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Presumed Agent Orange Exposure in Vietnam Veterans is Associated with Lower Urinary Tract Symptoms

Steven C. Castle[1*], Abigail Viado[2], Frank Catapano[3], Cathy C. Lee[4]

[1,2,3,4]Geriatric Research Education and Clinical Center (GRECC), VA Greater Los Angeles; Department of Medicine, UCLA School of Medicine.

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Corresponding Author: Steven C. Castle, Geriatric Research Education and Clinical Center (GRECC), VA Greater Los Angeles; Department of Medicine, UCLA School of Medicine.

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Abstract

Background

As part of a clinical innovation project to look at the impact of presumed Agent Orange Exposure (AOE) in Vietnam Veterans, we enrolled Vietnam Veterans in the Gerofit Group Exercise Program and assessed their fitness and cognition. To look into the potential of a Veteran having presumed AOE, we used qualitative and quantitative screening methods described below.

Case Presentation

We incidentally observed that the AOE Veterans had active bladder symptoms (Lower Urinary Tract Symptoms or LUTS). A literature review failed to identify any human studies, but we did find 3 mouse model studies that supported the idea that AO or Dioxin exposure to mice in utero or during lactation resulted in active bladder issues when the mice became older due to enhanced neuromodulation of the bladder from the dioxin. So, we used the Lower Urinary Tract Dysfunction Symptom Index-10 (LURN SI-10) to measure the severity of LUTS and compared those with presumed and without presumed AOE.

Conclusion

Presumed AOE Veterans had significantly higher LURN SI-10 scores, and this supports the conclusion that Veterans presumed to be exposed to Agent Orange are more prone to bladder issues.

Introduction

We are conducting a study to look at the possible impact of presumed Agent Orange Exposure (AOE) on mobility and balance. This was part of an ongoing Clinical Innovations Project funded by the National Office of Geriatrics and Extended Care of the Veterans Health Administration, initially funded in 2023. Presumably, 2.7 million US Military may have been exposed to AO between 1962 -71 **[2]**. It is estimated that over 300,000 US Veterans and over 400,000 Vietnamese died from AOE between 1962 and 1971. The US sprayed 20 times more AO than the manufacturer recommended. AO is 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD or Dioxin) and persists in humans for a half-life of 7-11 years and persists indefinitely in the environment. "The Vietnamese Red Cross estimates that 3 million Vietnamese have been affected by dioxin, including at least 150,000 children born after the war with serious birth defects" (Wells-Dang A, usip.org/publications). Presumptive conditions of AOE have demonstrated an increase in healthcare utilization, and the PACT Act was passed in August 2022 to expand healthcare and benefits to Veterans with presumed toxic exposures like burn pits or AO. Presumptive conditions from AOE are listed on this website: https://www.pendercountync.gov/va/agent-orange-presumptive-conditions/ , and we intend to look further into possible impact on cognition and mobility. This project and Gerofit are quality improvement/quality assurance projects and approved by the institutional review board at the VA Greater Los Angeles Healthcare System, and participants are not required to sign consents.

In a literature search and discussion with national experts to detect presumed AOE, we came up with a Qualitative (Does Veteran have no, minor, moderate, or significant concern) and a Quantitative Veteran Herbicide Exposure Index based on 6 questions that rate their presumed exposure risk as negative, low, moderate, or high **([3], see Figure 1)**.

Figure: 1

AGENT ORANGE EXPOSURE RISK (vers061223):

Military Branch: Dates of service:

_VN (12 nautical miles off coast), _Thailand, Laos, Cambodia (Mimot or Krek, Kampong Cham Province), Guam or Am Samoa, Korean DMZ, Operation Ranch Hand, Army Chemical Corp, Fly on C-123

Qualitative Pt report of Likely Agent Orange Exposure (include possible 'Brown Water Navy'):
-Level of concern: 0-none, 1-Low, 2-Mod, 3-High:

Presumptive Conditions from Agent Orange Exposure:
AOR or Claim filed in the past:

Quantitative Veteran Herbicide Exposure Index

1. Did you ever spray herbicides in Vietnam?
2. Did you ever handle herbicide spray equipment or containers in Vietnam?
   -Did you work on Operation Ranch Hand or in the Army Chemical Corps (ACC)
3. Were you present when others were spraying herbicides in Vietnam?
4. Did you ever get herbicides on your skin or clothing in Vietnam?
5. Did you ever pass through and area in Vietnam that looked like it had been defoliated
   That was sprayed with a chemical to kill vegetation, trees or grass)?
   Were you based at Bien Hoa, Da Nang or Phu Cat?
   Where you in a Naval Ship off the coast of VN, or in AF on bases listed above?

