

# HEMATURIA EVALUATION: AN OPPORTUNITY TO ENHANCE THE VALUE OF CARE?

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# Hematuria as a Marker of Occult Urinary Tract Cancer: Advice for High-Value Care From the American College of Physicians

Matthew Nielsen, MD, MS, and Amir Qaseem, MD, PhD for the High Value Care Task Force of the American College of Physicians

**Background:** The presence of blood in the urine, or hematuria, is a common finding in clinical practice and can sometimes be a sign of occult cancer. This article describes the clinical epidemiology of hematuria and the current state of practice and science in this context and provides suggestions for clinicians evaluating patients with hematuria.

**Methods:** A narrative review of available clinical guidelines and other relevant studies on the evaluation of hematuria was conducted, with particular emphasis on considerations for urologic referral.

**High-Value Care Advice 1:** Clinicians should include gross hematuria in their routine review of systems and specifically ask all patients with microscopic hematuria about any history of gross hematuria.

**High-Value Care Advice 2:** Clinicians should not use screening urinalysis for cancer detection in asymptomatic adults.

**High-Value Care Advice 3:** Clinicians should confirm hemepositive results of dipstick testing with microscopic urinalysis that

*demonstrates 3 or more erythrocytes per high-powered field before initiating further evaluation in all asymptomatic adults.*

**High-Value Care Advice 4:** Clinicians should refer for further urologic evaluation in all adults with gross hematuria, even if self-limited.

**High-Value Care Advice 5:** Clinicians should consider urology referral for cystoscopy and imaging in adults with microscopically confirmed hematuria in the absence of some demonstrable benign cause.

**High-Value Care Advice 6:** Clinicians should pursue evaluation of hematuria even if the patient is receiving antiplatelet or anticoagulant therapy.

**High-Value Care Advice 7:** Clinicians should not obtain urinary cytology or other urine-based molecular markers for bladder cancer detection in the initial evaluation of hematuria.

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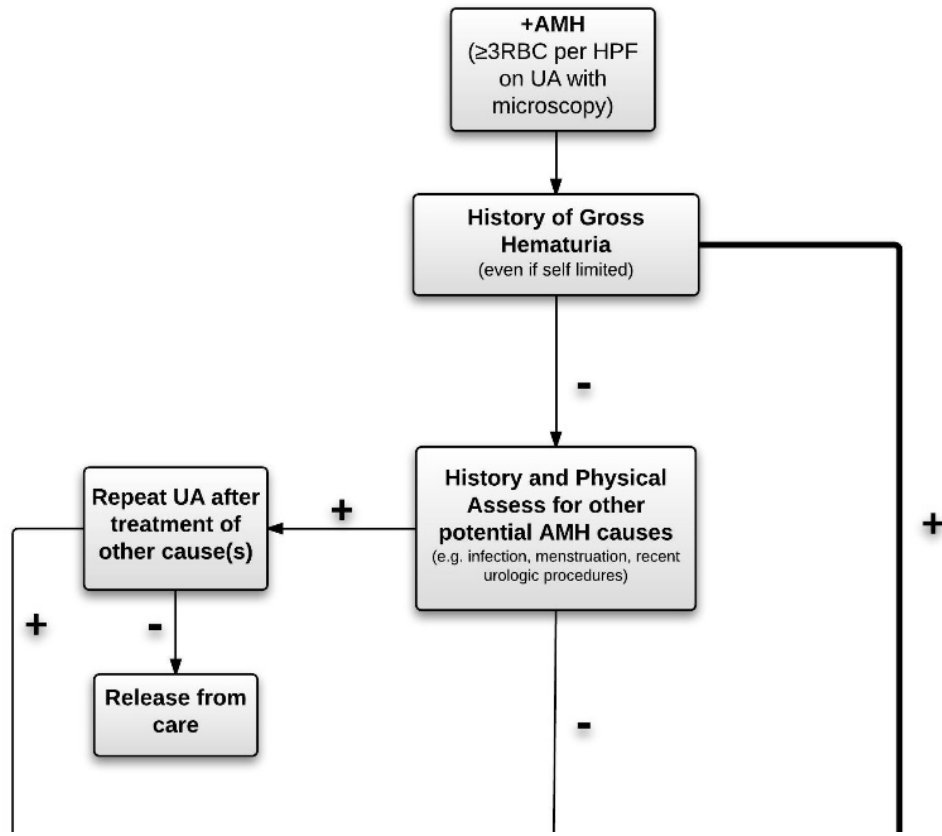


**Table 1. Organizational Recommendations for the Initial Evaluation of Average-Risk Patients With Asymptomatic Microscopic Hematuria**

Recommendation	Year	Reference	Case Definition			Components of Evaluation		
			Dipstick	Microscopic Urinalysis Results, erythrocytes/HPF	Positive/Total Test Results, n/N	Age Threshold, y	Cystoscopy	Preferred Imaging Method
American Urological Association guideline	2012	12	Inadequate	≥3	1	≥35	All patients	CT urography
American Urological Association best practice policy	2001	16	Inadequate	≥3	2/3	≥40	All patients	CT urography or IVP/ultrasonography
Canadian Urological Association guideline	2008	30	Inadequate	≥2	2	≥40	All patients	Renal ultrasonography
British Association of Urological Surgeons guideline	2008	32	≥1 heme	Not required	2/3	≥40	Not specified	Not specified
Dutch Guideline on Hematuria	2010	31	Inadequate	≥3	2/3	≥50	All patients	Renal ultrasonography

CT = computed tomography; HPF = high-powered field; IVP = intravenous pyelography.





