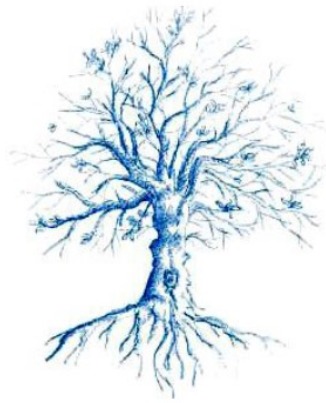




Urothelial cancer surveillance in Lynch syndrome – guidelines and launch

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HNPCC Register

Gastro Unit

Hvidovre Hospital



Urothelial cancer is acknowledged as an HNPCC-related cancer in 1999

- Urothelial cancer is included in the HNPCC tumor spectrum with the Revised Amsterdam II criteria – *VASEN et al., 1999*
- Though no guidelines are established regarding urothelial surveillance, they refer to *SIJMONS et al., 1998*

Clinical Urology: Original Articles

URINARY TRACT CANCER AND HEREDITARY NONPOLYPOSIS COLORECTAL CANCER: RISKS AND SCREENING

R.H. SIJMONS, L.A.L.M. KIEMENEY, J.A. WITJES,



Dutch cohort

1,321 individuals from 50 HNPCC families
Relative Risk of Urothelial cancer was 14.04

Conclusions: As yet nothing is known of the clinical impact of screening for urinary tract cancer in cases of hereditary nonpolyposis colorectal cancer. In a research setting screening by excretory urography of hereditary nonpolyposis colorectal cancer families with a strong history of upper urinary tract cancer should be considered.

SIJMONS et al., 1998

First European guideline for urothelial cancer surveillance introduced in 2007

REVIEW

Guidelines for the (hereditary non-pc

H F A Vasen, G Möslin, A A
I Frayling, W Friedl, F J Hes,
Sinisalo, J R Sampson, A Stor

Table 7 Surveillance protocol in Lynch syndrome and familial clustering of colorectal cancer

Disorder	Lower age limit (years)	Examination	Interval (years)
Lynch syndrome	20–25	Colonoscopy	1–2
	30–35	Gynaecological examination, transvaginal ultrasound, aspiration biopsy	1–2
	30–35	Gastroduodenoscopy*	1–2
	30–35	Abdominal ultrasound, urinalysis and cytology urine†	1–2
Familial clustering of colorectal cancer without evidence of MSI‡	45–50 or 5–10 before age at diagnosis of first CRC in family	Colonoscopy	3–5

CRC, colorectal cancer; MSI, microsatellite instability.

*If gastric cancer runs in the family or in countries with a high incidence of gastric cancer.

†If urinary tract cancer runs in the family.

‡Amsterdam positive families.

VASEN *et al.*, 2007
Mallorca Group



Urine cytology is not an efficient screening tool and surveillance is ceased in Denmark (2008-2010)

[Home](#) > [Familial Cancer](#) > Article

Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer

Published: 04 April 2008

Volume 7, pages 303–307, (2008) [Cite this article](#)

T. Myrhøj, M.-B. Andersen, and I. Bernstein

Danish cohort

977 individuals - 1,868 screenings
2 patients (0.1%) found by screening
(two small non-invasive bladder cancers)

14 patients (1.4%) were false negative
(5 interval cancers)

Sensitivity = 29%

12 (85.7%) were found in Lynch syndrome carriers (92% in *MSH2*)

2010

Surveillance was recommended to cease by letter to all affected Lynch syndrome carriers

Discussion UC is not a proper method of screening for UTC in HNPCC. However, the study can not reveal if screening for UTC in special families ought to be recommended. Consequently, further studies needs to be performed in order to evaluate an appropriate screening programme.

