Understanding bladder outlet obstruction: Pathophysiology and Diagnosis

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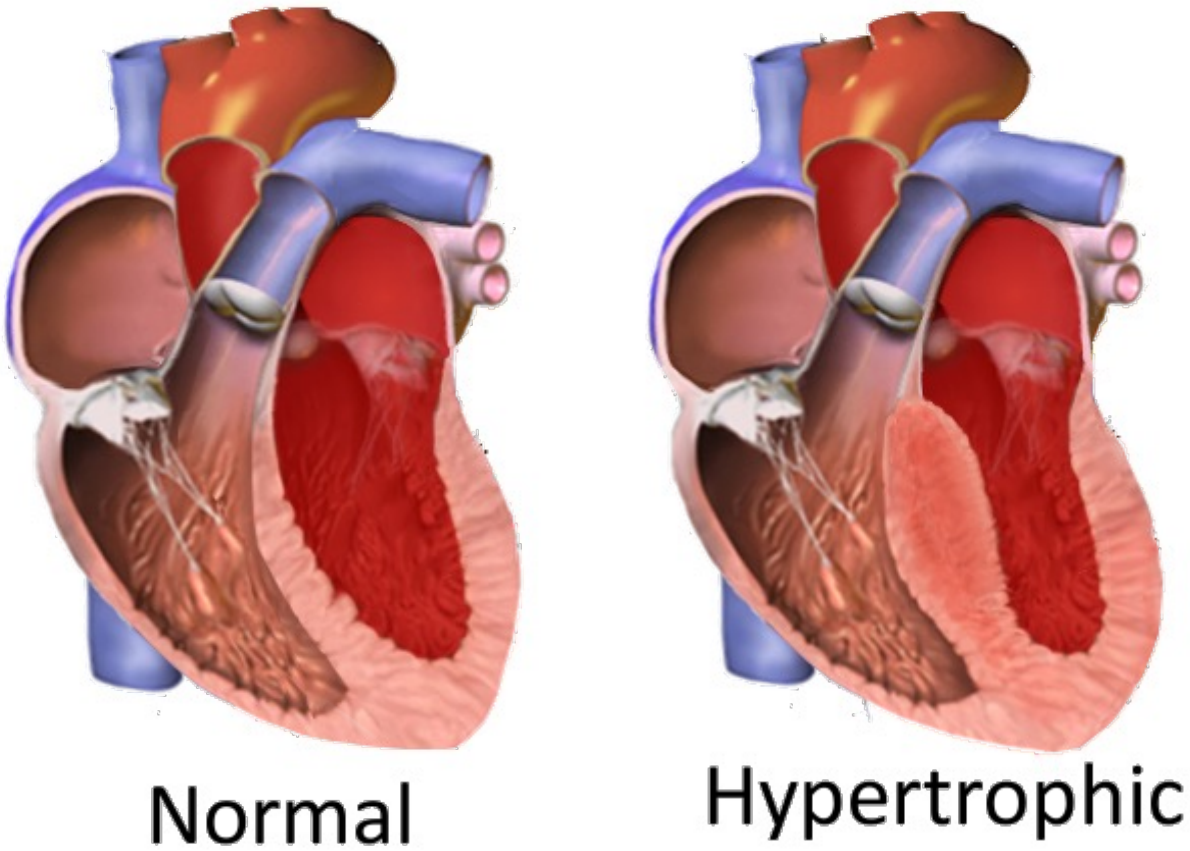
Bladder outlet obstruction (BOO)

- Bladder outlet obstruction is the generic term for obstruction during voiding.

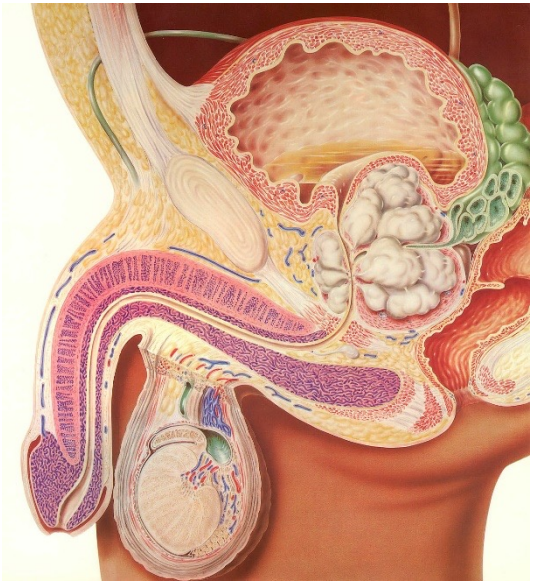
- Detrusor muscle has to overcome a higher resistance to empty the bladder.

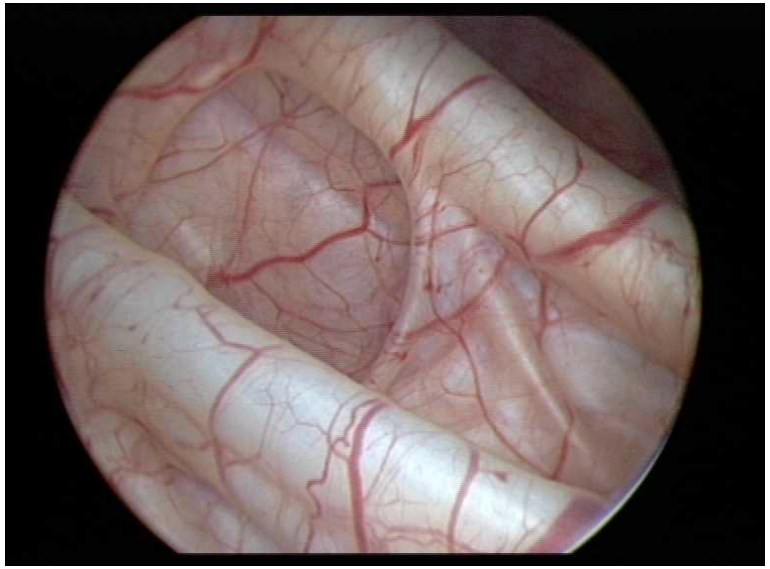
Abrams et al.. Neurourol Urodyn 2002.
Rademakers et al. Neurouro Urodyn 2017



Bladder outlet obstruction (BOO)

- is characterised by increasing detrusor pressure and reduced urine flow rate.





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CONTRACTILE PROTEIN EXPRESSION IN BLADDER SMOOTH MUSCLE IS A MARKER OF PHENOTYPIC MODULATION AFTER OUTLET OBSTRUCTION IN THE RABBIT MODEL

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From the Departments of Urology, University Hospital Berne, Berne, Switzerland, and University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

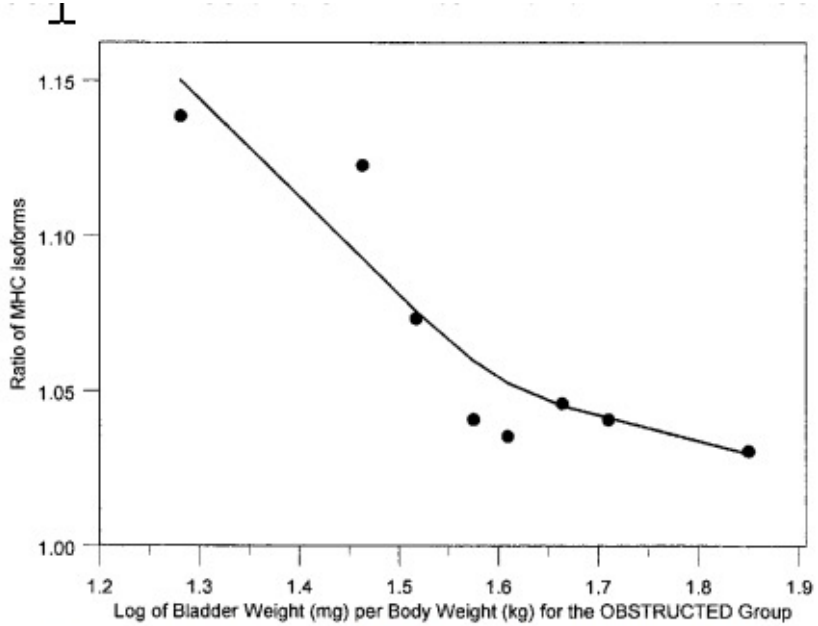


FIG. 3. Correlation curve of bladder weight and SM2-to-SM1 ratio in obstructed bladders (Pearson correlation coefficient significant at $p = 0.01$).

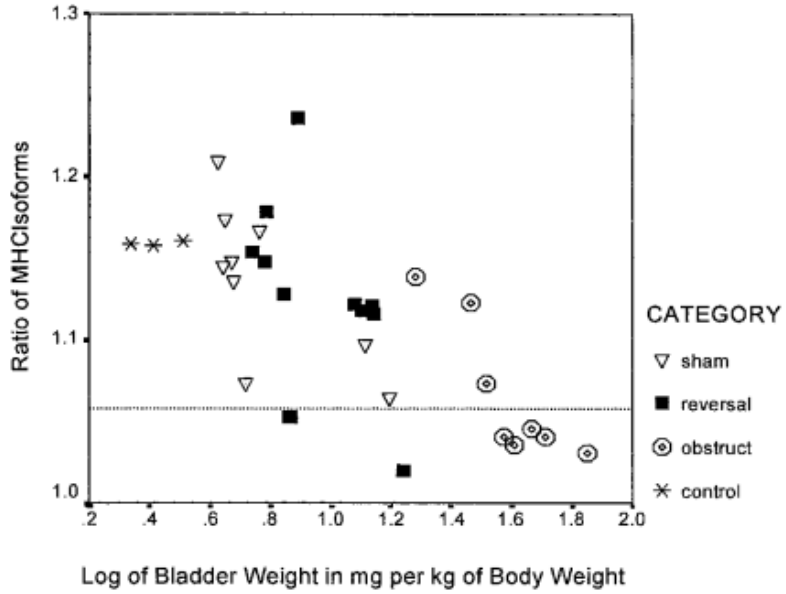


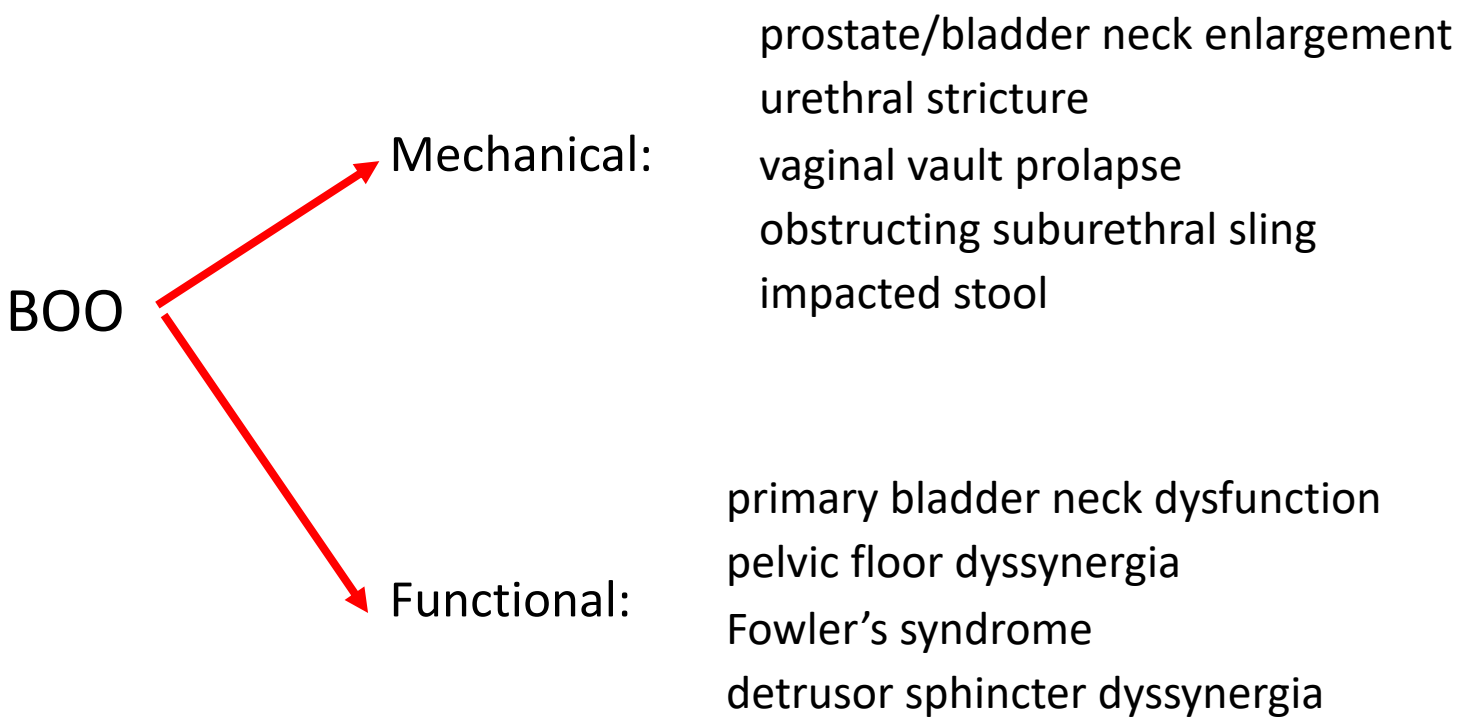
FIG. 4. SM2-to-SM1 ratio in control, sham operated, obstructed and reversed bladders. Dotted line indicates proposed cutoff. *MHC*, myosin heavy chain.