## Areas of uncertainty (Table 1)

- Age threshold for urology evaluation (35-50)
- Imaging modality of choice (CT for all vs. risk-stratified approach to CT vs. ultrasound for all)
- Nephrology evaluation as concurrent vs. alternative pathway



# Limitations of Evidence

**Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation**

M Rodgers, J Nixon, S Hempel, T Aho, J Kelly, D Neal, S Duffy, G Ritchie, J Kleijnen and M Westwood

*Health Technology Assessment 2006; Vol. 10: No. 18*

American Urological Association (AUA) Guideline

**DIAGNOSIS, EVALUATION and FOLLOW-UP OF ASYMPTOMATIC MICROHEMATURIA (AMH) IN ADULTS: AUA GUIDELINE**

Rodney Davis, J. Stephen Jones, Daniel A. Barocas, Erik P. Castle, Erick K. Lang, Raymond J. Leveillee, Edward M. Messing, Scott D. Miller, Andrew C. Peterson, Thomas M.T. Turk, William Weitzel

- Health Technology Assessment (2006, UK National Institute for Health Research)
  - 79 different diagnostic algorithms relevant to hematuria, none of which formally evaluated in terms of effect on patient outcomes
- 2012 AUA Guideline on AMH
  - None of 22 specific recommendations supported by evidence higher than Grade C



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- Uncertainty regarding indications for referral and components of evaluation identified as major gap in current practice / policy
- Concerns about harms of CT urogram
  - Major difference between guidelines
  - Substantially differential effectiveness / yield?
  - Highest radiation dose of common CT protocols
  - Harm >> benefit for large subgroups
  - Emerging evidence base supporting risk-stratified approach





# Stratifying Risk of Urinary Tract Malignant Tumors in Patients With Asymptomatic Microscopic Hematuria

Ronald K Loo, MD; Stephen F. Lieberman, MD; Jeff M. Slezak, MS; Howard M. Landa, MD; Albert J. Mariani, MD; Gary Nicolaisen, MD; Ann M. Aspera, MD; and Steven J. Jacobsen, MD, PhD