MYRHØJ et al., 2008

Revised European guideline removes urothelial surveillance recommendations in 2012

- Based on the Danish results from Myrhøj and colleagues, **no urothelial surveillance** was recommended in 2012

Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts

Hans F A Vasen,¹ Ignacio Blanco,² Katja Aktan-Collan,³ Angel Alonso,⁵ Stefan Aretz,⁶ Inge Bernstein,⁷ Lucio B. de Souza,⁸ Gabriel Capella,² Chrystelle Colas,¹⁰ Christoph Engel,¹¹ Maurizio Genuardi,¹³ Karl Heinimann,¹⁴ Frederik J Heslop,¹⁵ John A Karagiannis,¹⁶ Fiona Laloo,¹⁷ Annika Lindblom,¹⁸ Pal Møller,²⁰ Torben Myrholm,⁷ Fokko M Nagengast,²¹ Yann Parc,²² Maurizio Ponz de Leon,²³ Laura Renkonen-Sinisalo,²⁴ Julian R Sampson,¹² Astrid Stormorken,²⁰ Rolf H Sijmons,²⁵ Sabine Tejpar,²⁶ Huw J W Thomas,²⁷ Nils Rahner,²⁸ Juul T Wijnen,⁴ Heikki Juhani Järvinen,²⁴ Gabriela Möslin,²⁹ (the Mallorca group)

In view of the lack of evidence for the benefit of surveillance for urinary tract cancer, the Mallorca group does not recommend surveillance for urinary tract cancer in LS outside the setting of a research project.



VASEN et al., 2012
Mallorca Group

New recommendations based on cancer characteristics are published in 2010 and 2015

- Dutch recommendations are defined (*VAN DER POST et al., 2010*) as
 - 1. Ultrasound of the bladder and UUT with urine cytology in every *MSH2* mutation carrier starting at age 40, performed every 1-2 years
- American Urological Association is recommended to add urothelial surveillance in Lynch syndrome (*MORK et al., 2015*) using
 - 1. Urine dipsticks for microscopic hematuria
 - 2. CT scan including a urographic phase when follow-up of CRC is performed
 - 3. Cystoscopy with a retrograde pyelography
- Urine analyses should be the initial analyses (*LINDOR et al., 2006; KOONSTRA et al., 2009*)



...and again in 2021

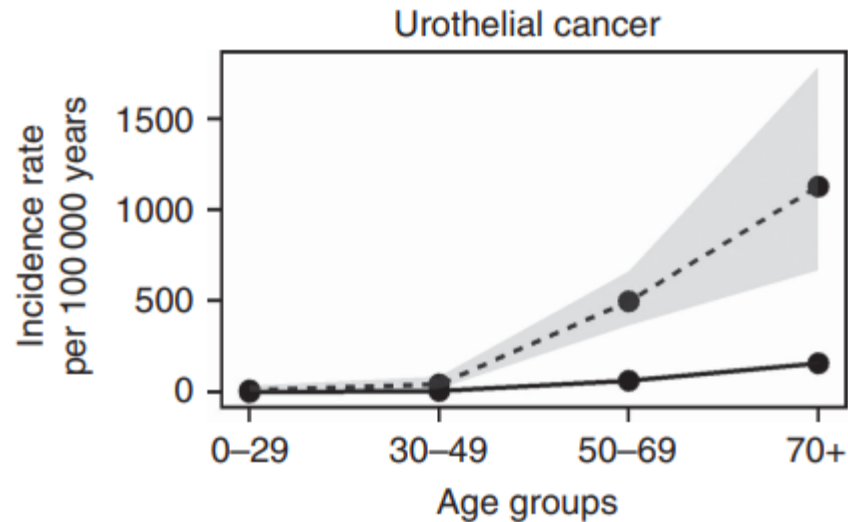
- Lynch syndrome accounts for 20% of all upper urinary tract cancer (*AUDENET et al., 2012*)
- Urothelial cancer ranks third (5%) after colon cancer (63%) and endometrial cancer (9%) within HNPCC (*ROUPRET et al., 2008*)
- Patients diagnosed with LS have a 22-fold higher risk of urothelial cancer (*ROUPRET et al., 2008*)
- LS-associated UC is known to have a female predominance and to occur at a younger age (*JOOST et al., 2015*)
- Development of UC has been shown to be strongly associated with MSH2 variants in up to 73% (*JOOST et al., 2015*)

Urological surveillance in LS should include imaging of the UUT, urine analysis, cytology, and cystoscopy, especially in patients with MSH2 germline variants.

