Known or suspected NMIBC.	- Recurrence rate - Progression rate.	- HAL-, 5-ALA-BLC and NBI had significantly lower recurrence rates compared with WL (OR 0.58, 0.34 and 0.47, respectively, p<0.001) - 5-ALA-TURBT demonstrated lower recurrence rates than HAL-TURBT - Progression rates did not differ from that of WL-TURBT.	Recurrence rates can decrease using BLC- or NBI-TURBT instead of WL-TURBT.
Yuan, 2013 [63]	RCTs	12	2,258	To assess the therapeutic outcome of BL-TURBT in NMIBC.	- Known or suspected NMIBC - BL-TURBT using HAL and 5-ALA in comparison with WL-TURBT.	- Recurrence rate - Time to first recurrence - Recurrence-free survival rate at 1 and 2 years - Progression rate.	- The recurrence rate was significantly lower in the BL group (p<0.00001) - Time to first recurrence was significantly delayed by 7.39 weeks in the BL group (p<0.0001) - The recurrence-free survival rate was significantly longer in the BL group at 1 and 2 years (p<0.00001 and p=0.0004).	BL-TURBT was effective to delay recurrence, however it did not lead to significant lower progression rates.
Burger, 2013 [9]	RCTs and within-patient comparisons	9	2,212	Assessment of available clinical data for BLC using HAL on the detection of Ta/T1 tumors, CIS and recurrence.	- Primary and recurrent NMIBC - Only HAL-guided BLC - Prospectively enrolling patients.	- Detection of Ta/T1 lesions and CIS (within-patient comparative) - Recurrence rate up to 12 months (two-arm comparative).	- 24.9% patients with at least one additional Ta/T1 tumor were identified only by BLC. - 40.8% of CIS lesions were identified only by BLC.	HAL-guided BLC significantly improves detection rates leading to a reduction of recurrence in short- to mid-term follow-up.

Table 8. Real World Evidence

Reference	n	Patient cohort	Key endpoints	Key results	Summary
Andersson, 2021 [64]	70	- Patients with positive or suspicious urine cytology findings despite normal WLFC results and normal findings on computerized tomography urography.	- Detection rate - Patient experience.	- 48% of lesions were only detected using BLFC. - The majority of lesions detected with BLFC were CIS. - BLFC was well tolerated by patients.	BLFC in the outpatient setting helped to solve unclear cases of positive or suspicious urine cytology with negative WLFC findings.
Daneshmand, 2018 [56]	533	- Inclusion criteria according to Blue Light Cystoscopy with Cysview Registry.	- Sensitivity and specificity of BLC, WLC and combined BLC/WLC for detection - Number of patients with change in AUA risk category.	- Sensitivity of WLC, BLC and the combination of both for detection was 76%, 91% and 98% respectively. - BLC in combination with WLC increased detection rates for CIS and papillary lesions - BLC detected lesions that were unseen with WLC in 25% of patients.	BLC increased detection rates of papillary lesions and CIS compared with WLC alone.
Stout, 2022 [65]	1,336	- Inclusion criteria according to Blue Light Cystocopy with Cysview Registry - Rigid cystoscopies.	- Perceived clinical utility of BLC. - Changes in perceived utility over time.	- Urologists perceived BLC to be of some utility (38.1%), of moderate assistance (25.4%), to be essential (19%) and of no real utility (17.5%) - Significantly more urologists perceived BLC to be essential in 2019 compared with 2014 (28.3% vs. 11.5%, p=0.006).	BLC was of utility for the majority of urologists. Perceived utility has been increasing over time. Urologists who identify more lesions with BLC than WLC perceive BLC to me more useful.
Chappidi, 2022 [66]	282	- Inclusion criteria according to Blue Light Cystoscopy with Cysview Registry - Patients who received BCG - Treatments within the past 12 months prior to BLC.	- Proportion of cystoscopies with HG recurrence detected only with BLC. - Percentage of cystoscopies with recurrence that were missed with WLC alone. - Worse disease stage detected due to BLC. - False-positive detection rates.	- 5.7 % (16/282) of cystoscopies had recurrence only identified with BLC. - 12.6% (16/127) of the total recurrences would not have detected with WLC alone. - 6.0% (17/282) of all cystoscopies had a higher stage detected with BLC. 16 of these were negative on WLC, of which 14 were CIS. - Lesion-specific WLC and BLC false-positive rates were 58.4% (267/457) and 58.5% (333/569).	BLC helped identify high-grade recurrences after recent BCG that would have been missed with WLC.
Ahmadi, 2022 [10]	55	Patients who had at least 1 WL-negative and BL-positive invasive lesion ≥T1 as highest stage.	Detection rate.	- In 45% of patients BLC detected additional WL-/BL+CIS and/or T1 lesions - BLC helped to identify high risk pathological features leading to radical cystectomy.	BLC improved detection of invasive lesions with the rate of pathological upstaging being significant.
Matulewicz, 2021 [67]	723	- Inclusion criteria according to Blue Light Cystoscopy with Cysview Registry - Primary or recurrent Tis, Ta or T1 NMIBC and smoking status was known.	Association between smoking status and NMIBC recurrence.	- There was a NMIBC recurrence in 259 of 723 patients (35.8%) - No significant association with recurrence could be observed for smoking status.	There was no significant association between smoking status and recurrence in patients with predominantly high-risk recurrent NMIBC.