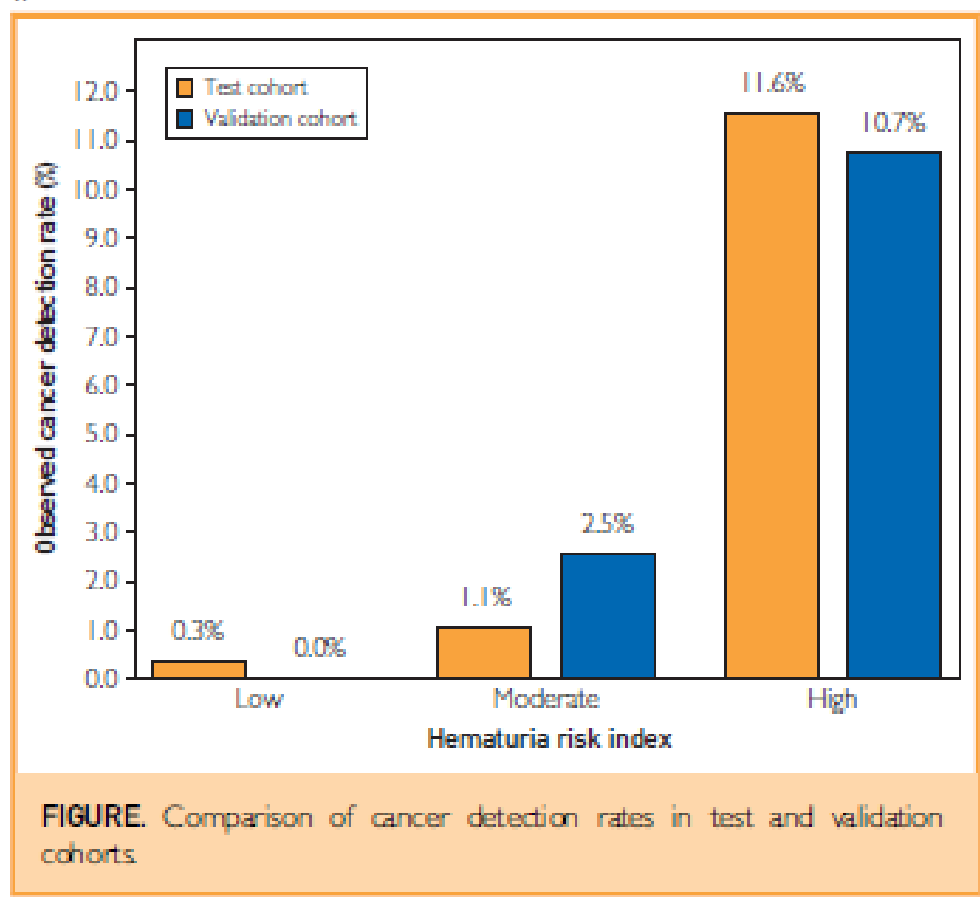


FIGURE. Comparison of cancer detection rates in test and validation cohorts



## Stratifying Risk of Urinary Tract Malignant Tumors in Patients With Asymptomatic Microscopic Hematuria

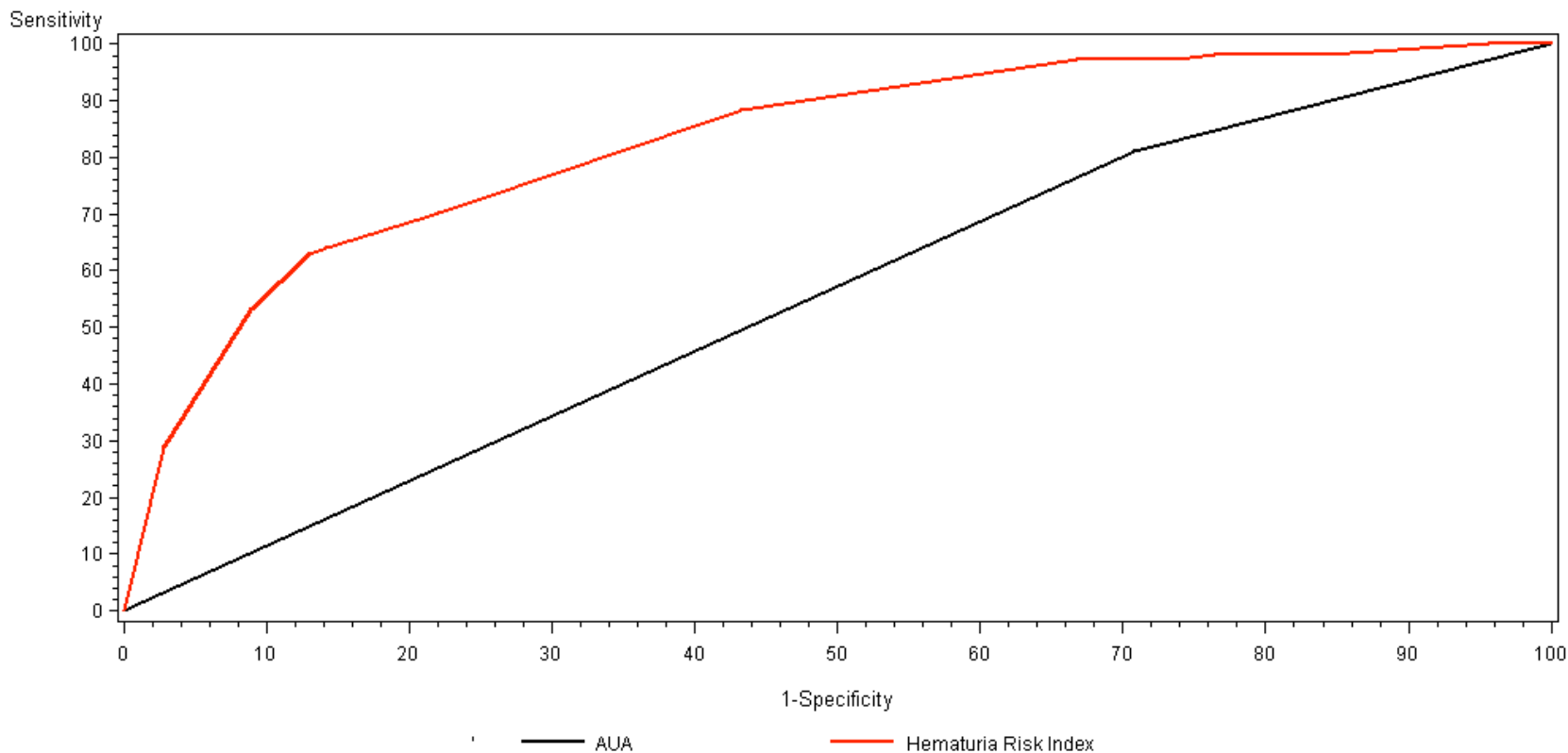
Ronald K. Loo, MD; Stephen F. Lieberman, MD; Jeff M. Slezak, MS;  
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- Overall cancer diagnosis: 2.9%
  - AUA Guidelines' pooled data analysis: 3.3%
- Upper tract findings:
  - Loo et al (n=4414): 0.3% RCC; **zero** upper tract TCC
  - Edwards et al (n=4020, 46.8% GH)
    - 3.7% bladder cancer, 1% RCC
    - 0.2% upper tract TCC (n=10; 7=GH, 3=NVH)
      - **none** in men <50, women <70