Lower urinary tract dysfunction → Lower Urinary Tract Symptoms

Storage symptoms	Voiding symptoms	Post-micturition symptoms
• Altered bladder sensation • Increased daytime frequency • Nocturia • Urgency • Urgency incontinence	• Hesitancy • Intermittency • Slow stream • Splitting/spraying • Straining	• Feeling of incomplete bladder emptying • Post-micturition dribble

Abrams et al. Neurourol Urodyn 2002
Knutson T et al. Neurourol Urodyn 2001

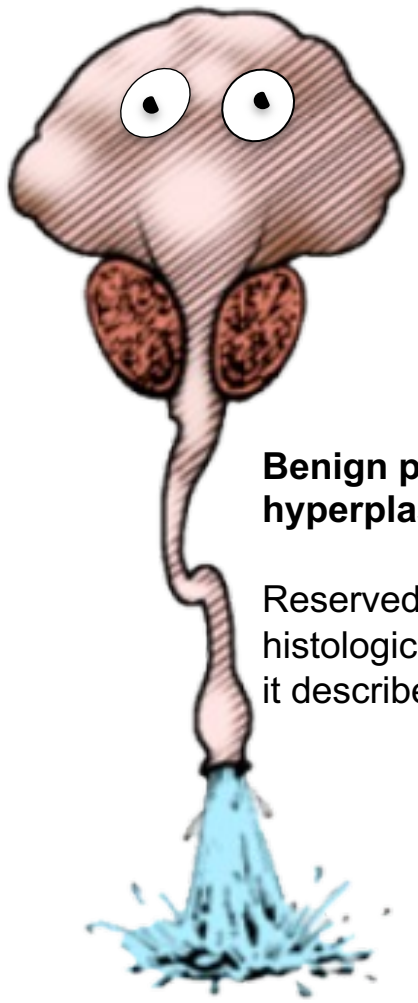
Bladder outlet obstruction (BOO)



The most common sources of BOO

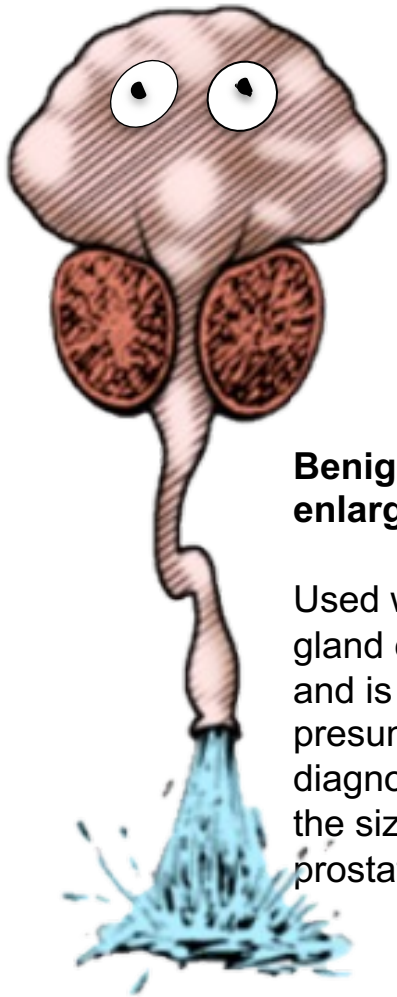
- Women: not well categorized in the literature, obstructing slings?.
- Men: benign prostatic enlargement and prostate cancer

Terminology



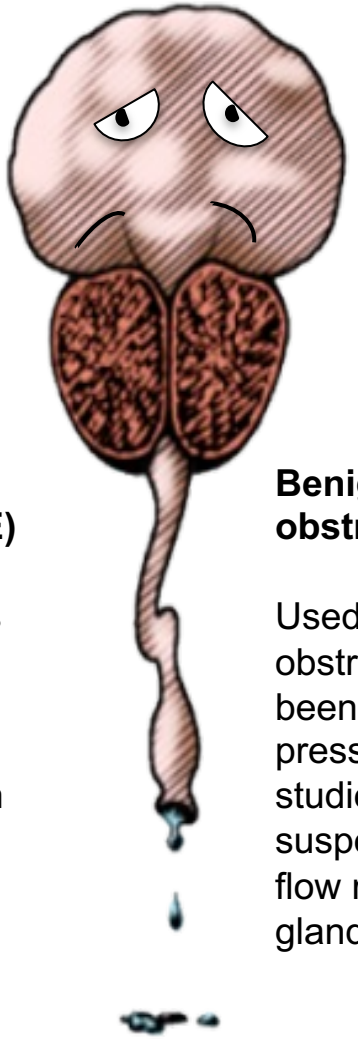
Benign prostatic hyperplasia (BPH)

Reserved for the histological pattern it describes.



Benign prostatic enlargement (BPE)

Used when there is gland enlargement and is usually a presumptive diagnosis based on the size of the prostate.



Benign prostatic obstruction (BPO)

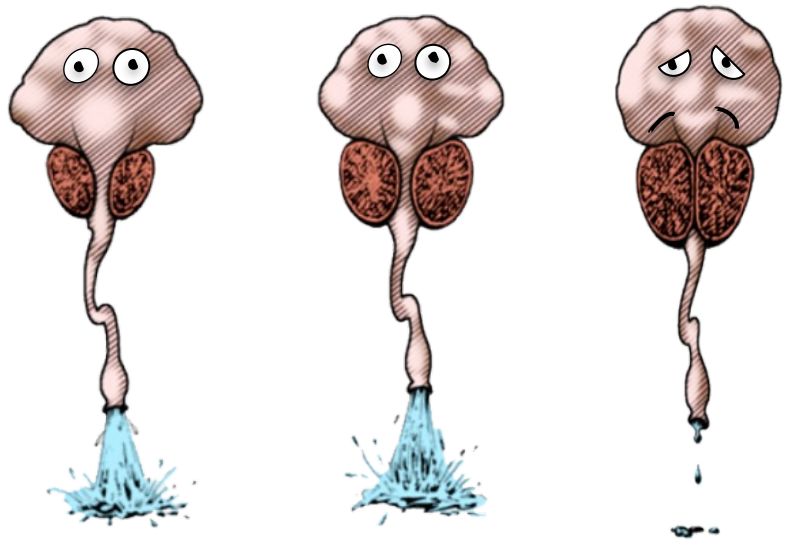
Used when obstruction has been proven by pressure flow studies, or is highly suspected from flow rates and if the gland is enlarged.

1.Abrams P BMJ 1994

2.McVary KT, et al. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH). 2010. Available at: https://www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf. Accessed June 2016.

Benign prostatic hyperplasia

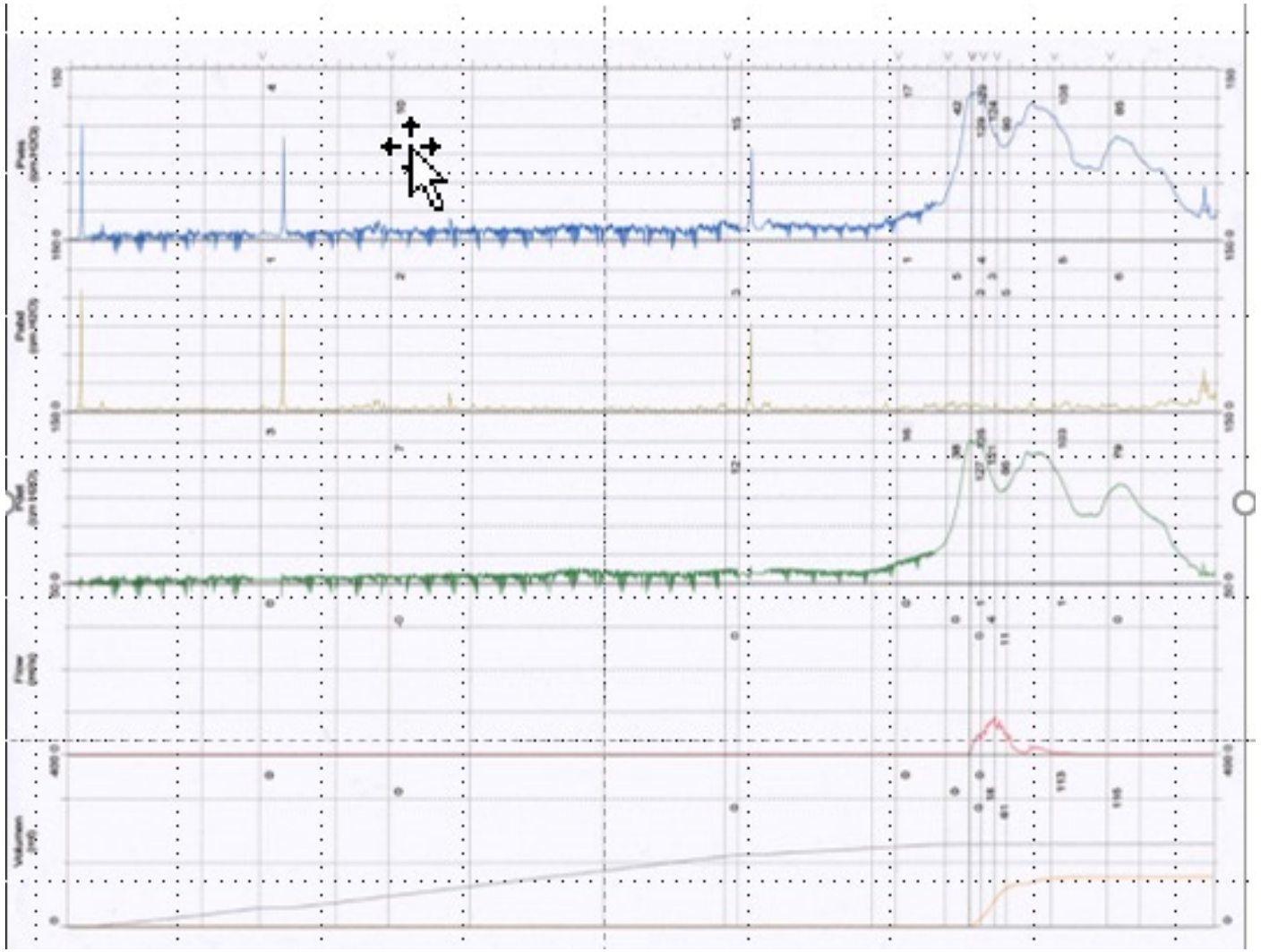
- A common condition in ageing men
  - By 60 > 50% have some degree of hyperplasia
  - By 80 > 90% have some degree of Hyperplasia
- Lower urinary tracts symptoms LUTS
  - Men > 50 years 50-75%
  - Inceases with age
- Only 40% with BPO complain of LUTS