2.4 State and describe any important data on clinical outcome and safety which has not yet been published.

A network meta-analysis comparing BLC with NBI has been conducted which has not yet been published.

[redacted]

3 Patient perspective

3.1 State and describe data concerning patient experience as regards the choice between the technology and comparator(s).

From DaBlaCa kliniske retningslinjer:

"Patientværdier og – præferencer En øget detektionsrate ved PDD frem for almindeligt hvidt lys skal opvejes i forhold til det øgede tidsforbrug for patienten. Dette spiller ikke samme rolle ved NBI, idet det ikke kræver tidligere fremmøde eller præoperativ installation for patienterne. Opgørelser af patienttilfredshed tyder dog på, at patienterne gerne påtager sig at bruge mere tid og de minimale ekstra gener ved installationen forud for PDD for at opnå en større sikkerhed for korrekt diagnose og behandling som man formoder PDD giver i forhold til almindeligt hvidt lys"

"Patient values and preferences an increased detection rate with PDD rather than ordinary white light must be balanced against the increased time consumption for the patient. This does not play the same role with NBI, as it does not require previous attendance or preoperative instillation for the patients. Calculations of patient satisfaction indicate, however, that patients are happy to undertake to spend more time and the minimal extra inconvenience of the instillation prior to PDD to achieve a greater certainty of correct diagnosis and treatment, which one presumes PDD provides compared to ordinary white light" [19].

3.2 State and describe any issues regarding accessibility and inequality for specific patient groups in use of the health technology.

More recently, many Danish hospitals have migrated from BLC to the use of narrow-band imaging (NBI). This has restricted patient access to BLC in many parts of Denmark.

4 Organisation

4.1 State and describe the organisational conditions in the health care sectors which are likely to be changed or influenced if the Danish Health Technology Council recommends use* of the health technology.

While the use of blue light cystoscopy can be a valuable tool for diagnosing and treating bladder cancer, there are potential issues related to task shifting and function creep that may arise from its use. One

potential issue is compatibility of IT and hardware. Blue light cystoscopy requires specialized equipment and, in some hospitals, or clinics, this may not be compatible with existing IT and hardware systems currently in use. This could lead to additional costs and challenges integrating the new technology into existing systems.

Physical framework issues may also arise. The equipment required for this procedure may require specific physical setups or modifications to existing facilities, such as additional space or special lighting conditions. This could lead to additional costs and logistical challenges in implementing the new technology.

In summary, while the use of blue light cystoscopy can be a valuable tool for diagnosing and treating bladder cancer, there are potential issues related to task shifting and function creep that may arise from its use. These issues may include compatibility issues with existing systems, increased or changed training requirements, physical framework issues, and the need for specialized staff engagement.

4.2 Describe current experience with the health technology and its use.

In Denmark, BLC was systematically used as standard procedure for the detection and treatment of bladder cancer from 2007 in all regions until 2018, when NBI began to become implemented in some regions. In 2019, according to the Danish guidelines, both BLC and NBI were recommended for patients with suspected or confirmed bladder cancer who are undergoing surgery to remove the cancerous tissue [19,35.38].

Several clinical trials conducted on the use of BLC for bladder cancer detection and treatment included sites in Denmark. These trials have shown that BLC is highly effective for identifying cancerous tissue and reducing the recurrence rate of bladder cancer. Overall, BLC is considered an important diagnostic tool in the detection and treatment of bladder cancer in Denmark.

Table 9 Sales in number of Packs of Hexvix incl. parallel import

Years	2020	2021	2022	1Q 2023
Region Hovedstaden	855	930	521	111
Region Sjælland	496	427	74	0
Region Syddanmark	1,032	343	467	49
Region Midtjylland	21	0	0	0
Region Nordjylland	261	151	0	0
Total in Denmark	2,665	1.851	1.062	160

The number of packs is equal with number of procedures done with BLC. The table show that patients currently only have access to BLC in two regions (data from 2023).

The number of procedures done with BLC have decreased over the last years from 4,400 in 2017 to approximately 1,000 yearly in 2022/23.