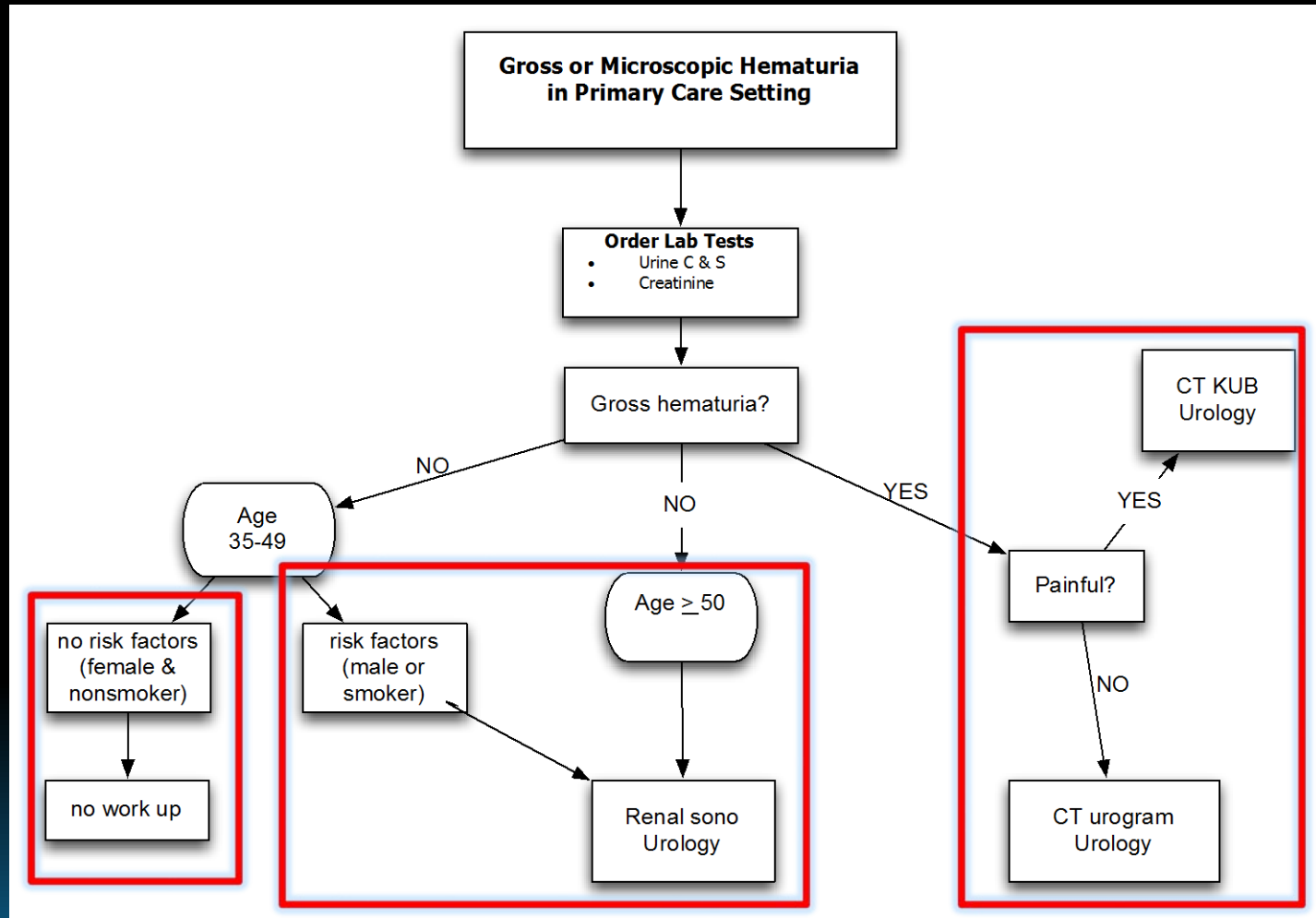


# Area Under the Curve

## Comparison of ROC Curves for Hematuria Risk Index and AUA Guideline



# KP Risk Index—Implemented 2012



Low risk: 33%

Moderate risk: 53%

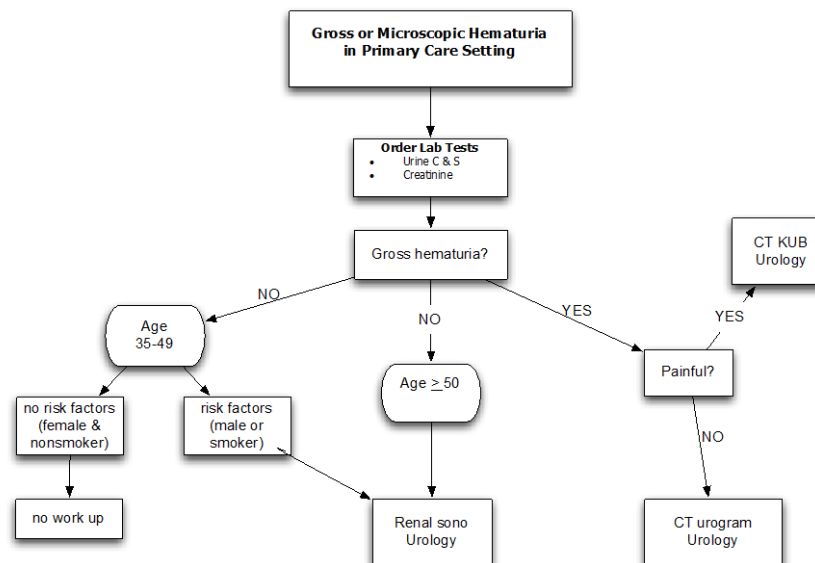
High risk: 14%

# What are the tradeoffs?

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“A model is a lie that helps you see the truth.”

Howard Skipper, PhD



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# Model-based comparison of alternatives

## PATIENT CHARACTERISTICS

Hematuria Cohort studies

## INITIAL ENCOUNTER

Clinical guidelines

## POST-ENCOUNTER

Literature review

## HYPOTHETICAL COHORT

### Assign:

- Sex
- Age
- Cancer status
- Cancer location
- History of gross hematuria
- Smoking status
- Urine RBC count

### AUA

- All patients aged  $\geq 35$  years: cystoscopy + CT

### Risk stratification (KP/HRI)

- Low risk: no further work-up
- Moderate risk: cystoscopy + renal ultrasound
- High risk: cystoscopy + CT

### Canadian guidelines

- Patients aged  $\geq 40$  years: cystoscopy + renal ultrasound

### Dutch guidelines

- Patients aged  $\geq 50$  years: cystoscopy + renal ultrasound

### Assess outcomes:

- Costs
- Cancer detection rates
- Missed cancer cases
- False positive cases
- Short-term complications
  - Contrast allergy
  - Contrast nephropathy
  - Dysuria
  - UTI
- CT radiation-induced harms
  - Secondary cancers
  - Attributable deaths



# Incremental cost-effectiveness results

Cost-effectiveness of different evaluation strategies of AMH patients (N=100,000)

Guideline	Total costs to cohort	Cancer cases detected*	Incremental costs	Incremental cancer cases detected	ICER (cost per cancer case detected)
Dutch	\$42,470,698	3,234	-	-	-
Canadian	\$44,303,924	3,288	\$1,833,227	54	\$34,072
KP/HRI strategy	\$46,623,885	3,358	\$2,319,960	70	\$32,939
AUA	\$81,640,142	3,495	\$35,016,257	137	\$254,745

\*Total number of detected cancer cases (bladder, renal, and ureteral/renal pelvis).

ICER - incremental cost-effectiveness ratio.