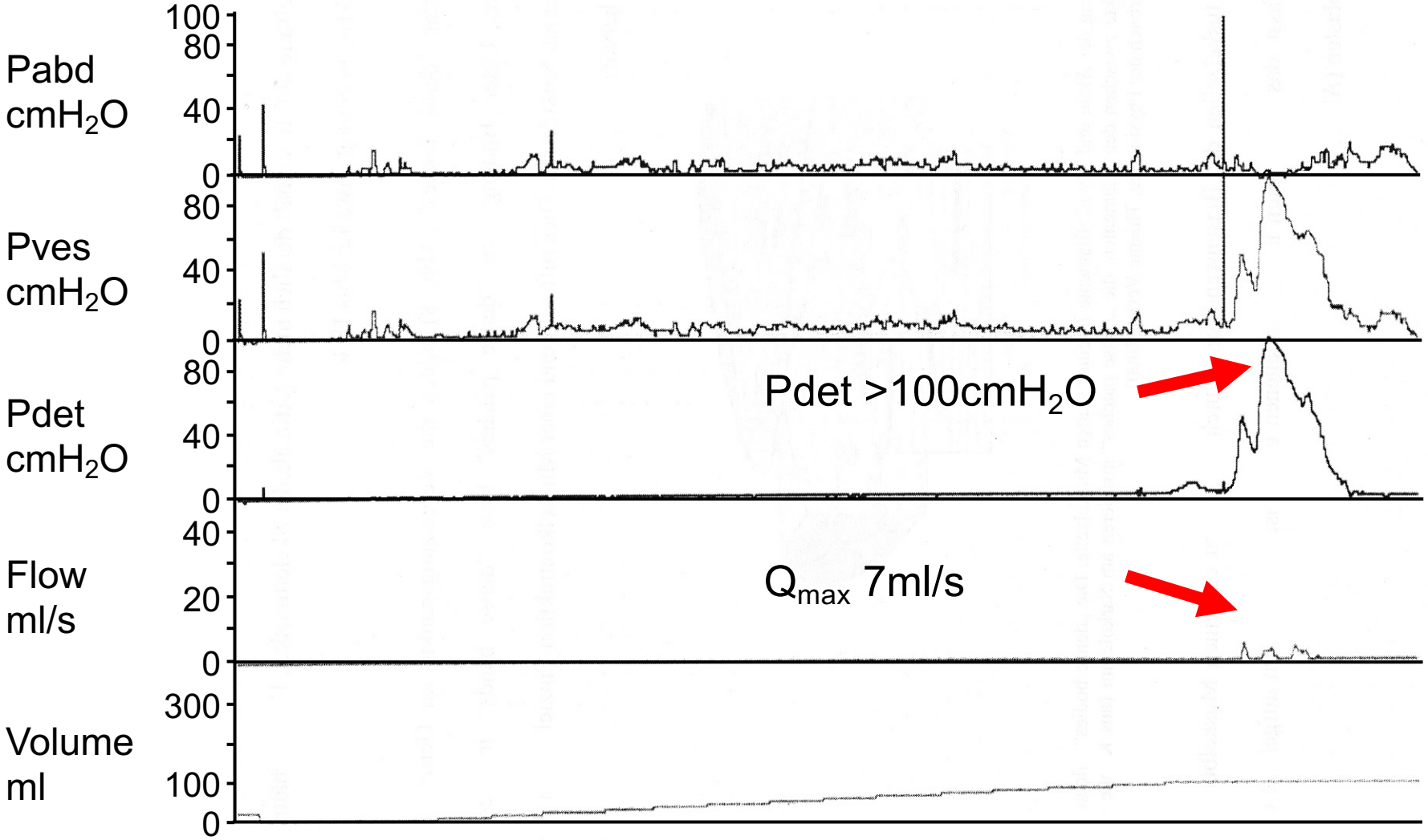
- Only a minority (around 30%) will and require medical treatment and/or surgical intervention.

Lee et al. Investig Clin Urol 2016
Egan Urol Clin North Am 2016
Irwin et al., BJU Int 2011
Berry et al. J Urol 1984

Benign prostratic obstruction (BPO)

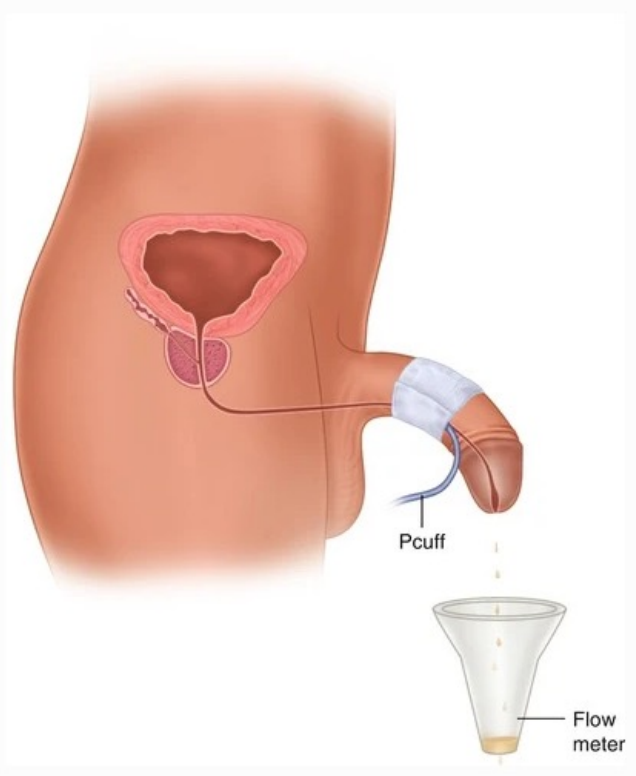


Suburethral sling



Metaanalysis of non invasive diagnostic tests

- Detrusor wall thickness DWT
- Penile cuff test PCT
- Resistive Index RI
- Intravesical prostatic protrusion IPP
- Qmax
- Prostate volume PV
- Postvoid residual PVR



Detrusor wall thickness and penile cuff test had the highest level of accuracy.

Vignoli Noninvasive urodynamics Springer 2016
Cheng et al. Front Urol 2022

EAU Guidelines

Summary of evidence	LE
Data regarding the diagnostic accuracy of non-invasive tests is limited by the heterogeneity of the studies as well as the small number of studies for each test.	1a
Specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.	1a

Recommendation	Strength rating
Do not offer non-invasive tests as an alternative to urodynamics/pressure-flow studies for diagnosing bladder outflow obstruction in men.	Strong

EAU Guidelines

Summary of evidence	LE
Pressure-flow studies is not a test for routine use prior to prostate surgery for all patients	3

Recommendations	Strength rating
Perform pressure-flow studies (PFS) only in individual patients for specific indications prior to invasive treatment or when further evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform PFS in men who have had previous unsuccessful (invasive) treatment for LUTS.	Weak
Perform PFS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform PFS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak
Perform PFS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post void residual > 300 mL.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak

Prostate Surgery for Men with Lower Urinary Tract Symptoms: Do We Need Urodynamics to Find the Right Candidates? Exploratory Findings from the UPSTREAM Trial

NO!

Conclusions:

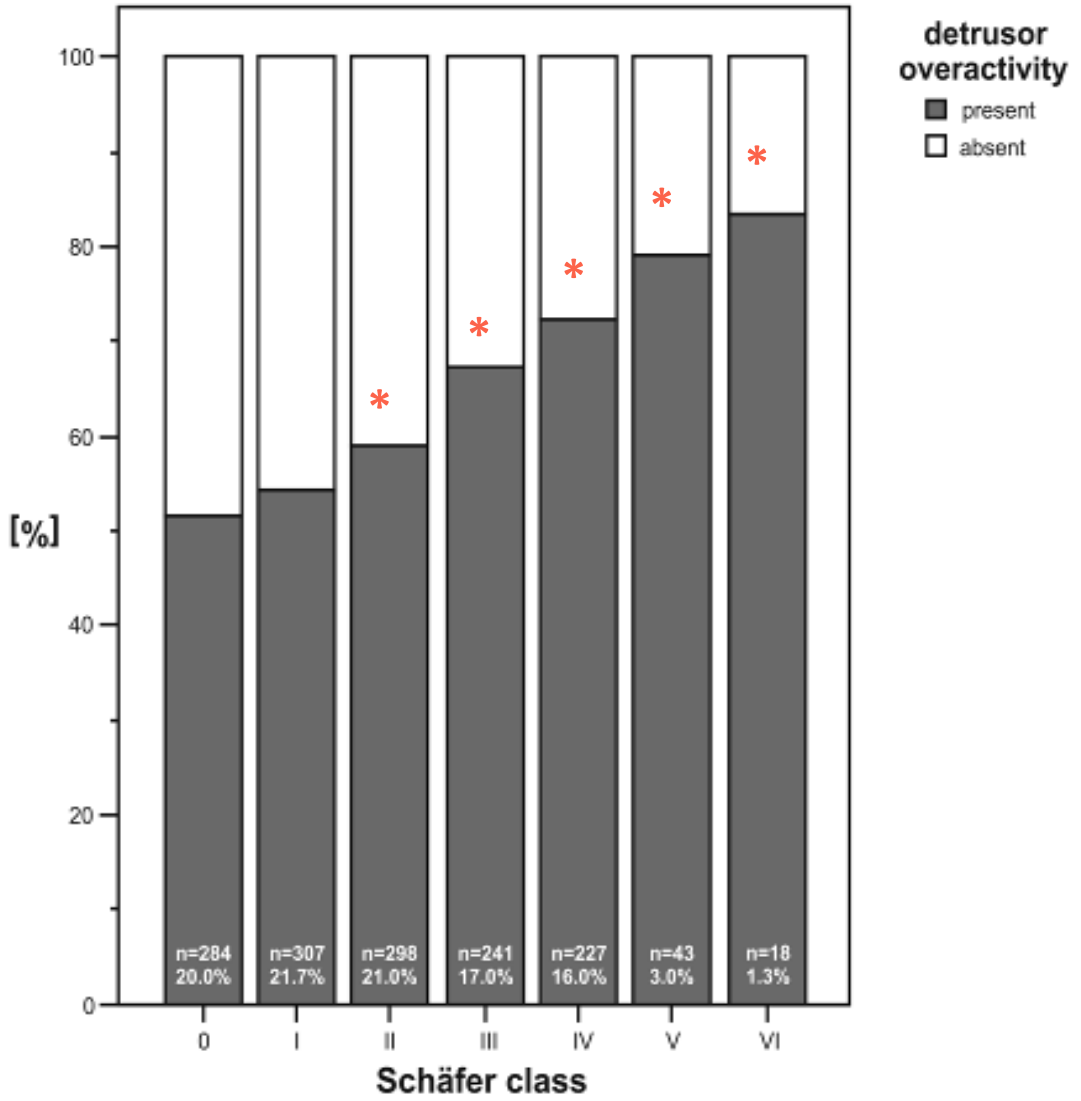
- This study shows that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively.
- For men with uncomplicated LUTS, the symptom improvement after treatment and the number of operations done are similar, irrespective of whether or not urodynamic tests are conducted in addition to routine tests.

Young et al., Eur Urol 2022.

Prevalence of Detrusor Overactivity before TURP

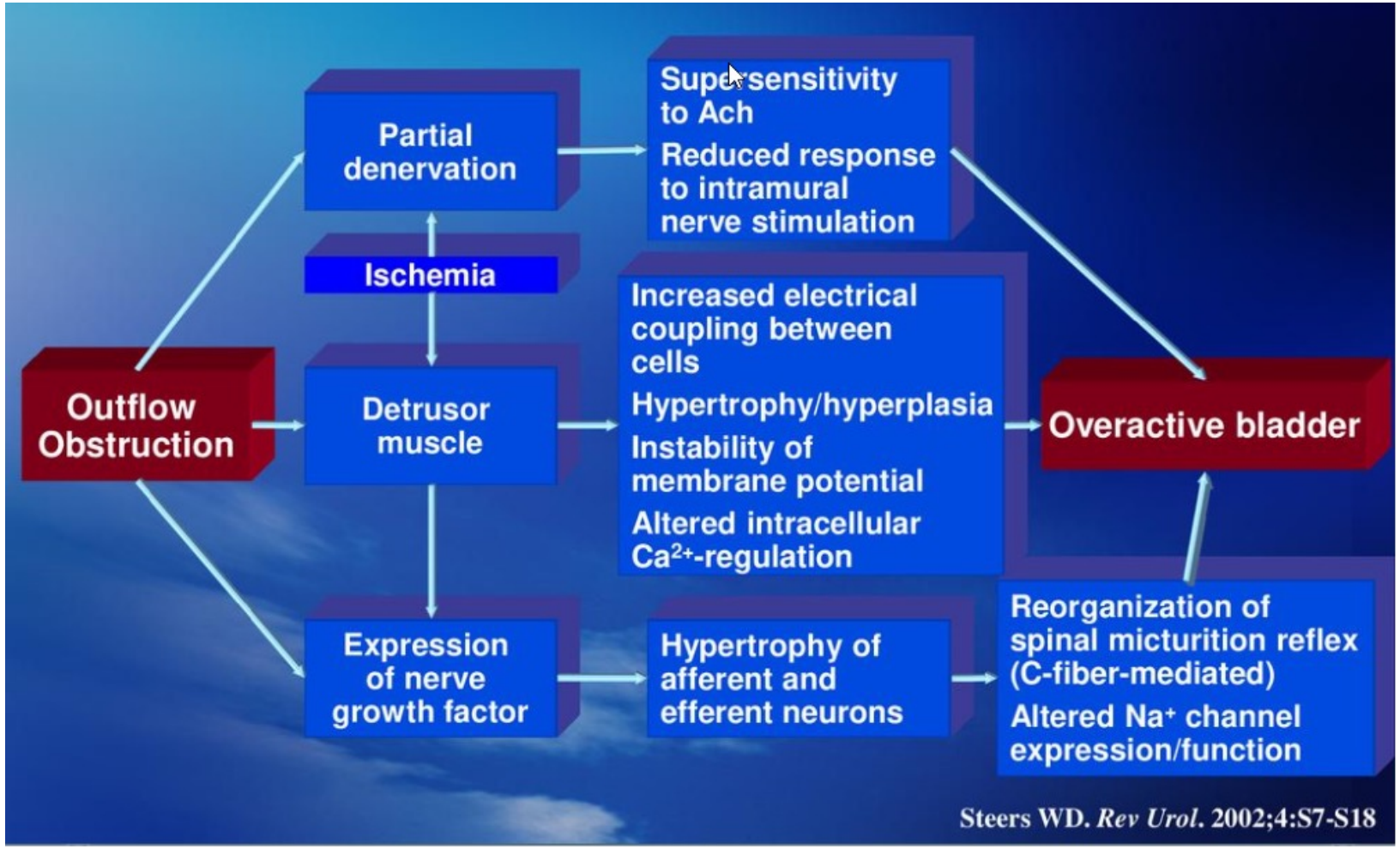
- Prevalence OAB and BPO:
  - Symptom scores: 40%
  - Urodynamics: 60%

- Risk factors:
  - age
  - prostate volume
  - bladder outlet obstruction



Oelke M et al. *Eur Urol.* 2008
Yi et al. BMC Urology 2019

Potential etiology of OAB in men with BPO



Bladder outlet obstruction is a common disease, however we still have limited understanding of the molecular mechanisms involved in the bladders reaction to obstruction.