5 Budget and Finances

5.1 State and describe a list of published peer-reviewed economic analyses of the technology.

Table 10 Published peer-reviewed economic analyses of the technology

Author	Title	Method design	Effect measure	Comparator
Rouprêt et al., 2018 [Paper in French] [68]	Cost-effectiveness of transurethral resection of the bladder with blue light in patients with non-muscle invasive bladder cancer in France.	Cost-utility model.	QALY	WLC
Gakis et al., 2019 [Paper in German] [69]	Cost-effectiveness analysis of blue light cystoscopy with hexylaminolevulinate in transurethral resection of the bladder.	Cost-effectiveness analysis.	QALY, Life expectance, Cost	WLC
Heer et al., 2022 [70]	A Randomized Trial of PHOTOdynamic Surgery in Non-Muscle-Invasive Bladder Cancer.	Cost-effectiveness analysis.	Cost/patient, QALY	WLC
Malmström et al., 2009 [71]	Fluorescence-guided transurethral resection of bladder cancer using hexaminolevulinate: analysis of health economic impact in Sweden.	Budget impact	Impact on: # cystoscopies, TURBTs & cystectomies	WLC
Bennison et al., 2014 [72]	Cost-effectiveness analysis of hexaminolevulinate (Hexvix) guided cystoscopy in Non-Muscle Invasive bladder Cancer patients (NMIBC) in Italy.	Cost effectiveness	QALY, disease recurrence, progression, # TURBTs	WLC
Sievert et al., 2009 [73]	Hexvix fluorescence cystoscopy for non-invasive bladder cancer management: An economic model of the impact on German healthcare cost.	Budget impact	Costs, # TURBTTs, utility score	WLC
Klassen et al., 2017 [74]	Contemporary cost-consequence analysis of blue light cystoscopy with hexaminolevulinate in non muscle invasive bladder cancer.	Cost effectiveness	Cost, resource use	WLC
Ontario Health [57]	Enhanced Visualisation Methods for First Transurethral Resection of Bladder Tumour in Suspected Non-muscle-invasive Bladder Cancer: A Health Technology Assessment.	Cost effectiveness Budget impact	QALY, Budget impact	NBI & WLC

Note: a number of reviews have been undertaken which have been excluded from the above table. Studies included above are limited to the use of BLC in the operating room (OR) setting.

5.2 Describe the overall results from the completed outline of costs.

The costs calculation depends on the purpose of the procedure (diagnosing or treatment).
It is anticipated costs in the primary sector, municipalities and patient's costs are independent of the procedure BLC or NBI. The cost-driving sector is the hospitals, and in the temporary cost-analysis we have focused on the costs in the hospital sector.

Table 11 The cost calculation for the procedure cystoscopy for suspicious bladder cancer

Hospitalsperspektiv

Er der (meningsfulde) omkostningsforskelle i denne sektor?	**Ja**
Omkostninger per patient til sundhedsteknologien	**12.081 kr.**
Omkostninger per patient til alternativet	**6.576 kr.**
Difference	**5.505 kr.**

SUNDHEDSTEKNOLOGI

Procedure Cystoscopy Diagnostic	Antal	DRG kode	DRG 2023	Tid (timer)	Sum	Kildehenvisning
Samme dagspakke: cystoskopisk og CT-urografi undersøgelser	1	11SP01	6.576	1	6.576 kr.	DaBlaCa [42]; DRG 2023,
Installation af lægemiddel i blæren	1	11PR04	1.233	1	1.233 kr.	DaBlaCa [42]; DRG 2023
					- kr.	
					- kr.	
...	...	...	...	...	...	
					7.809 kr.	

Materialer	Antal	Enhed	Enhedspris	Sum	Kildehenvisning
Apotekets Indkøbspris (AIP), pakn. med laveste Apotekets Indkøbspris	1	AIP kr.	4.272	4.272 kr.	Medicinpriser.dk 1.-14. maj 2023
Materiale 2	0			- kr.	
Materiale 3	0			- kr.	
Materiale 4	0			- kr.	
...	...	...	...	...	
Total				*4.272 kr.*	

ALTERNATIV

Personale	Antal	Enhed	Timeløn	Tid (timer)	Sum	Kildehenvisning
Samme dagspakke: cystoskopisk og CT-urografi undersøgelser	1	11SP01	6.576	1	6.576 kr.	DaBlaCa [42]; DRG 2023,
Installation af lægemiddel i blæren						
…	…	…	…	…	…	
Total					*6.576 kr.*	

Materialer	Antal	Enhed	Enhedspris	Sum	Kildehenvisning
Materiale 1					
Materiale 2					
Materiale 3					
Materiale 4					
…					
Total					

Table 12 The cost calculation for TURBT

Hospitalsperspektiv

Er der (meningsfulde) omkostningsforskelle i denne sektor?	**Ja**
Omkostninger per patient til sundhedsteknologien	**25.890 kr.**
Omkostninger per patient til alternativet	**20.385 kr.**
Difference	**5.505 kr.**