@mivlage

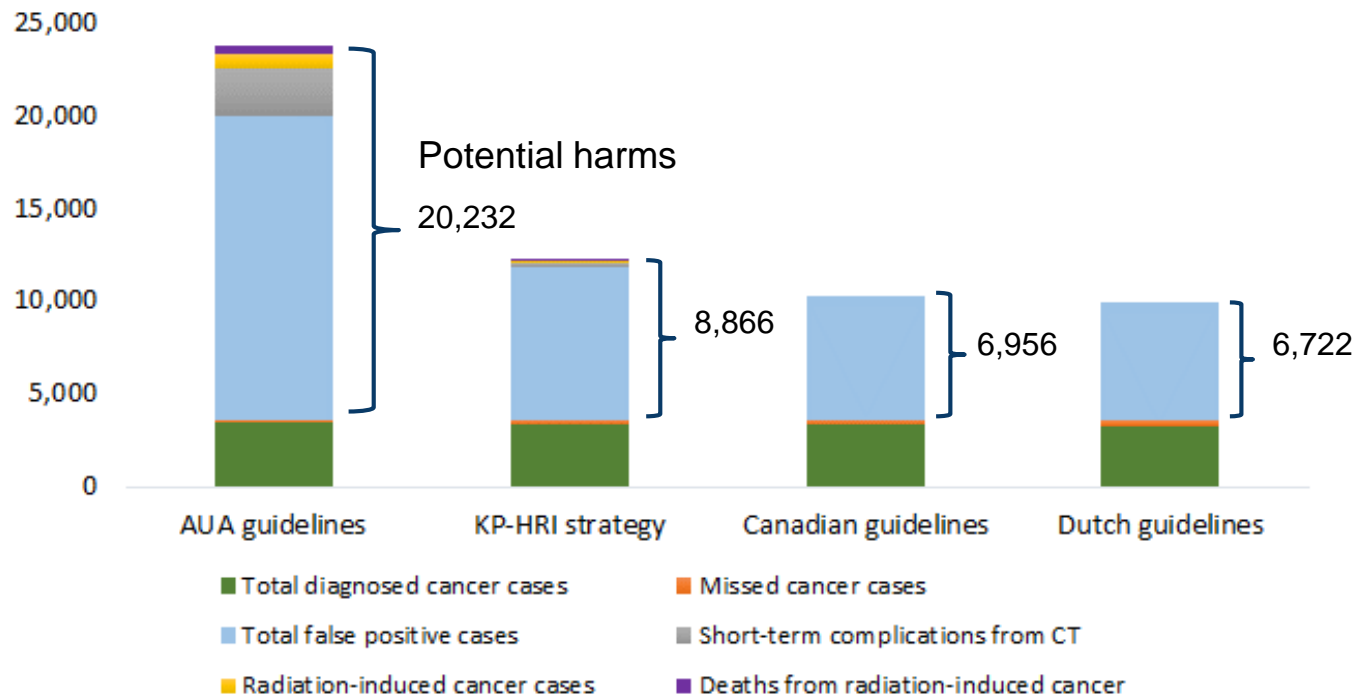


@StephWheelerUNC



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## Health economic outcomes for the simulated cohort (N=100,000)



	AUA guidelines	KP-HRI strategy	Canadian guidelines	Dutch guidelines
Total diagnosed cancer cases	3,492	3,358	3,290	3,237
Missed cancer cases	26	160	228	281
Total false positive cases <sup>a</sup>	16,390	8,254	6,728	6,441
Short-term complications from CT	2,595	310	0	0
Radiation-induced cancer cases	780	91	0	0
Deaths from radiation-induced cancer	441	51	0	0
Total costs per patient <sup>b</sup>	\$1,159	\$507	\$443	\$424

Note: KP-HRI - Kaiser Permanente recommendations using the Hematuria Risk Index

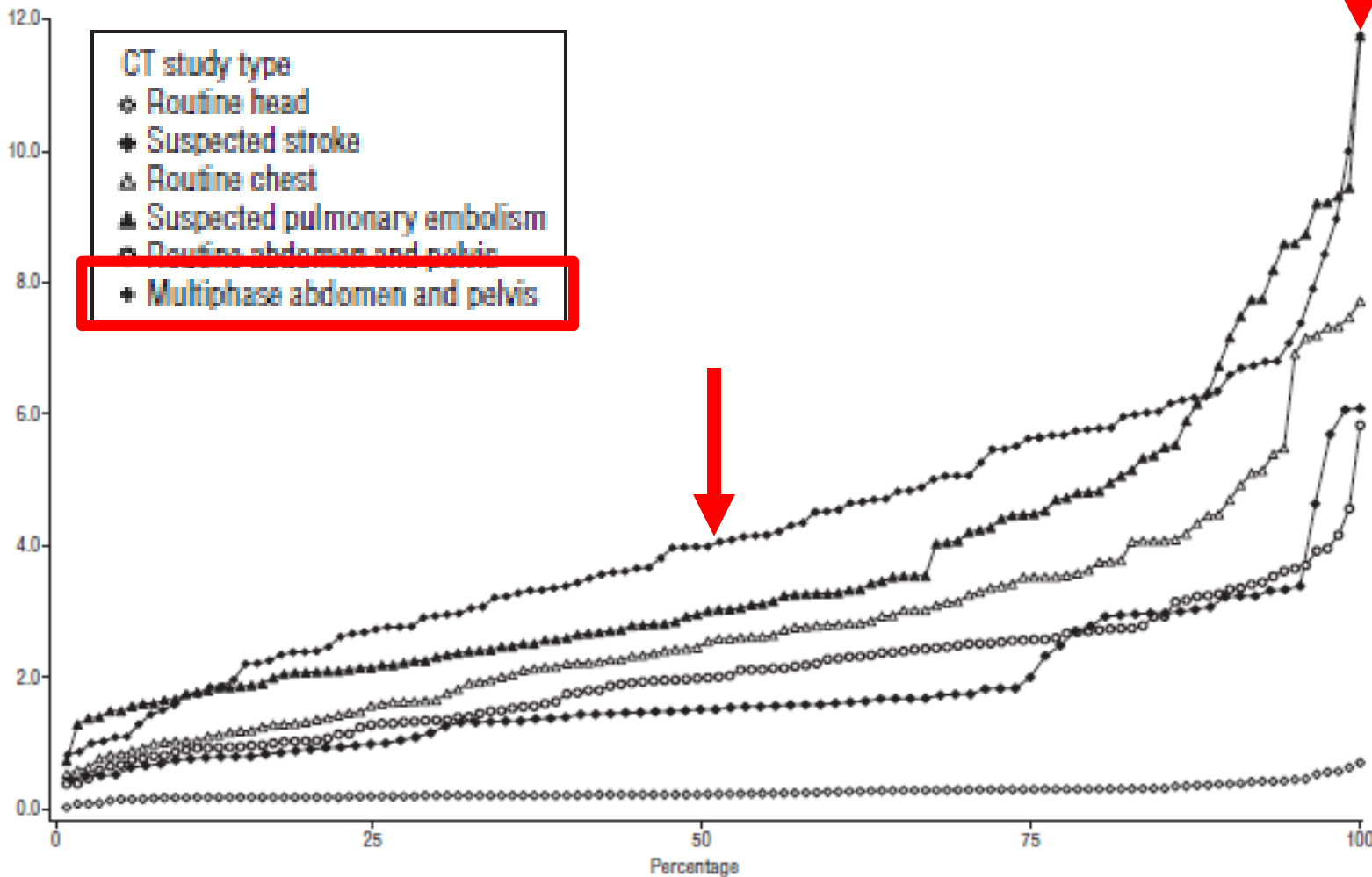
<sup>a</sup>False positive cases from all test evaluations (CT, cystoscopy, renal ultrasound)