Possible identification of a biomarker and potential target for treatment

Molecular changes in BPO

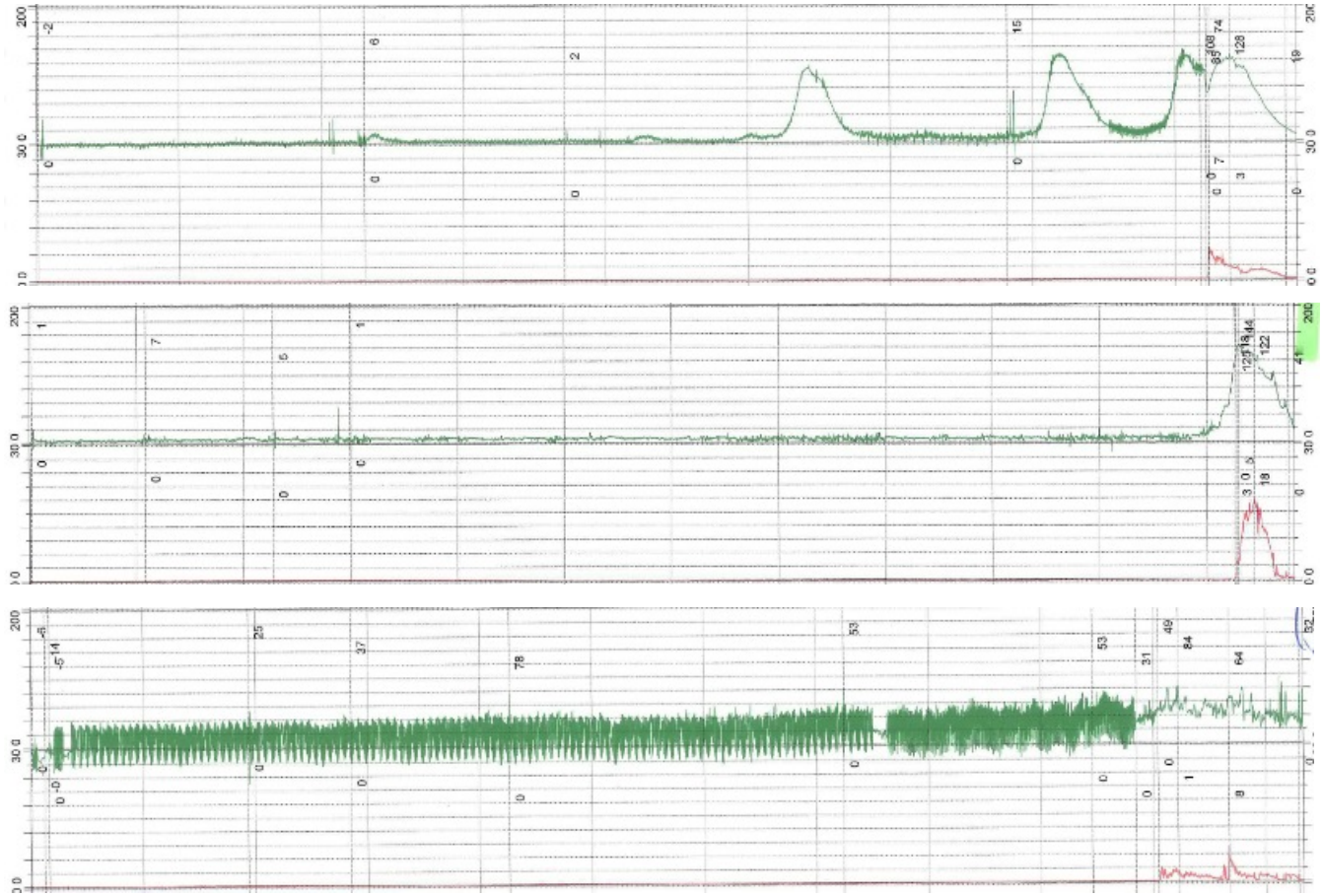
BPO phenotypes

Control

IPSS < 7 , no residual

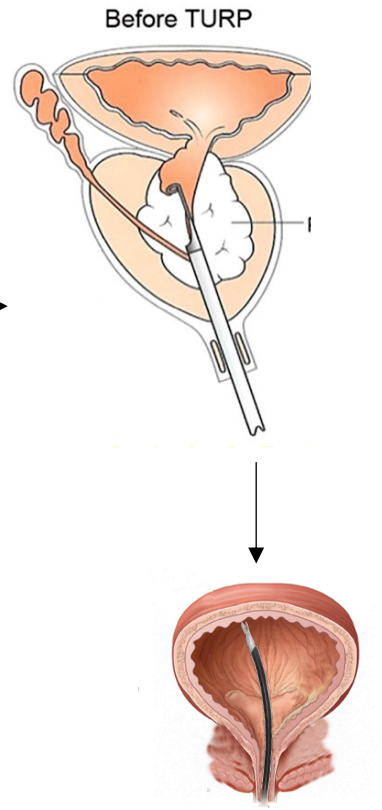
BPO

- DO
- BO
- UA



Gene expression analysis

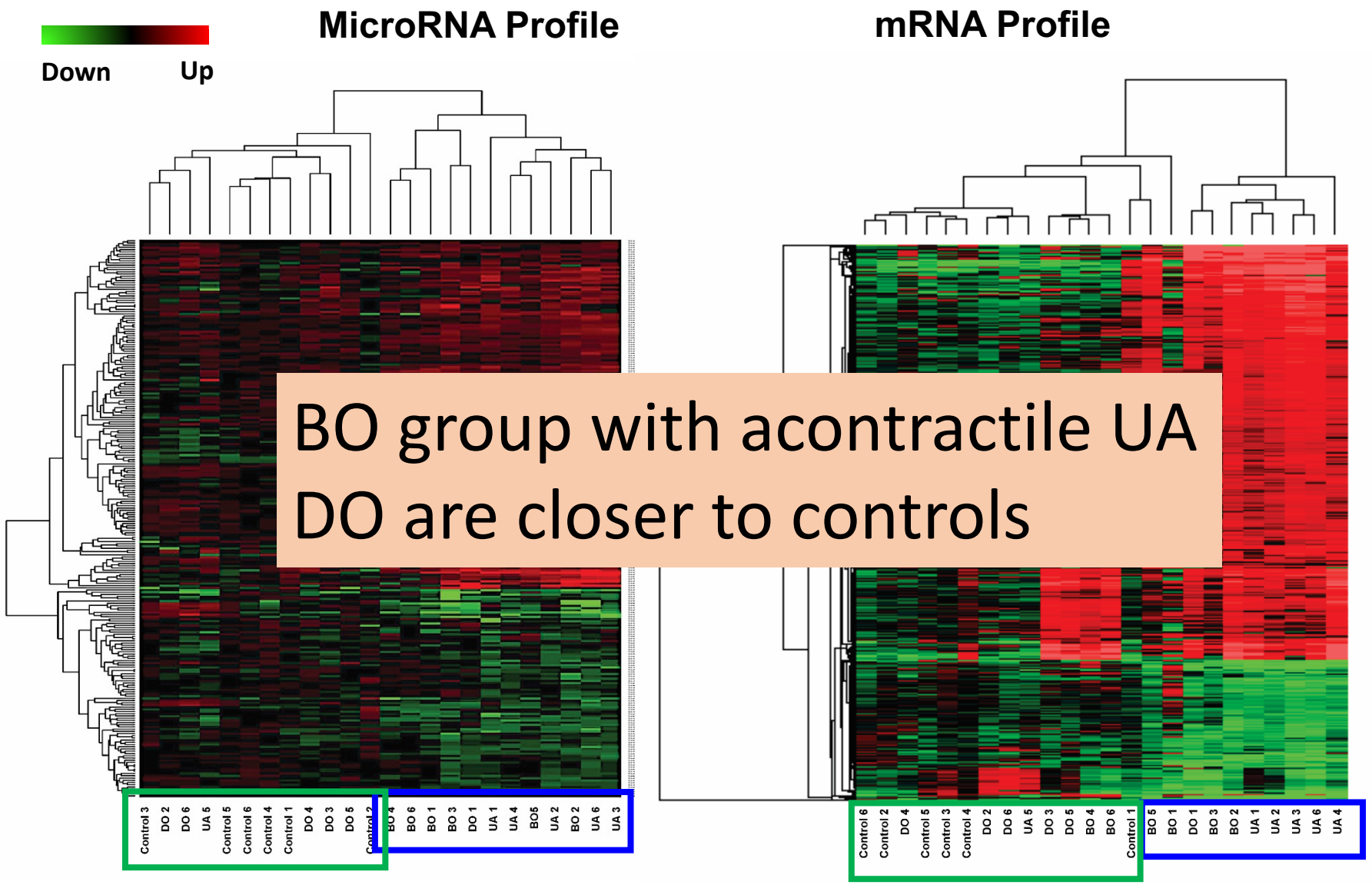
UDI functional assessment



mRNA Seq
proteomics

estimate the changes in signalling pathways, correlate with UDI

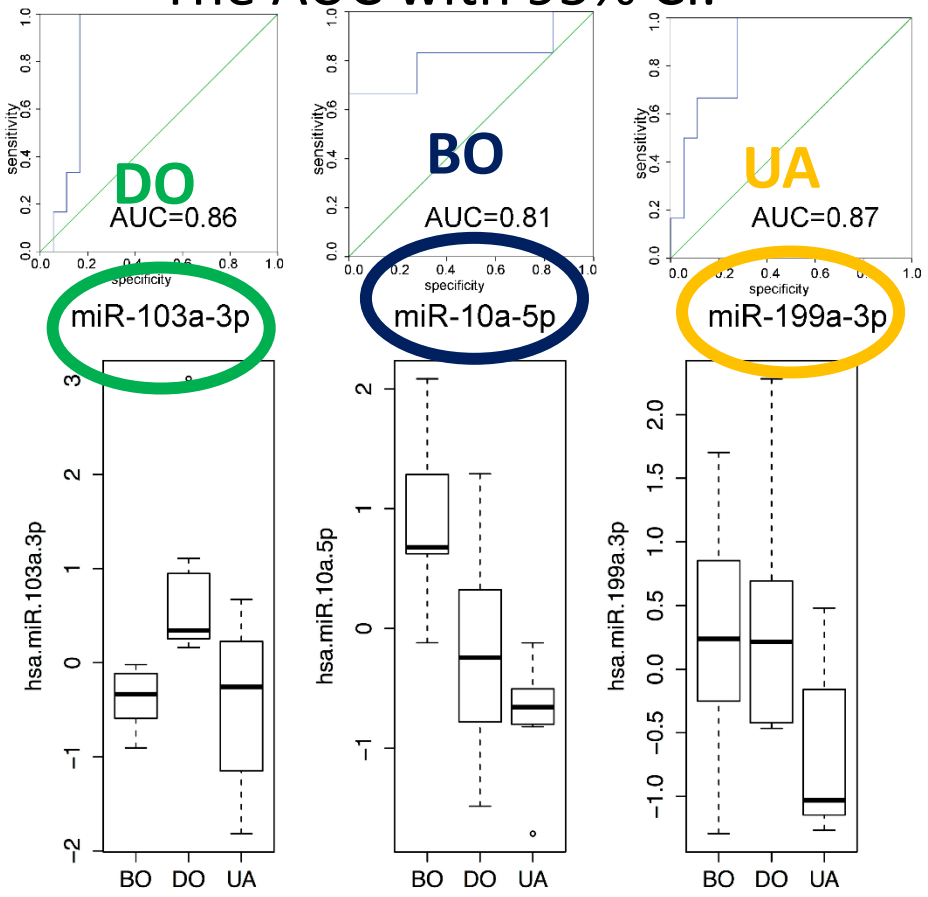
Gene expression profiles correlate with functional phenotypes

