FDA COLLABORATION ON ADJUVANT BLADDER CANCER TRIAL DESIGN AND ENDPOINTS

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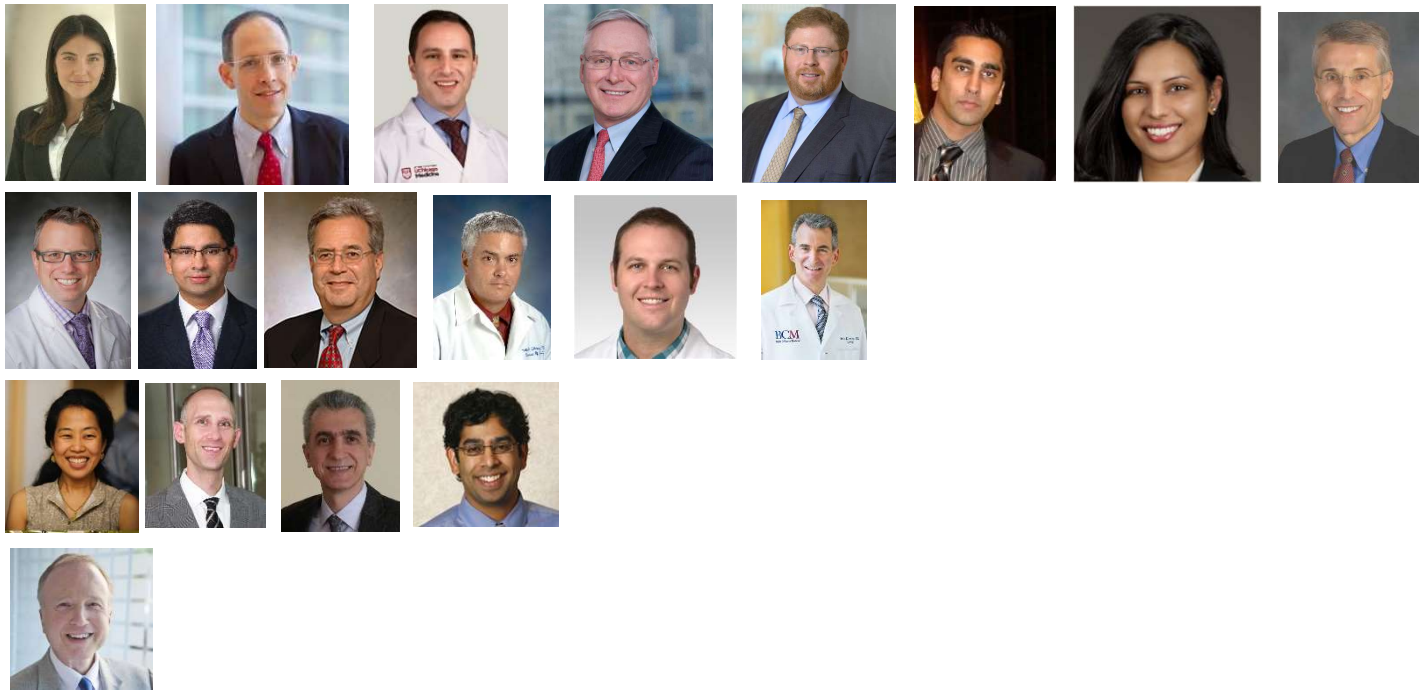
Bladder Cancer Advocacy Network (BCAN)

FDA Collaboration on Adjuvant Bladder Cancer Trial Design and Endpoints



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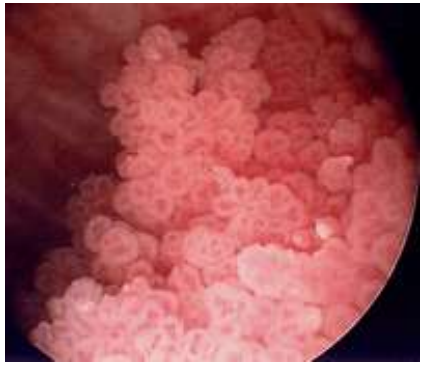
Apolo AB et al., JAMA Oncol 2019 *in press*

FDA Collaboration on Adjuvant Bladder Cancer Trial Design and Endpoints

- Eligibility patient and disease characteristics
- Radiologic considerations
- Managing new urothelial cancers within the urothelial tract
- Considerations for the patient