<sup>b</sup>Initial evaluation costs of multiphase abdominal/pelvic CT,

# Cancer risks are not trivial

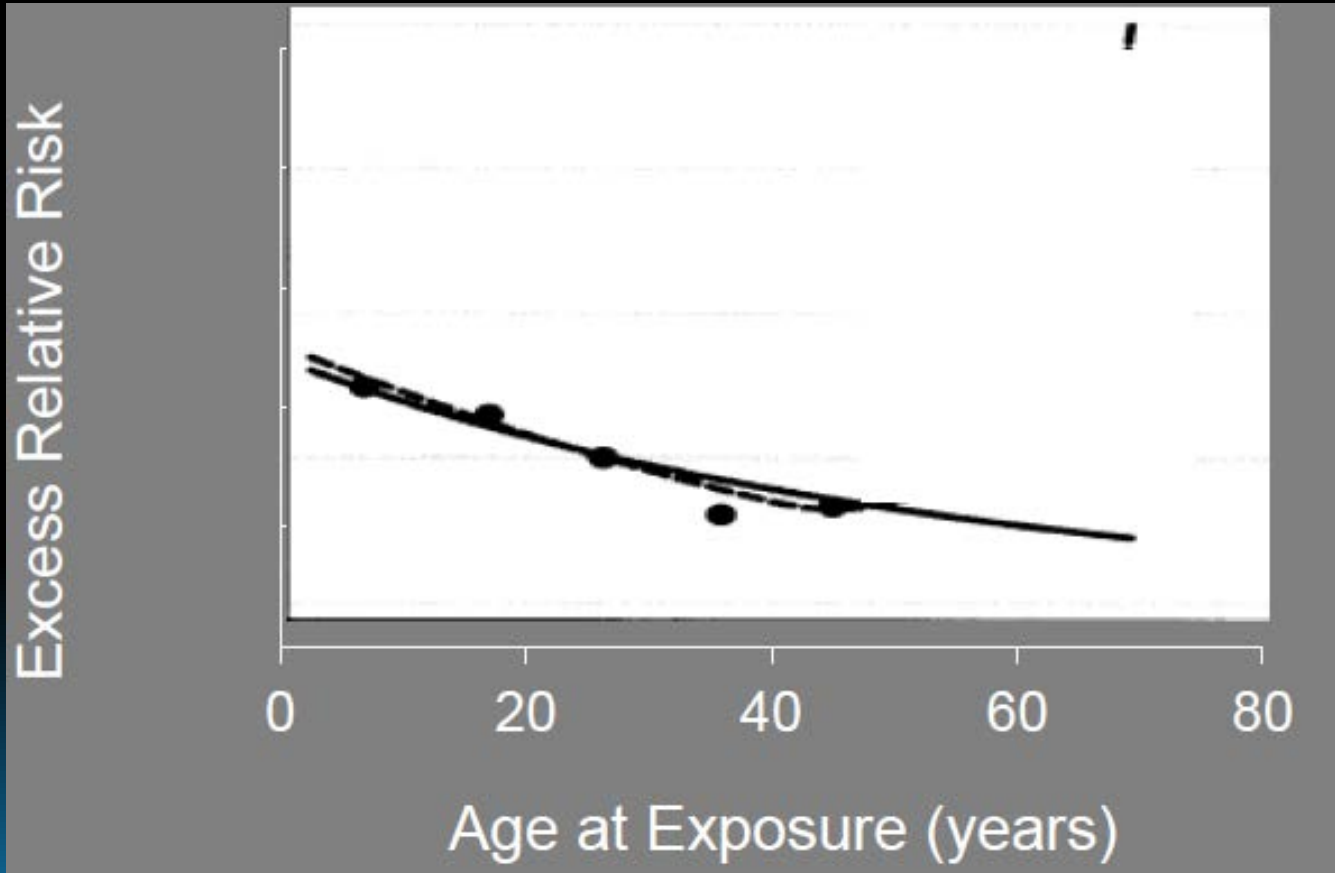


Lifetime Attributable Risk of Cancer  
(per 1000 patients)