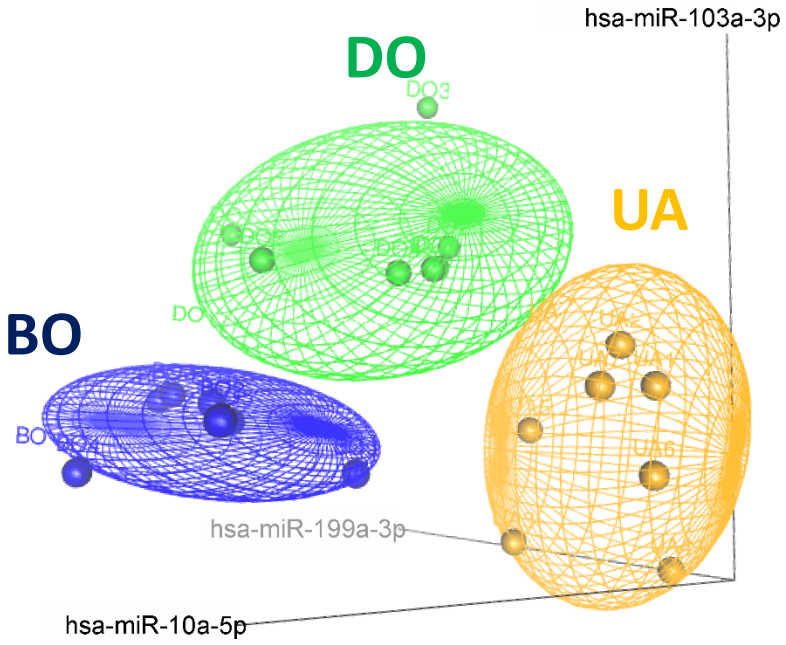


Gheinani AH *et al.* (2017) *JCI Insight* 26;2(2): e89560

miRNA biomarkers of BPO states

ROC curves from NGS data.
The AUC with 95% CI.





Three-dimensional
scatterplots
for 3 miRNA biomarkers

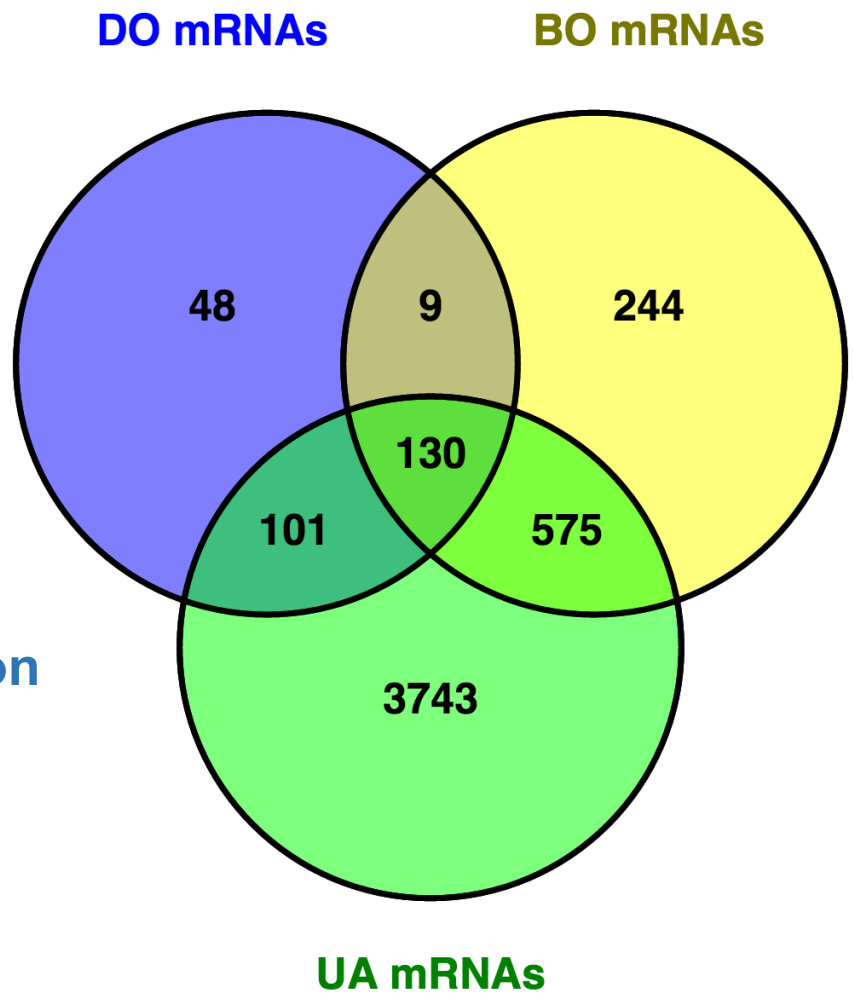
Gheinani AH *et al.* (2017) *JCI Insight* 26;2(2): e89560

Number of regulated mRNAs increases:

mRNAs DO < mRNAs BO < mRNAs UA
288 958 4549

Number of inflammatory pathways increases
DO < BO < UA

Adaptive inflammatory response, macrophage infiltration
TNF-α as top driver = highest in UA



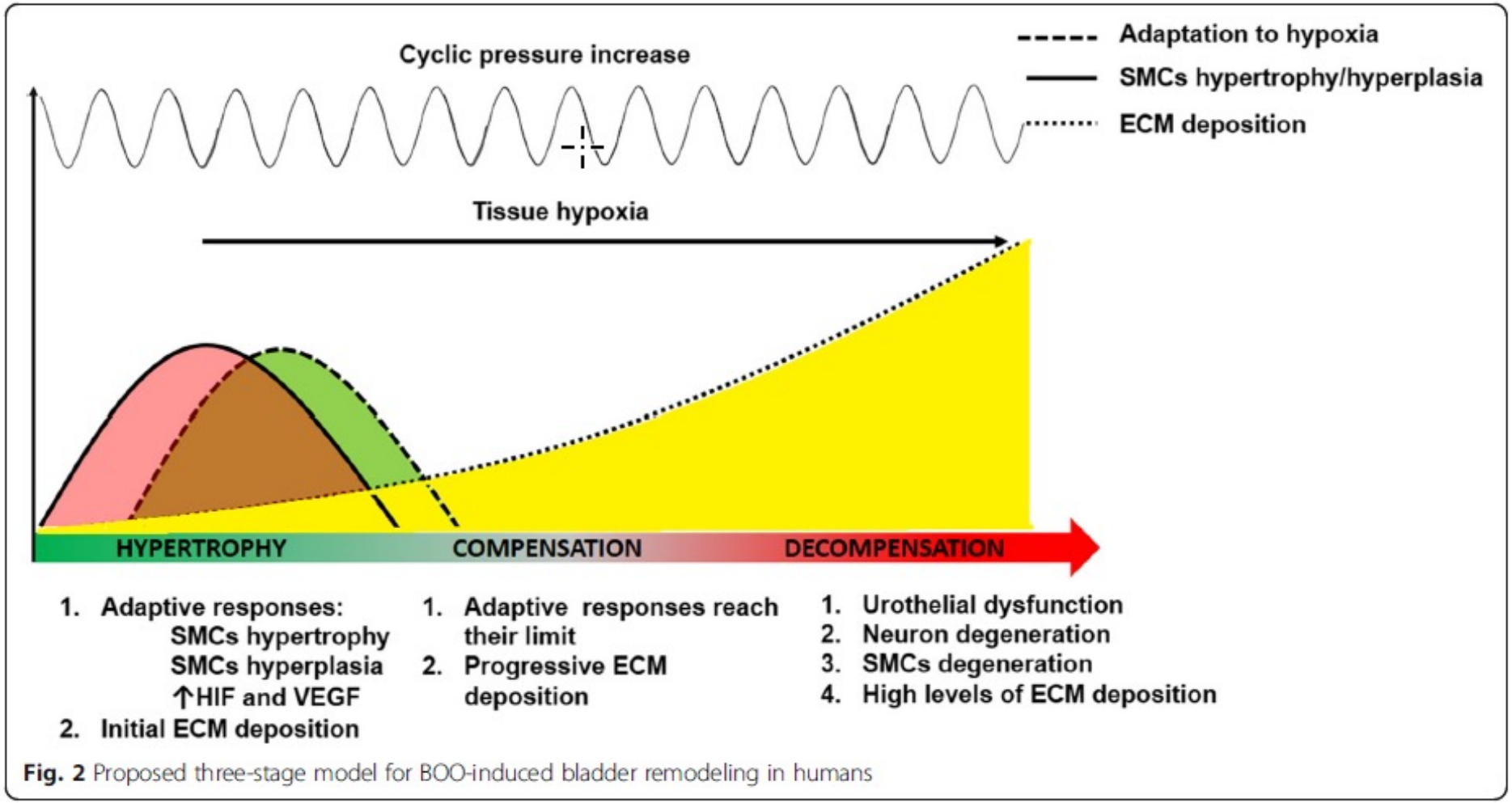


Fig. 2 Proposed three-stage model for BOO-induced bladder remodeling in humans

Fusco et al., BMC Urol 2018

The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated bladder outlet obstruction

ALUN W. THOMAS, ANDREA CANNON, ESTHER BARTLETT, JULIE ELLIS-JONES and PAUL ABRAMS
Bristol Urological Institute, Bristol, UK

Accepted for publication 11 July 2005

Patients with untreated BOO do not significantly deteriorate urodynamically in the long term, with only a minority (15%) deteriorating symptomatically.

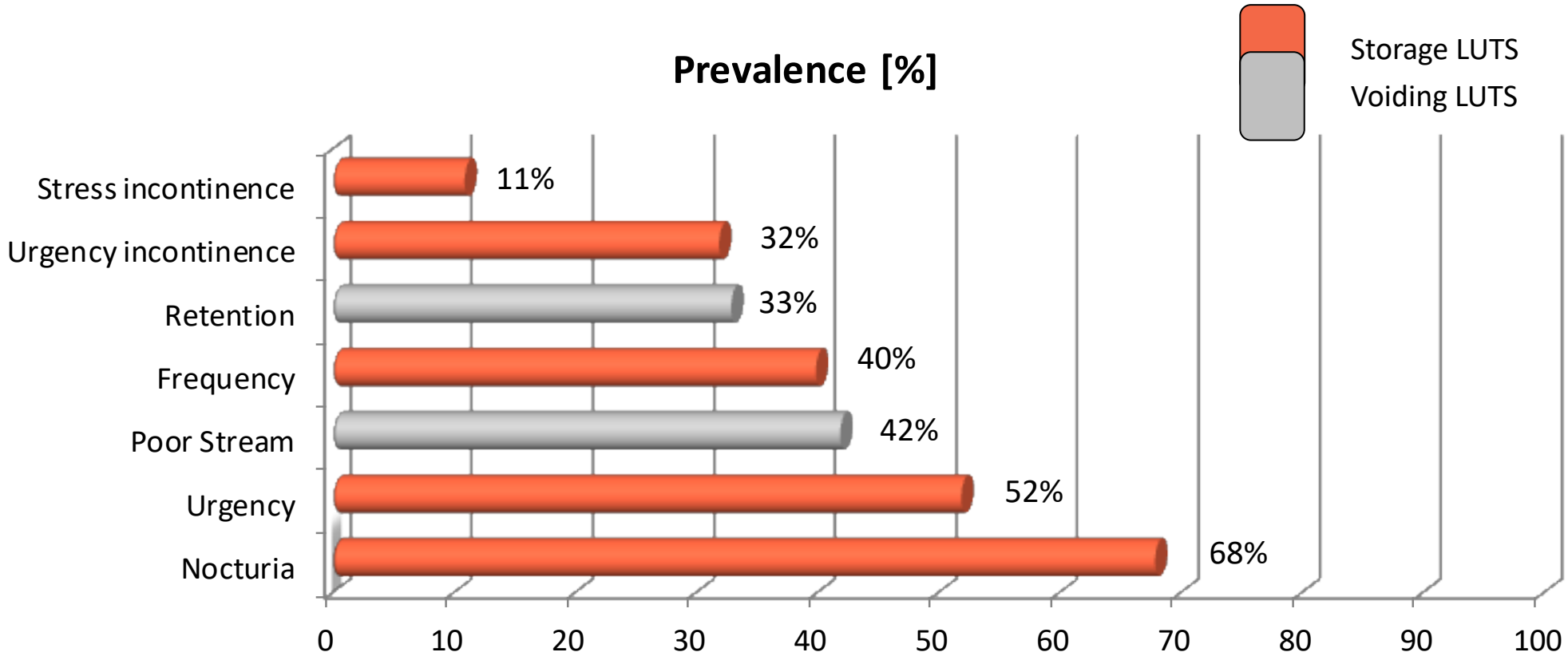
Urodynamic changes: detrusor contractiliy decreased. Prevalence DO increased

These findings justify a conservative approach to men with LUTS associated with BOO.