Apolo AB et al., JAMA Oncol 2019 *in press*

Eligibility patient and disease characteristics

Eligibility patient and disease characteristics

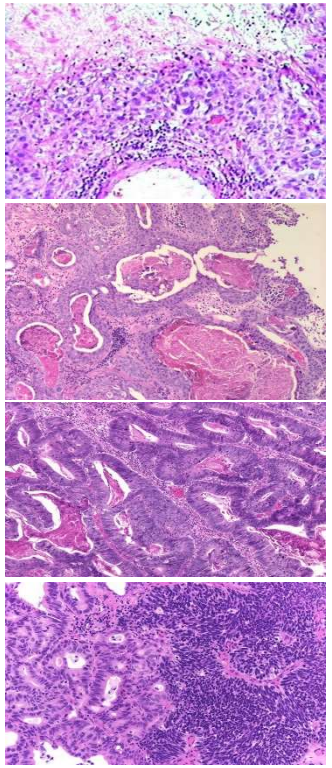
- Histologic subtypes
- Prior neoadjuvant therapy
- Site of disease
- Surgical considerations
- Timing of adjuvant therapy

Apolo AB et al., JAMA Oncol 2019 *in press*

Eligibility patient and disease characteristics

Histologic subtypes

- Patients with predominant *urothelial carcinoma histology* who have a component of variant histology should be included in adjuvant trials
- Patients with *pure non- urothelial carcinoma histology*, especially mixed endocrine/small cell tumors, if included, should be analyzed separately



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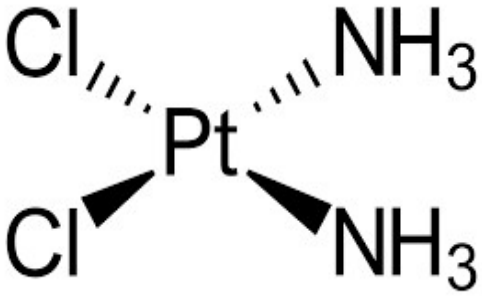
Eligibility patient and disease characteristics



Prior neoadjuvant therapy

- At least 3 cycles of neoadjuvant cisplatin-based chemotherapy with a planned cisplatin dose of 70 mg/m2/cycle is a reasonable eligibility criterion

- Patients who have received non-cisplatin-based or less than 3 cycles of cisplatin-based neoadjuvant treatment should be managed/stratified as having received no neoadjuvant chemotherapy

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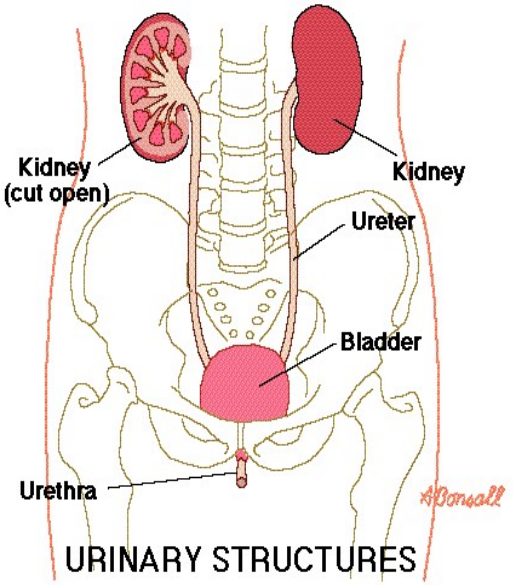
Eligibility patient and disease characteristics

Site of disease

- Muscle-invasive upper-tract urothelial carcinoma should be included on adjuvant trials



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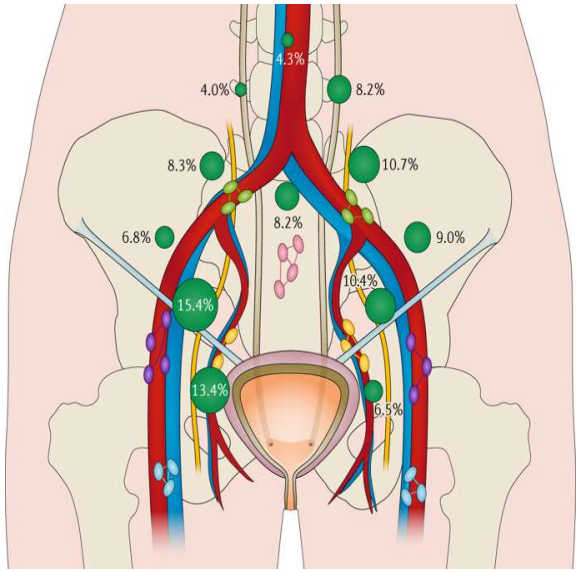
Eligibility patient and disease characteristics