LINDNER et al., 2021

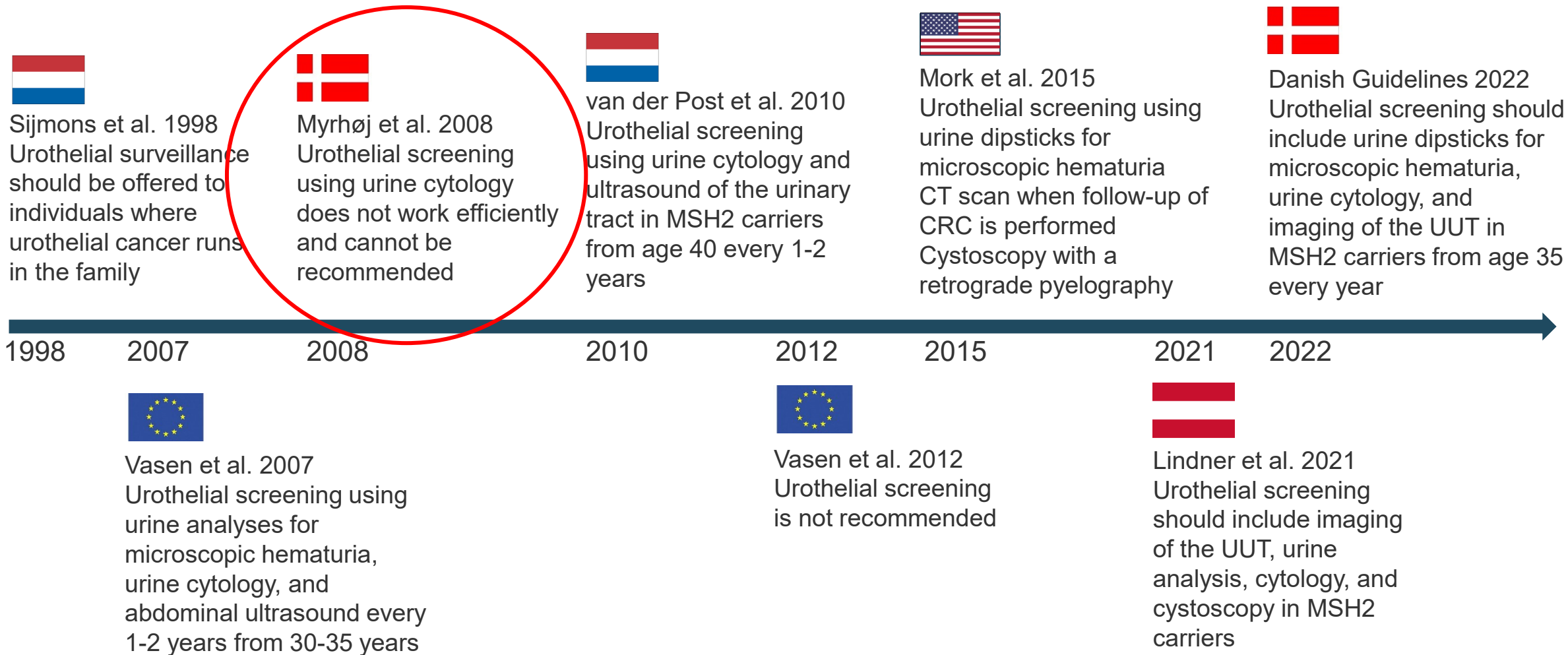
Denmark re-introduces urothelial surveillance in 2022

- **PLSD:** Urothelial (upper and lower tract) cancer are associated with high mortality (27-29%) compared to colon and gynecological cancer (8-15%) (*DOMINGUEZ-VALENTIN et al., 2023*)
- 75 urothelial cancer diagnoses among 60 Danish Lynch syndrome families (*THERKILDSEN et al., 2017*)



Danish Guidelines July 2022

1. Urologic screening in MSH2 families and where urothelial cancer runs in the families
2. Screening using urine analyses for microscopic hematuria, urine cytology and ultrasound
3. Every year for individuals ≥ 35 years



More evidence is needed...

- Prospective data
- Test the efficacy of **all** the different screening tools
- Possible if we collect **all** the data from the Danish urothelial cancer surveillance program since July 2022 into the HNPCC register (InfoBioMed)
- These results will also provide a benchmark for testing of newly developed screening tools