Thomas et al., BJU Int 2005

Which LUTS persist after prostatic surgery?

In retrospective case series, residual/recurrent LUTS after TURP were found in approx. 15-20% of patients (mean time from TURP 3.5 years)



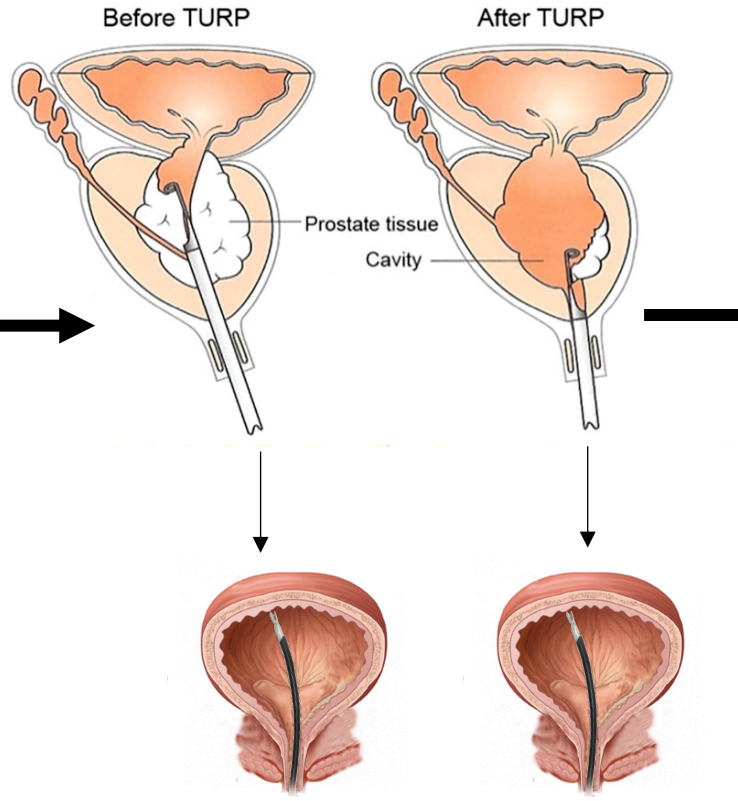
n = 129 men
(consecutive series, age 46-90 y, mean 72 y)

Seaman EK et al. *J Urol*. 1994; 152: 935 – 937.

Gene expression analysis before and after TURP

Same patient

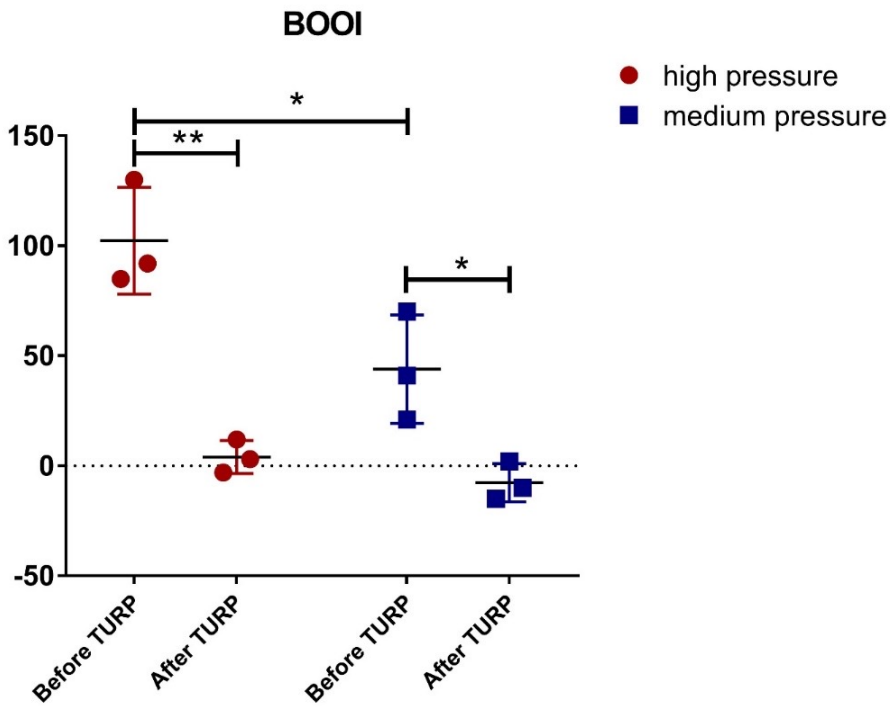
UDI functional assessment

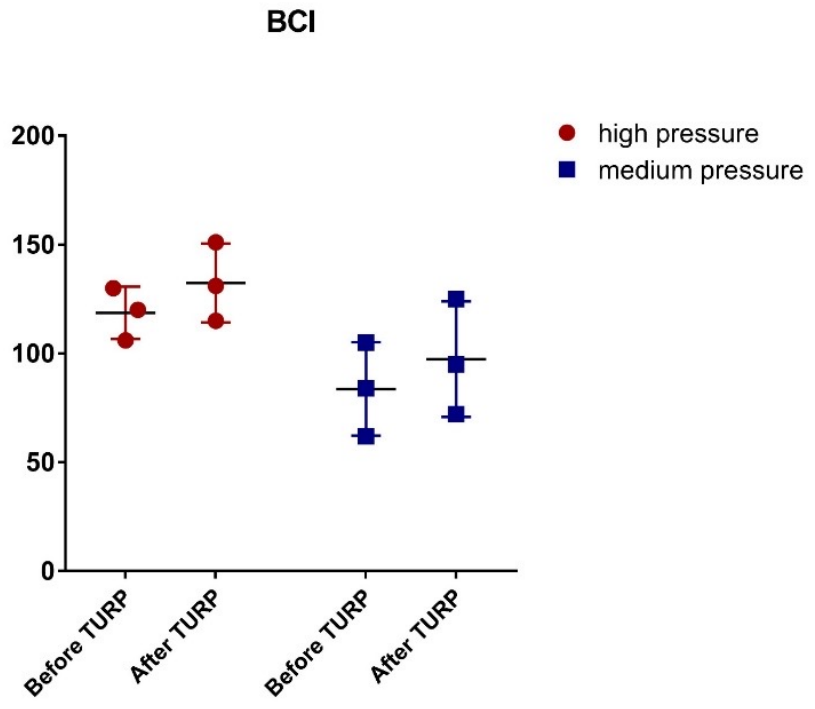


mRNA Seq proteomics

estimate the changes in signalling pathways, correlate with UDI

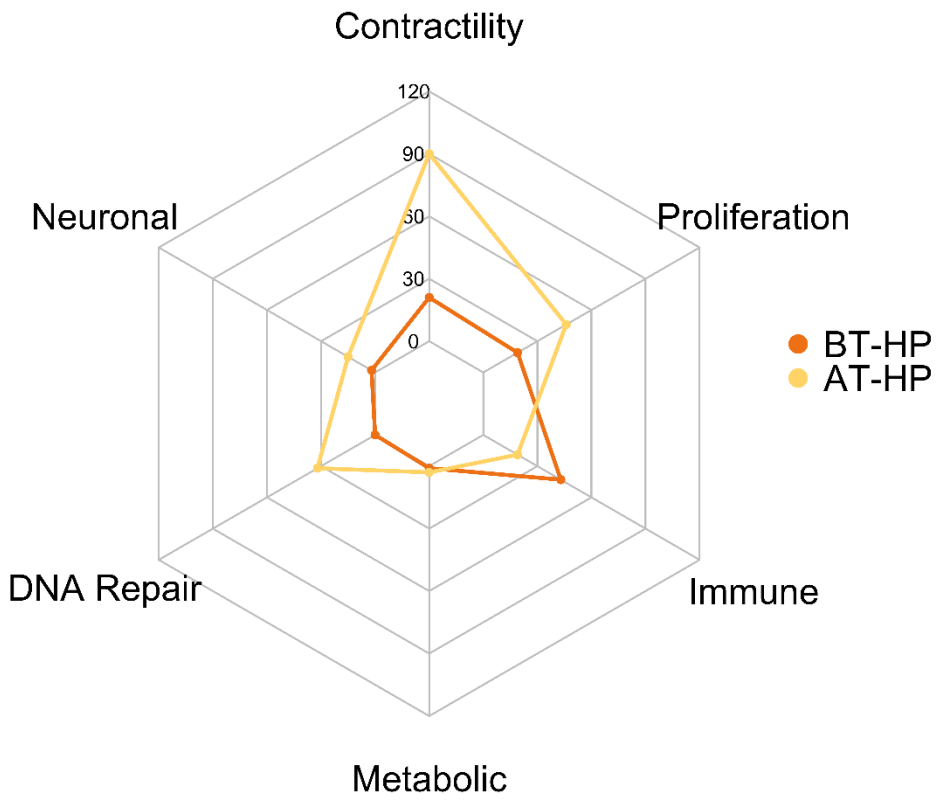
UDI findings before and after TURP in groups without DO





Molecular processes in groups without DO before and after TURP

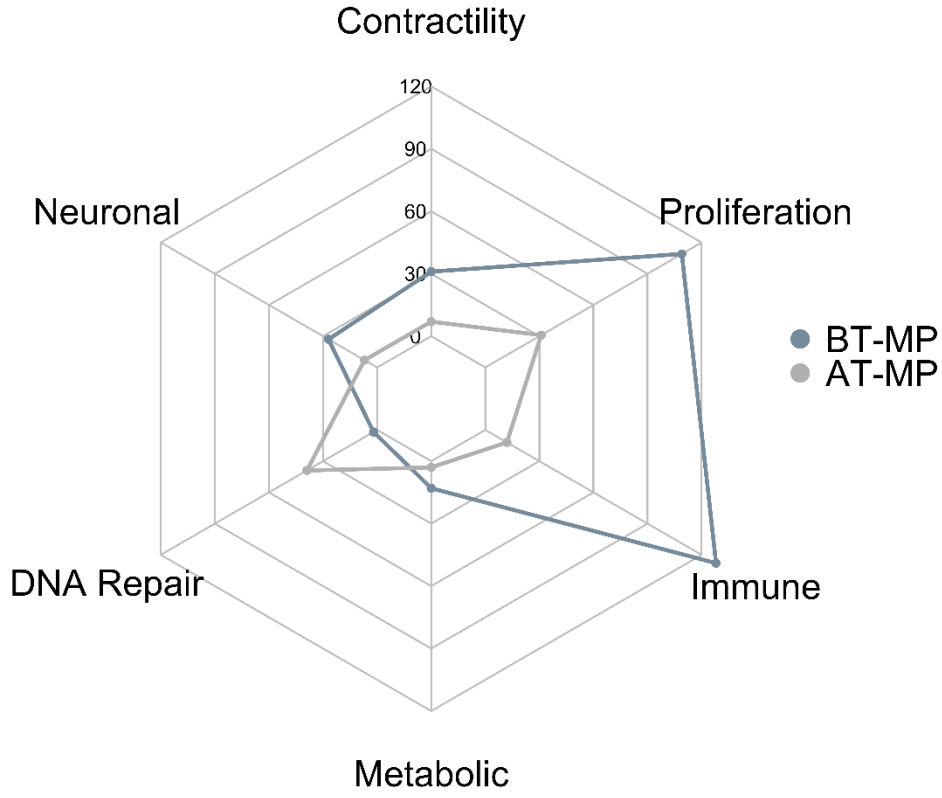
severe BOOI



After TURP :