SUNDHEDSTEKNOLOGI

Procedure Transuretheral resection of bladder cancer (TURBT)	Antal	DRG kode	DRG 2023	Tid (timer)	Sum	Kildehenvisning
Operation på blære, med cytostaticum eller blåt lys	1	11MP17	20.385	1	20.385 kr.	DaBlaCa [44]; DRG 2023,
Installation af lægemiddel i blæren	1	11PR04	1.233	1	1.233 kr.	DaBlaCa [44]; DRG 2023
					- kr.	
					- kr.	
…	…	…	…	…	…	
					21.618 kr.	

Materialer	Antal	Enhed	Enhedspris	Sum	Kildehenvisning
Apotekets Indkøbspris (AIP), pakn. med laveste Apotekets Indkøbspris	1	AIP kr.	4.272	4.272 kr.	Medicinpriser.dk 1. -14. maj 2023
Materiale 2	0			- kr.	
Materiale 3	0			- kr.	
Materiale 4	0			- kr.	
…	…	…	…	…	
Total				*4.272 kr.*	

ALTERNATIV

Personale	Antal	Enhed	Timeløn	Tid (timer)	Sum	Kildehenvisning
Operation gennem urinrør på blære, med cytostaticum eller blåt lys	1	11MP17	20.385	1	20.385 kr.	DaBlaCa [42]; DRG 2023,
					- kr.	
…	…	…	…	…	…	
Total					*20.385 kr.*	

Materialer	Antal	Enhed	Enhedspris	Sum	Kildehenvisning
Materiale 1					
Materiale 2					
Materiale 3					
Materiale 4					
…					
Total					

In the calculation above the cost of Hexvix® is the official price for the medicine (AIP) and not the discounted price Amgros pays for the medicine

The main cost driver is the cost of the medicine. The incremental cost for one procedure is approximately 5,500 DKK. As this is mainly made up of the cost of the medicine, the incremental cost is very sensitive to the discount received by Amgros.

To put this into perspective, the additional cost of 5,500DKK for one procedure is significantly less that the DRG for one cystectomy (Cystectomy m. robot m ondartet sygdom 11MP04) 234.681. Bladder cancer patients who have had their bladder removed are likely to incur further additional costs in both the primary sector and the municipal system.

6 Other relevant enclosures

In conclusion, the aim of bladder cancer management is to identify, accurately diagnose and completely resect all bladder tumours. Thus accurate tumour staging is critical for optimized management and for avoiding recurrence and progression of disease. Patients should receive access to the most appropriate techniques in the management of bladder cancer. BLC when used during TURBT compared to WLC alone has been demonstrated to improve detection sensitivity of "difficult to find", high-risk bladder tumours and allows for a more complete resection as well as reduction in residual disease and missed lesions, enabling a more accurate staging and risk stratification-based care, reducing recurrence rates and progression. In contrast, the long-term impact of the use of NBI has not been robustly evaluated for regression.

Although comparative evidence between NBI and BLC is sparse, our recent analysis identified BLC as the most probabilistic effective intervention when visualising bladder cancer during cystoscopy. This is supported by a robust body of evidence of BLC, which is reflected in European bladder cancer guidelines as well as several other international guidelines, recommending the utilisation of enhanced cystoscopy in general, and particularly only BLC if there is suspicious of CIS and need for targeted biopsies.

Today in several regions in Denmark there is not equal access to fluorescence cystoscopy with blue light. Patients across Denmark have equal access to cystoscopy with white light and NBI, but not to BLC. It's considered that access to photodynamic diagnostic fluorescence technology such as BLC will continue to be important. Several new emerging NMIBC treatment options and trends, including targeted personalized therapies (precision medicine), further increase the need for optimized diagnostic performance. New diagnostic technologies in the urologist's armamentarium e.g., higher definition imaging and equipment, biomarkers, omics, liquid biopsy, artificial intelligence, microscopic enhancement technologies such as optical coherence tomography (OCT), optical biopsy, and advancements in radiology and software, virtual cystoscopy, etc) will likely be used and combined in the NMIBC diagnostic algorithm, based on their performance, clinical value, and evidence. Among such diagnostics, BLC is the most validated technology, which has been demonstrated to improve clinical outcomes. Emerging data indicate that fluorescence contrast agents, such as HAL with BLC, can further complement or enhance the diagnostic performance of several such new diagnostic technologies [76]. The trend toward precision diagnostics and medicine is considered critical to improved prognosis and cost effectiveness in NMIBC care.

6.1 State and attach relevant publications on the health technology.

The list of references is attached in the attached reference list.

6.2 State and attach relevant documents on the health technology.

N/A

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