Surgical considerations

- Patients with microscopic positive margins (R1) should be eligible, though statistical stratification may be considered
- It is not clear if gross positive margins (R2) should be included in studies
- Bilateral (standard) lymph node dissection is both favored and sufficient for accurate staging information



Perera M et al., Nature Reviews Urology 2018

Apolo AB et al., JAMA Oncol 2019 *in press*

Eligibility patient and disease characteristics

Timing of adjuvant therapy

- Adjuvant therapy can be initiated as soon as the patient recovers from surgery, with a goal of 1 to 4 months post-surgery

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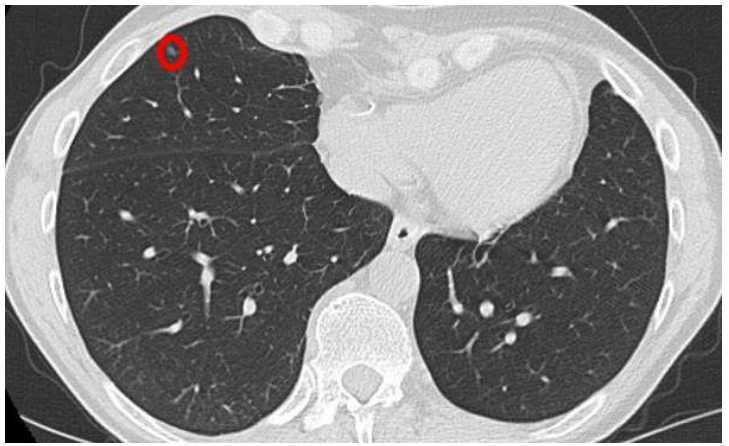
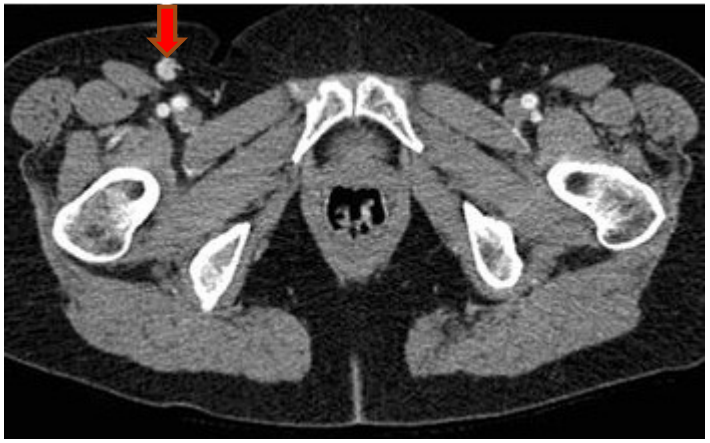
Radiologic considerations

Radiologic considerations

- Standardizing radiologic eligibility criteria of “NED scans



- Standardizing radiologic progression criteria in follow-up scans



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Managing new urothelial cancers within the urothelial tract

FDA Collaboration on Adjuvant Bladder Cancer Trial Design and Endpoints

Managing new urothelial cancers within the urothelial tract

- Second primary cancers
- Urethral second primary tumors
- Urine test utilization
- Augmented endoscopy
- Random bladder biopsies
- Systemic agents and BCG

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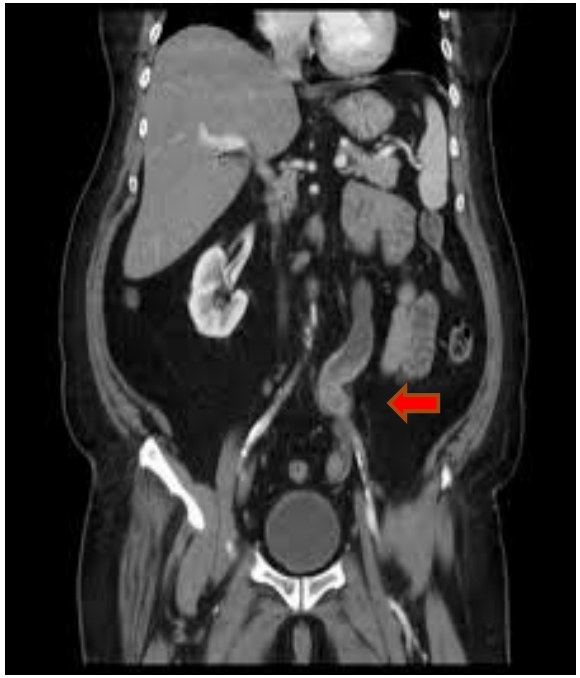
Managing new urothelial cancers within the urothelial tract