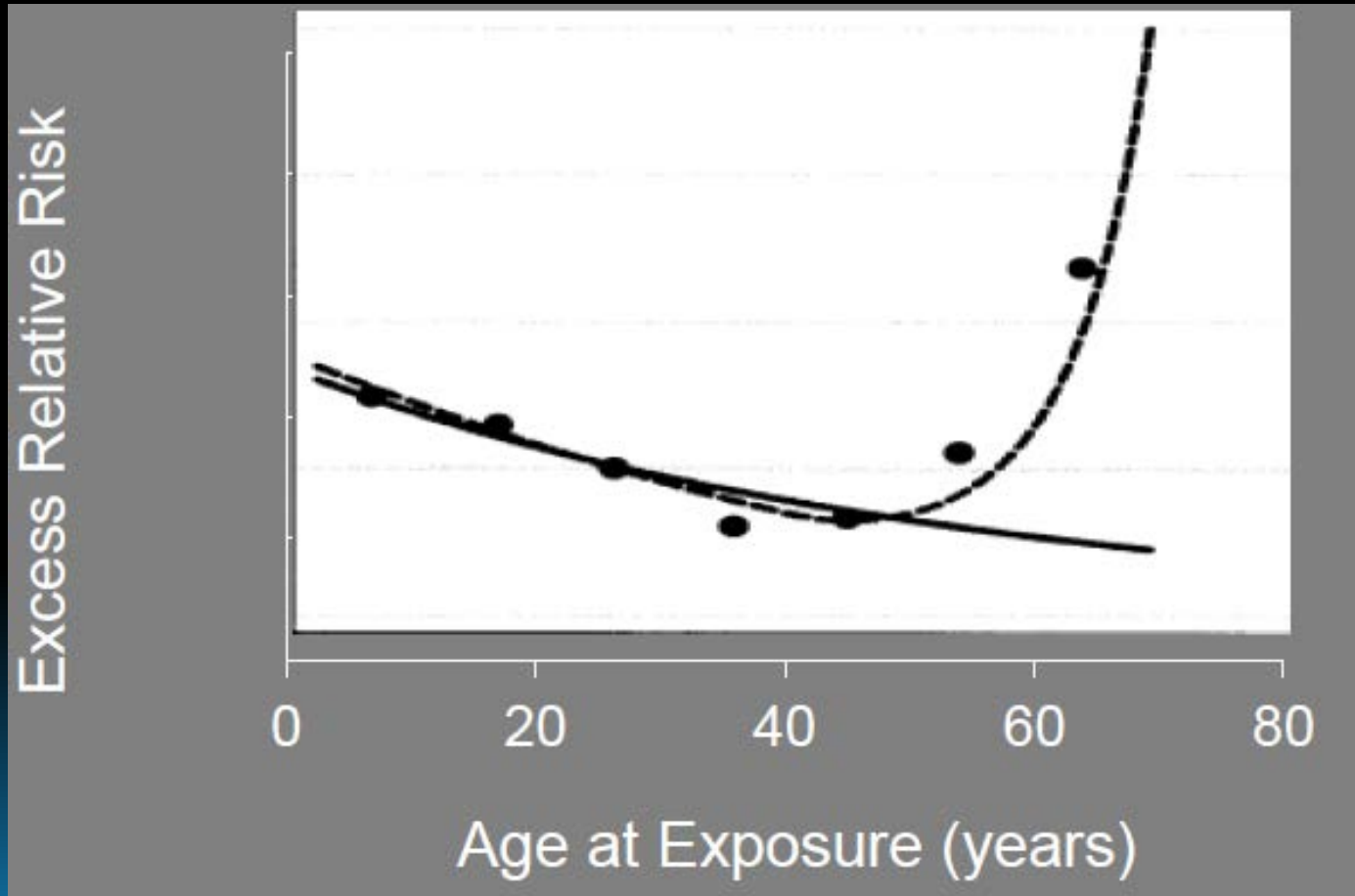




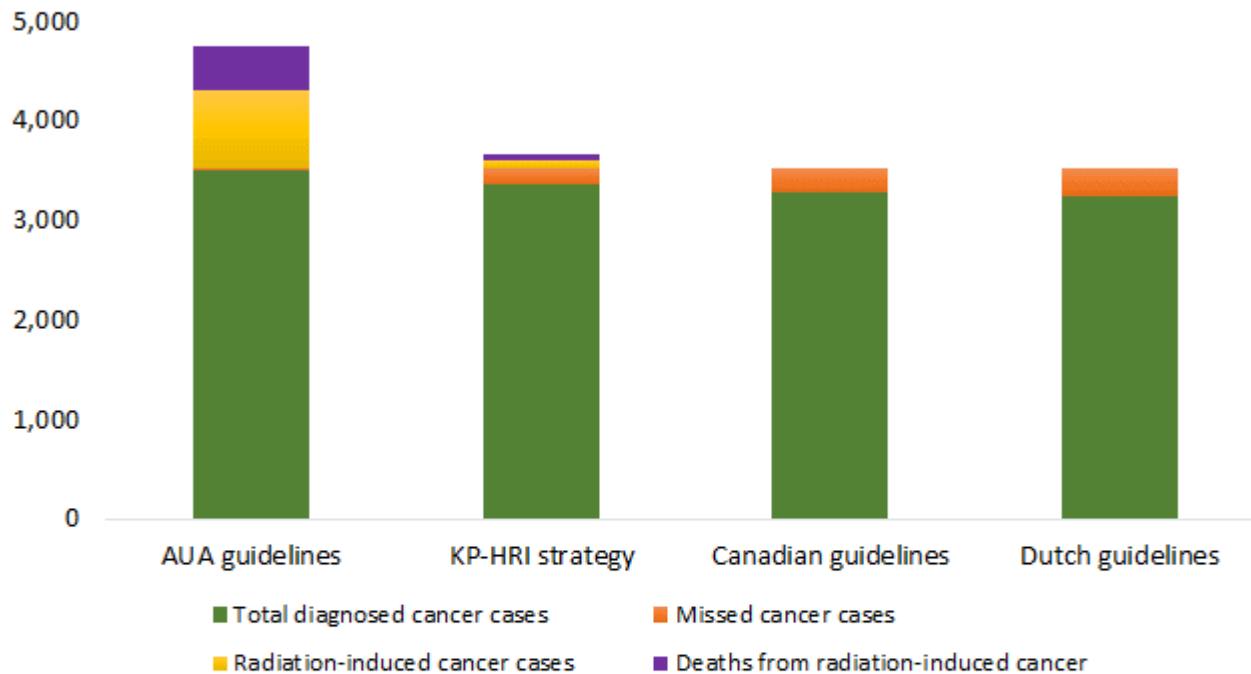
# Typical summary of Cancer Risks by Age at Exposure