- Reduced inflammation
- Increased contractility
- Increased proliferation

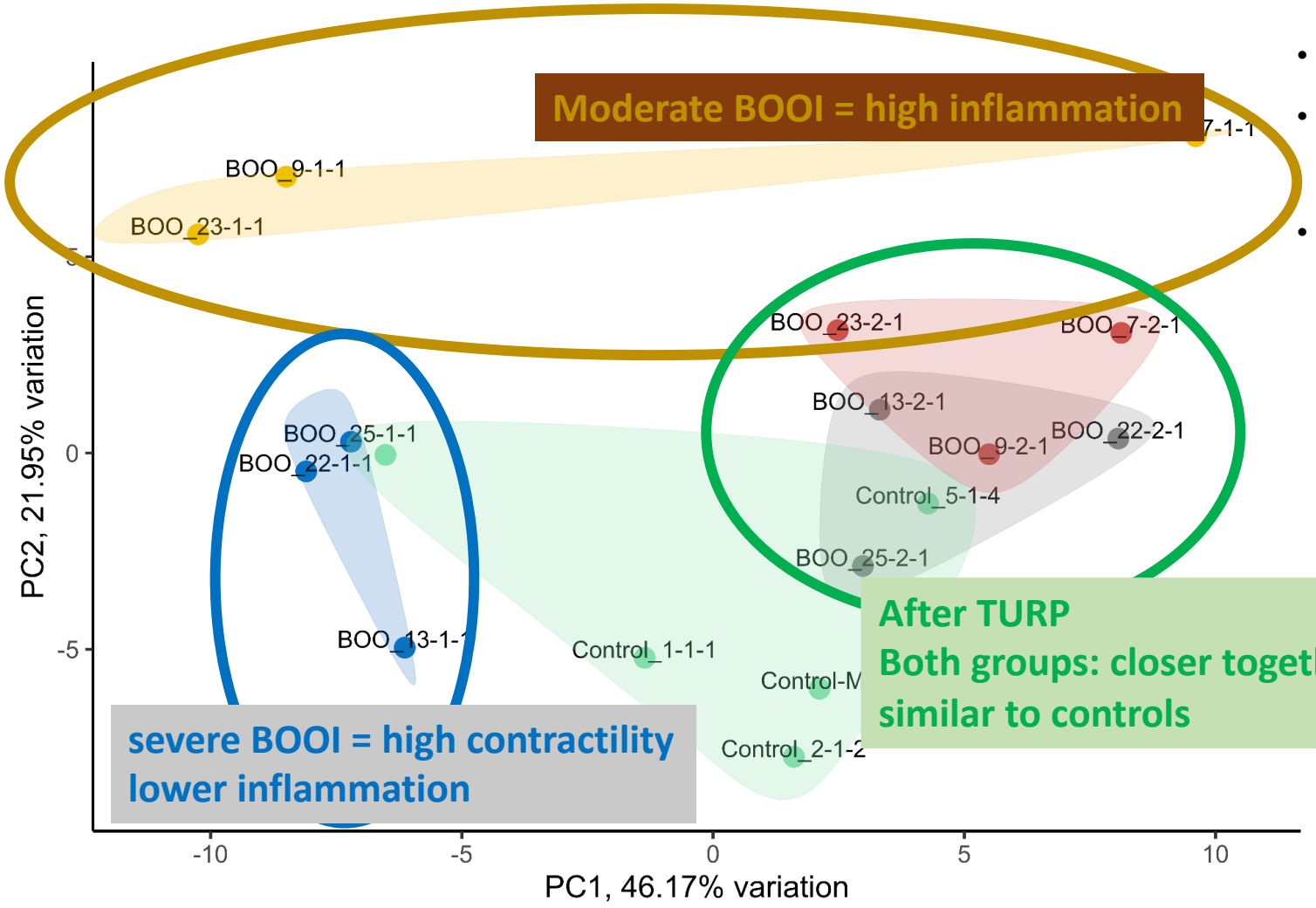
moderate BOOI



After TURP :

- Reduced inflammation
- Reduced contractility and proliferation
- Increased DNA repair

TUR-P brings improvements in HP and MP BPO groups

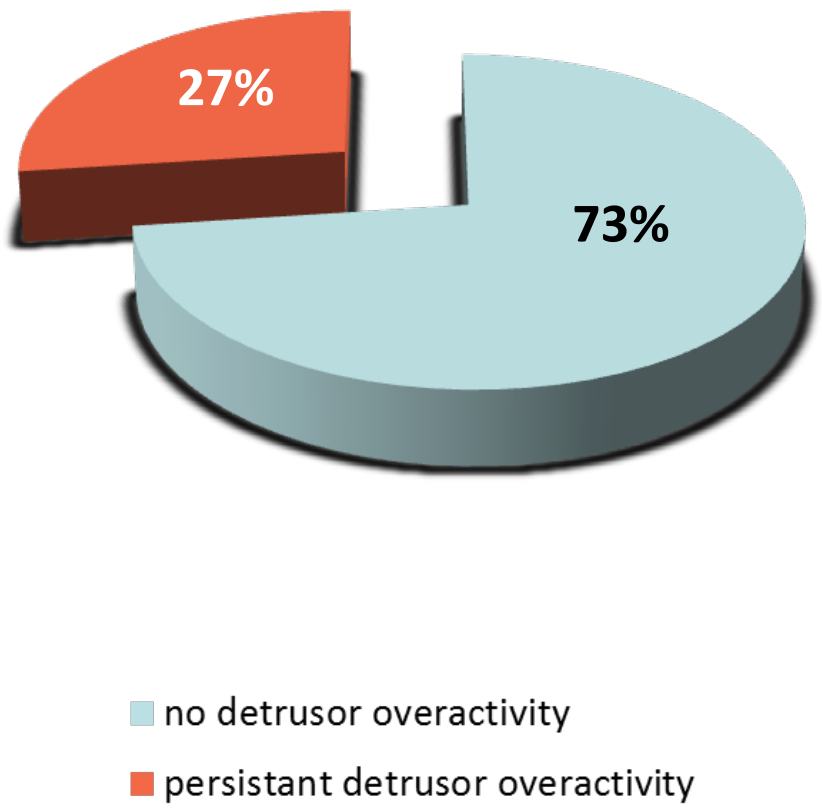


- Sample transcriptome clustering in Principal Component Analysis
- HP and MP groups are apart before TURP
- Gene expression changes show activation of inflammatory pathways
- HP and MP groups cluster together aftfer TURP

group
- after_high
- after_medium
- before_high
- before_medium
- control_control

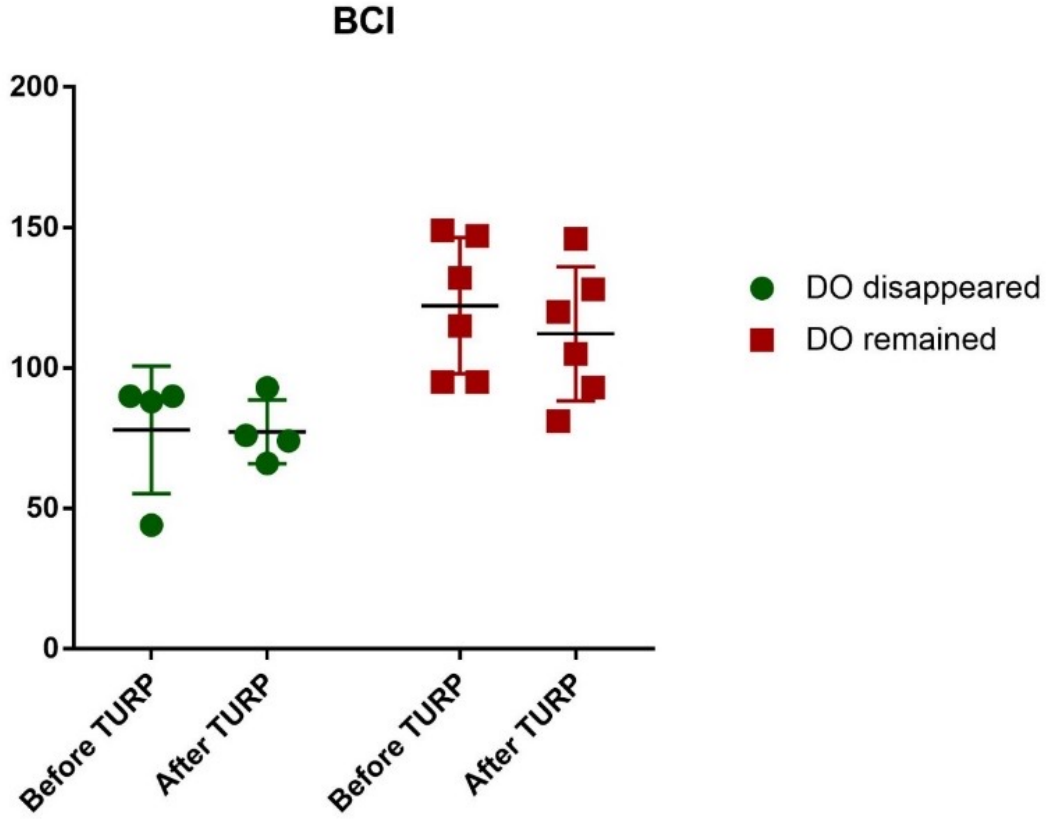
Prevalence of detrusor overactivity after TUR-P

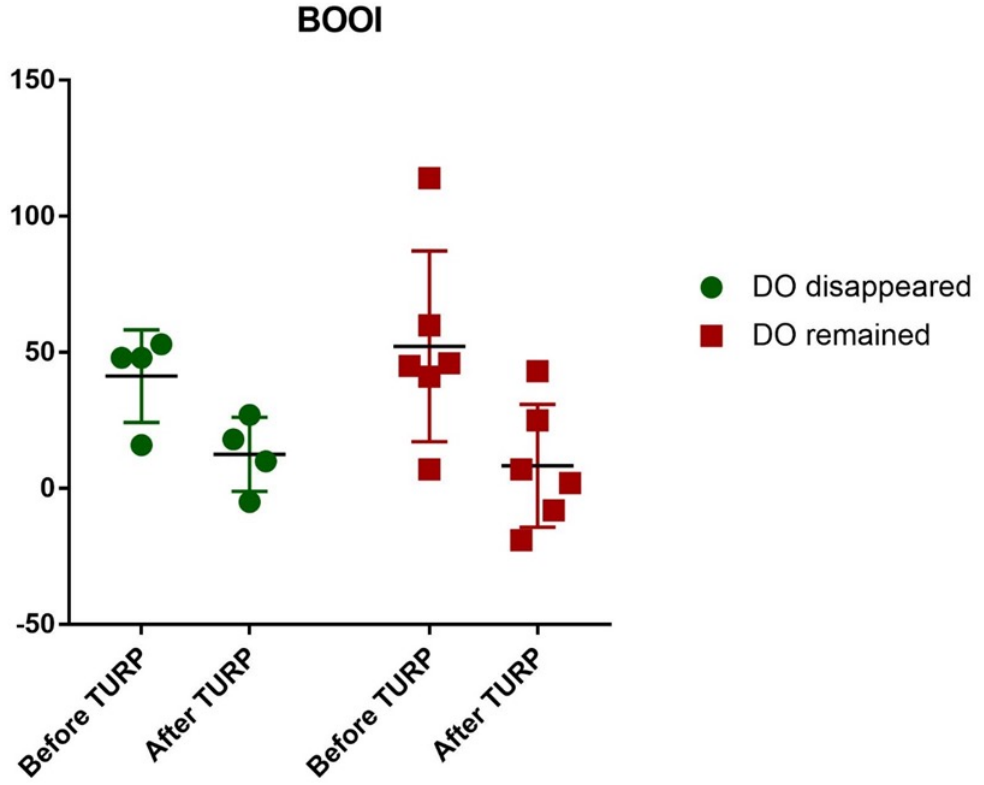
DO + BPO [1,2]



Roehrborn CG et al. ICUD-BPH Guidelines 1996
Machino R et al. *Neurourol Urodyn.* 2002
Knutson T et al. *Neurourol Urodyn.* 2001