Second primary cancers

- All new high-grade upper-tract primary tumors and all new MIBC tumors are considered as events for the disease-free survival endpoint
- It is not clear whether new bladder second primary tumors that are ≤ T1 should be counted as an event for the disease-free survival endpoint
- Patients with tumors that are both low-grade and non-muscle-invasive could remain on trial if they can be managed endoscopically



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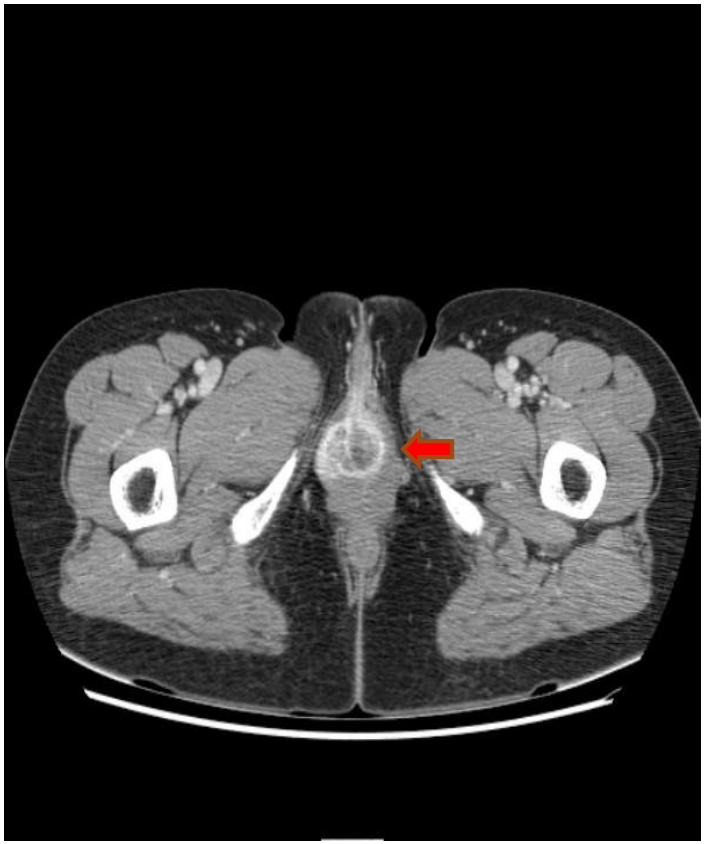
Managing new urothelial cancers within the urothelial tract

Urethral second primary tumors

- Patients with non-muscle invasive tumors manageable either endoscopically or with urethrectomy may remain on study

- Patients with muscle-invasive recurrences should be removed from trial and counted as disease recurrence



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Managing new urothelial cancers within the urothelial tract

Urine test utilization

- Trials should specify if urine tests should be used for post-operative surveillance and, if so, the specific test and testing interval required

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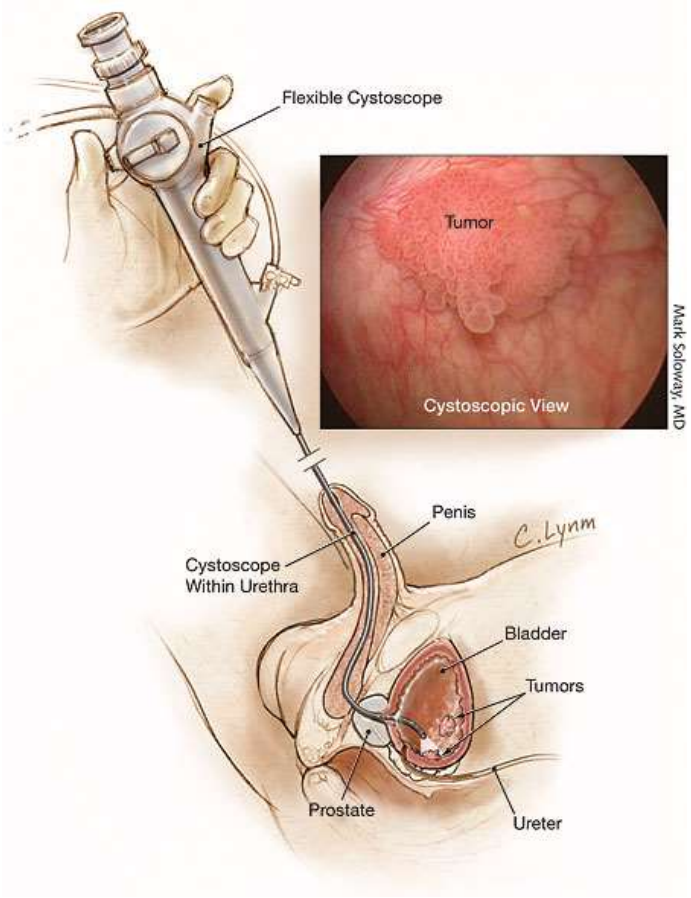
Managing new urothelial cancers within the urothelial tract