# Cancer Risk: Actually a U-Shaped Distribution



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Medicine used to be simple,  
ineffective and relatively safe.  
Now it is complex, effective, and  
potentially dangerous.

*Sir Cyril Chantler,  
Dean of Guy's Hospital, London*



## 5.1 For each recommendation provide:



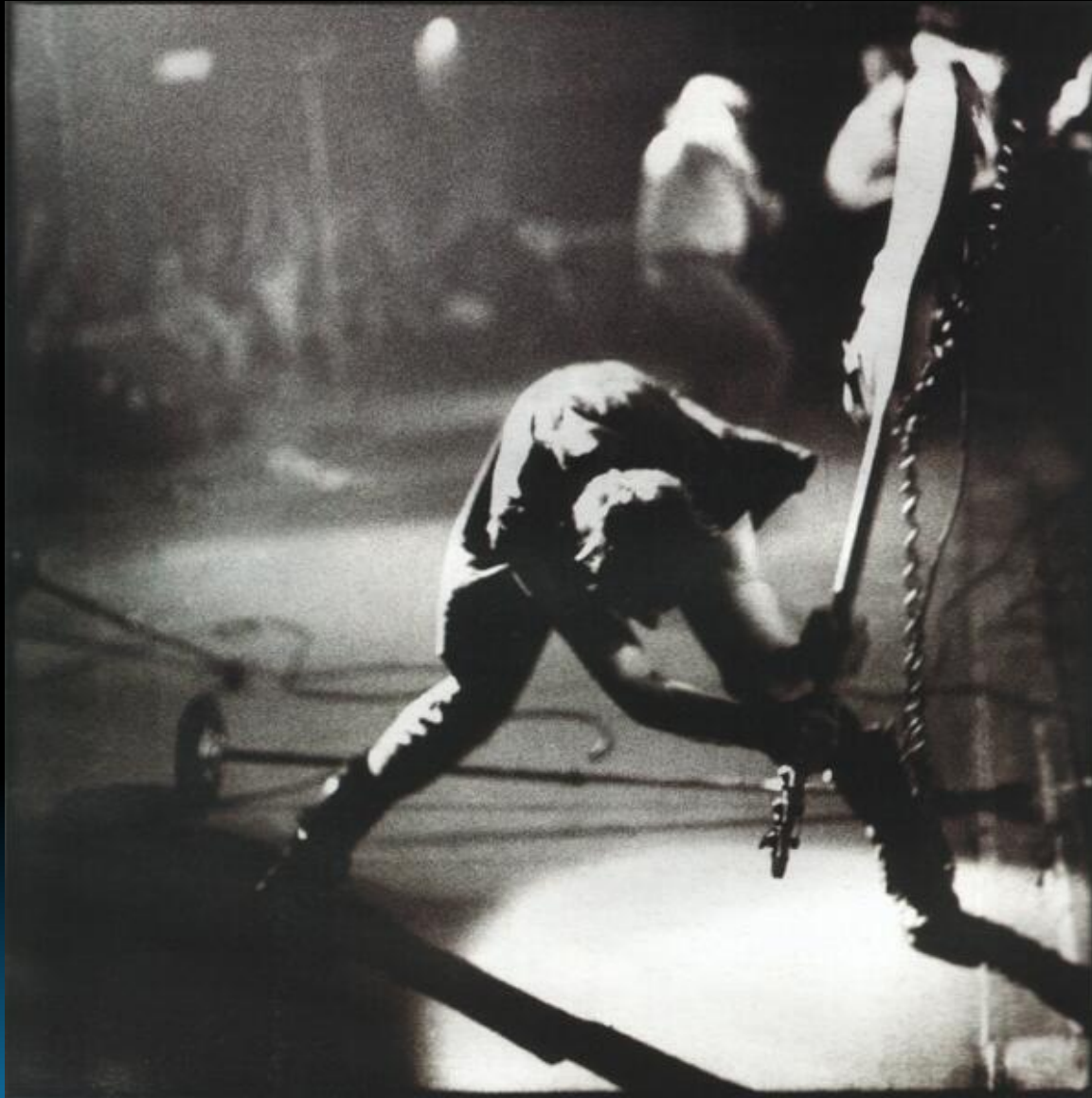
CLINICAL PRACTICE  
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- A summary of relevant available evidence, description of the quality, quantity and consistency of aggregate available evidence
- **A clear description of the potential benefits and harms**
- An explanation of the part played by values, opinion, theory and clinical experience in deriving the recommendation
- A description of any differences of opinion regarding the recommendation



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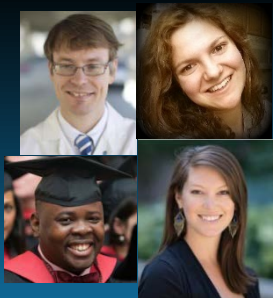
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# Thank You

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