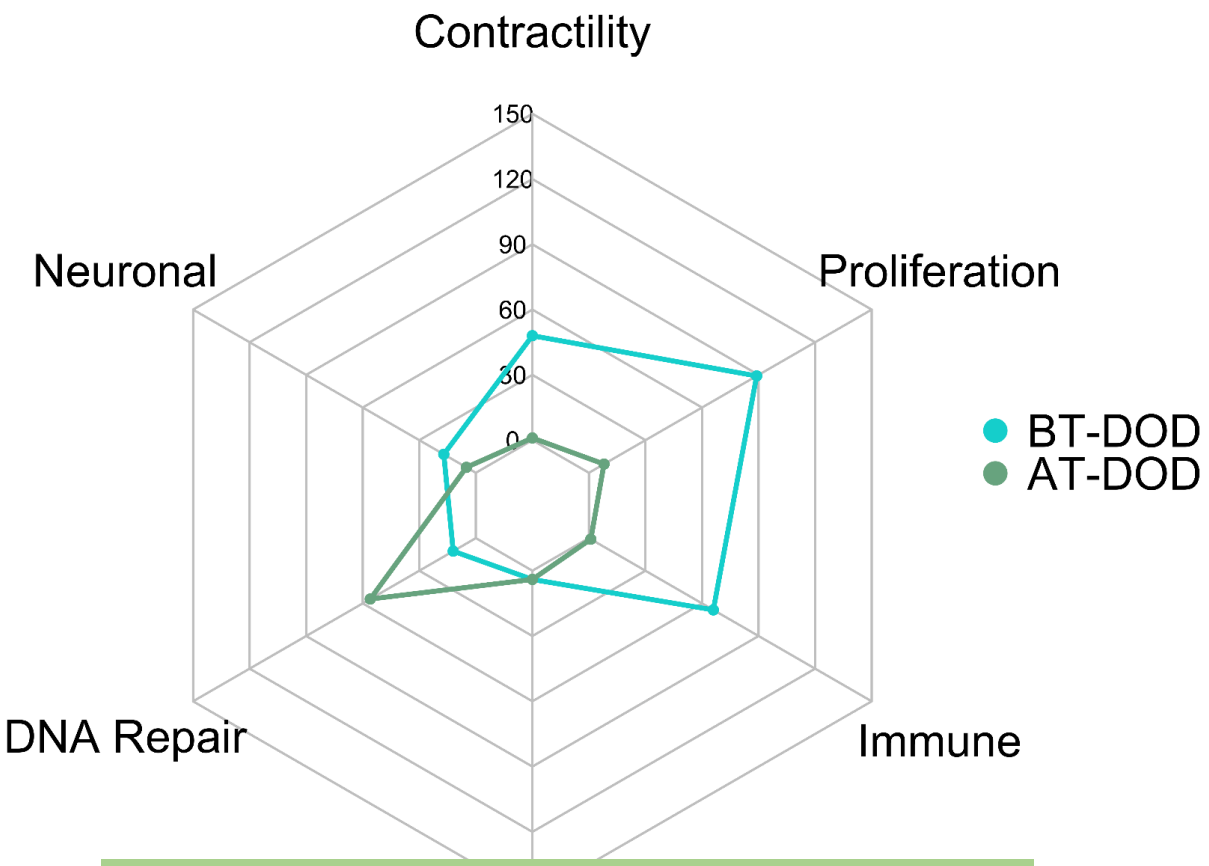
UDI findings before and after TURP in groups with DO





Molecular processes in groups with DO before and after TURP

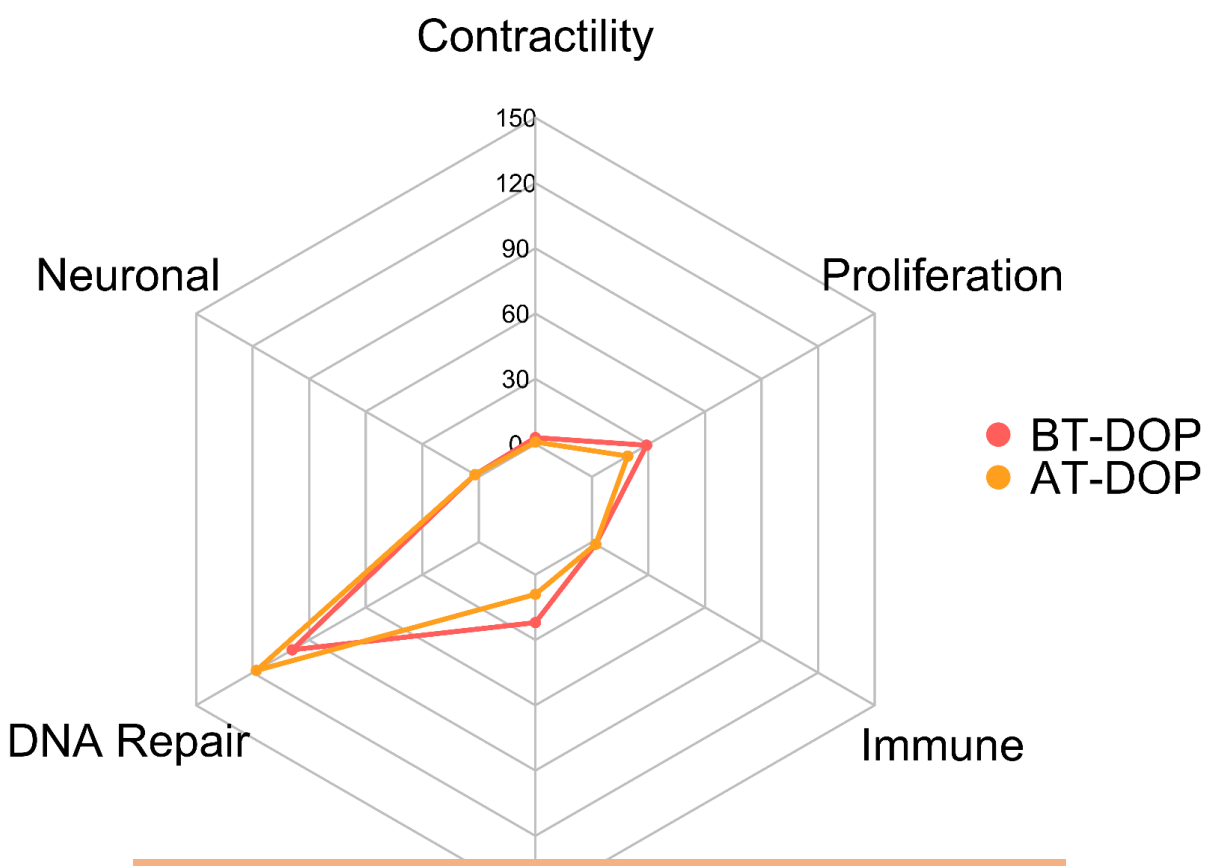
DO disappeared



After TURP :

- Change of pattern
- Reduced inflammation
- Reduced contractility and proliferation
- Moderate DNA repair

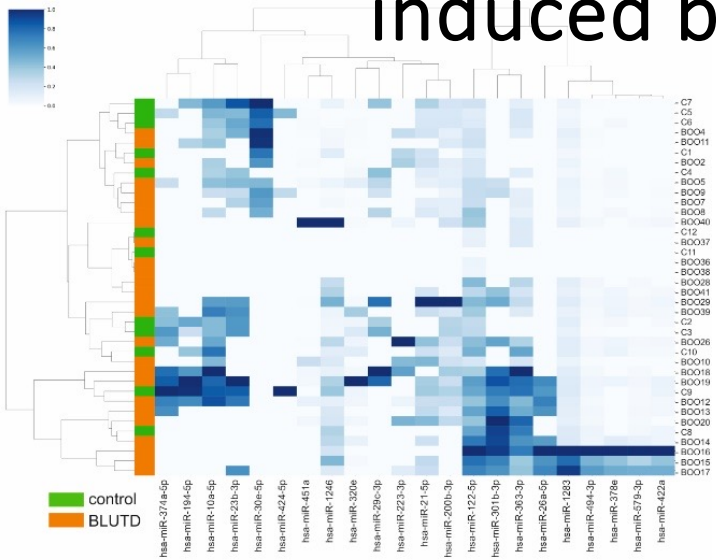
DO persisted

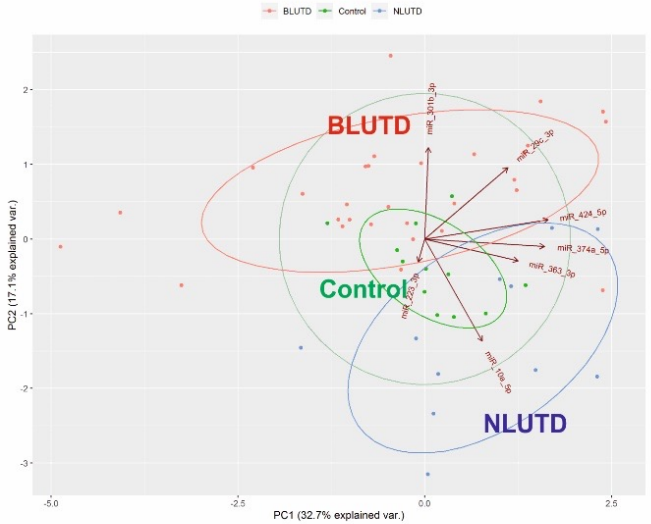


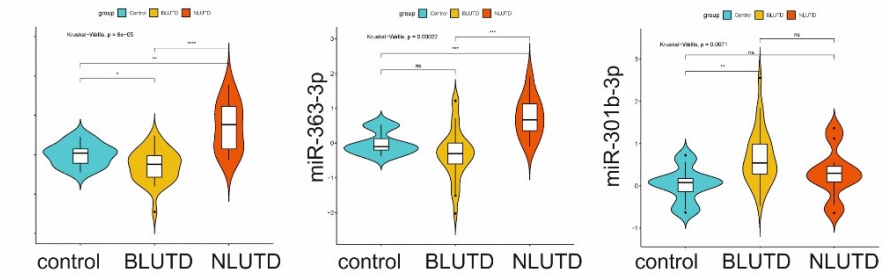
After TURP :

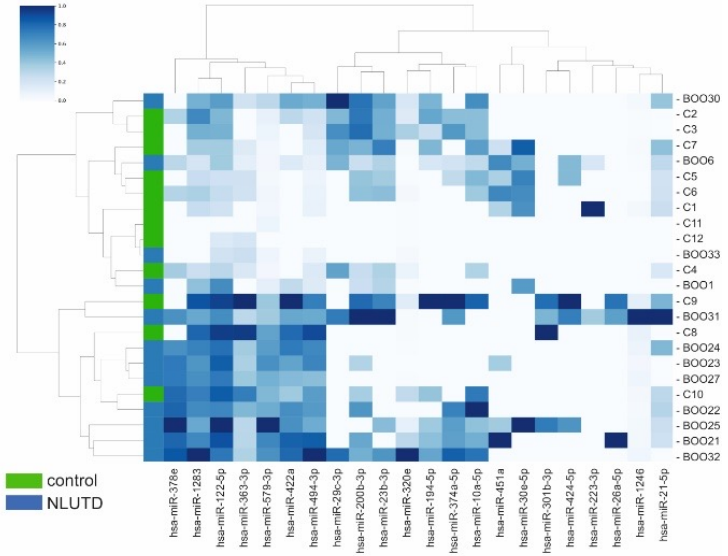
- Pathways still dysregulated
- Low contractility
- Highly increased DNA repair

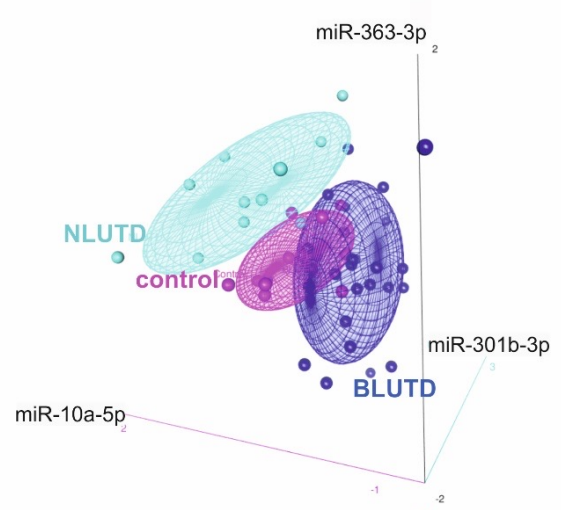
Urinary miRNA profiles discriminate between BOO-induced bladder dysfunction and healthy controls











Urinary miRNA signature (**miR-10a-5p, miR-301b-3p** and **miR-363-3p**) discriminates between controls and patients with LUTD (BLUTD and NLUTD)

Abundant urinary miR-320e can serve as normalization miRNA

von Siebenthal, M. *et al*., **Sci. Rep**.(2021) 11:10204

Summary

- Not all LUTS are caused by the prostate.
- BPO is not always symptomatic.
- BPO causes significant remodelling of the bladder with potential serious functional impairments.
- Inflammation may be an important factor in disease progression.
- OAB/DO persists in 25% after BPO treament (TUR-P).
- Distinct difference in gene expression in persistent DO
- Future directions: molecular markers in urine

Thank you!

Functional Urology Group

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