Augmented endoscopy

- Standard-of-care guidelines for endoscopic surveillance should be followed and defined at the start of trial



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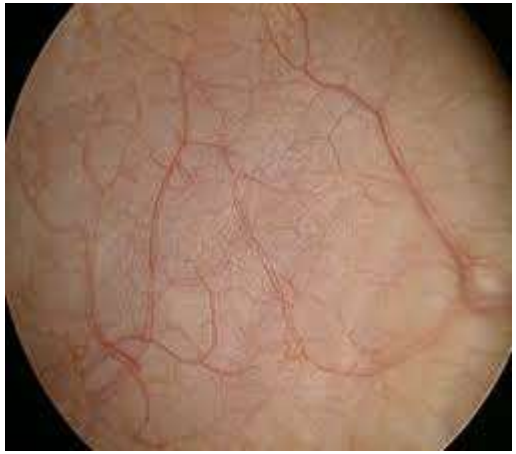
Managing new urothelial cancers within the urothelial tract

Random bladder biopsies

- Trials should specify whether random bladder biopsies should be obtained or not to rule out occult carcinoma in situ

- Further evidence is needed to inform whether this should be done for all patient with intact bladders



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Managing new urothelial cancers within the urothelial tract

Systemic agents and BCG

- Further evidence is needed to inform whether it would be appropriate to continue a systemic agent in conjunction with BCG or other intravesical therapy

Apolo AB et al., JAMA Oncol 2019 *in press*

Considerations for the patient

Considerations for the patient

- Rare cancers
- Biopsy
- Placebo
- Blinding

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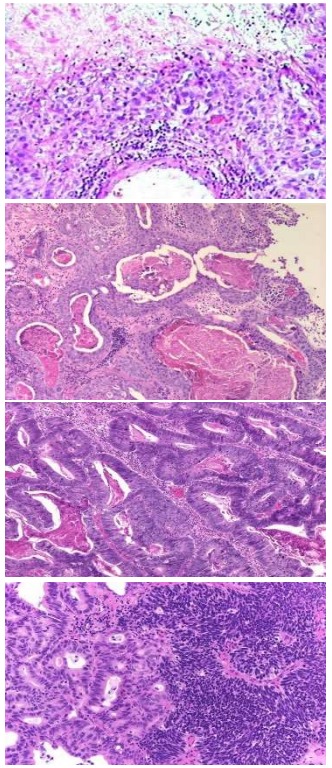
Considerations for the patient

Rare cancers

- There is concern about the consistency of histologic subtype classification/diagnosis and its potential impact on enrollment.



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Considerations for the patient

Biopsy

- Taking biopsies solely for the purposes of research should be carefully balanced with the best interests of the patient

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Considerations for the patient

Placebo

- Trial designs that eliminate the use of placebo, more heavily weight the arm with action/active agent, or allow crossover (where justified by trial data) are favored by patients.

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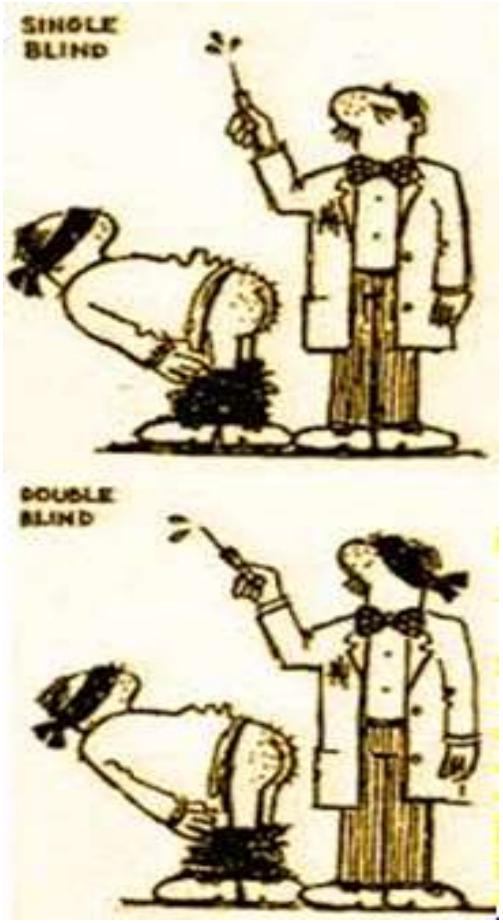
Considerations for the patient

Blinding

- Patients agree to blinding; however, they should be unblinded under certain circumstances..



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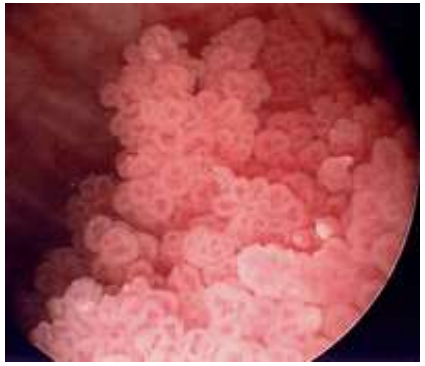

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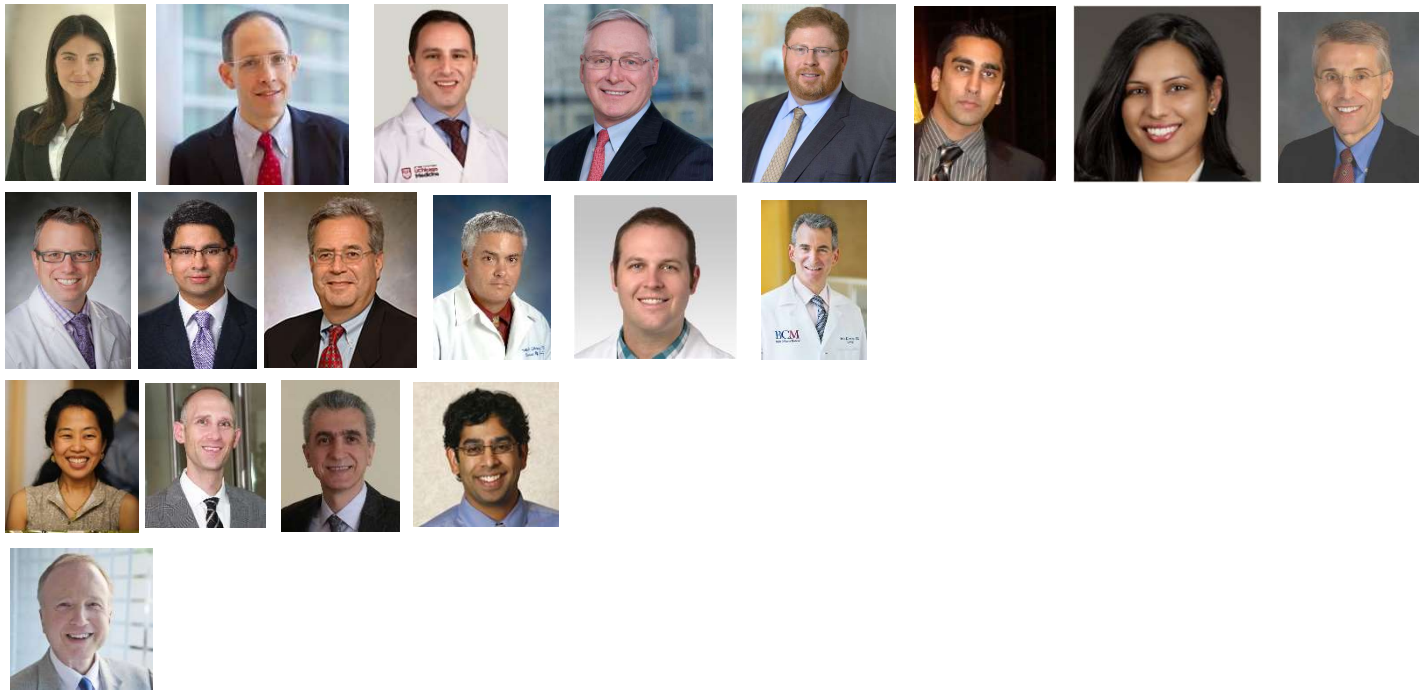

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