6. Do you think you were exposed to herbicides in any other way in Vietnam?
   Did you fly in C123 Aircraft?

High Exposure Index:	Yes to 1. or 2.
Moderate Exposure Index:	Yes to 3. or 4., but No to 2.
Low Exposure Index:	Yes to 5. or 6. only
Negative Exposure Index:	No to all 6.

Self-reported Health Status of Vietnam Veterans in Relation to Perceived Exposure to Herbicides and Combat Decoufle P, Am J Epidemiol 1992

Level of exposure by Base. Phan Van Manh Chemosphere 2021

https://doi.org/10.1016/j.chemosphere.2020.129024Z77.9/snomed102443008,
1991 Public Law 102-4, the "Agent Orange Act of 1991": "A Veteran who served in the Republic of Vietnam from **1/9/1962 to 5/7/1975** shall be presumed exposed to herbicides containing dioxin unless there is clear evidence establishing the Veteran was not so exposed." Brown M Brooklyn J Law Policy 2005

We widely distributed brochures about this program with the intention of enrolling Vietnam Veterans in our Gerofit Exercise program **[4]**, provided seminars to Veterans Service Organizations and primary care providers at our VA Facility to engage with Veterans with presumed exposure to AO, with the goal of enrolling them into Gerofit. For those identified with presumed AOE, we facilitated filing Claims with the Veterans Benefits Administration if they had not previously filed a claim and wanted to.

As we began to accumulate presumed AOE Veterans, it was subjectively noticed that presumed AOE Veterans had active bladder symptoms, or Lower Urinary Tract Symptoms (LUTS). A literature search did not identify any human studies or reports, but we found 3 rodent studies in which TCDD exposure occurred In Utero and/or during lactation to the mother, resulting in dysfunction of the lower urinary tract in adulthood. The bladders of the exposed mice were significantly heavier, and urodynamic voiding behavior showed a marked reduction in intervoid interval. It was found that the TCDD exposure resulted in enhanced recruitment of noradrenergic neurons with a permanent increase in noradrenergic axon density and excessive prostatic and urethral smooth muscle tone **[5]**. In speaking to some experts in LUTS, the Lower Urinary Tract Dysfunction Research Network developed the Symptom Index-10 (LURN SI-10), with a max score of 38, which was felt to be the best screening method for LUTS (Cella D Neurourology & Urodynamics 2019, see **Figure 2**). This was given to the Veterans. We compared the LURN SI-10 scores of three comparison groups:

- Negative Presumed AOE: Qualitative and Quantitative scores=0
- Presumed AOE:
  - Qualitative AND Quantitative AOE risk questionnaires both >0,
  - Qualitative OR Quantitative >0

Figure: 2

LURN SYMPTOM INDEX-10 (LURN SI-10)

Instruction: This questionnaire asks you about different urinary symptoms. Please read each question carefully, and then select the response that best describes your symptoms.

	Never	A few times	About half the time	Most of the time	Every time
1. In the past 7 days, how often did you feel a sudden need to urinate?	0	1	2	3	4
2. In the past 7 days, how often did you leak urine or wet a pad after feeling a sudden need to urinate?	0	1	2	3	4
3. In the past 7 days, how often did you leak urine or wet a pad while laughing, sneezing, or coughing?	0	1	2	3	4
4. In the past 7 days, how often did you leak urine or wet a pad when doing physical activities, such as exercising or lifting a heavy object?	0	1	2	3	4
5. In the past 7 days, how often did you have pain or discomfort in your bladder while it was filling?	0	1	2	3	4
6. In the past 7 days, how often did you have a delay before you started to urinate?	0	1	2	3	4
7. In the past 7 days, how often was your urine flow slow or weak?	0	1	2	3	4
8. In the past 7 days, how often did you dribble urine just after zipping your pants or pulling up your underwear?	0	1	2	3	4
Select number here --->	0	1	2	3	
9. In the past 7 days, during waking hours, how many times did you typically urinate?	(3 or fewer times a day)	(4-7 times a day)	(8-10 times a day)	(11 or more times a day)	
Select number here --->	0	1	2	3	
10. In the past 7 days, during a typical night, how many times did you wake up and urinate?	(none)	(1 time)	(2-3 times)	(More than 3 times)	

In the past 7 days, how bothered were you by urinary symptoms?	Not at all bothered	Somewhat bothered	Very bothered	Extremely bothered

Office Use: (note: last question is an unscored global rating)

Office Scoring: Questions 1-10: Sum of all responses x 10 / number of questions answered

_____ x 10 / _____ = _____

Q 1-10 Sum # questions answered LURN SI-10 score (Max Score is 38)

 Version 1.2

Results

A total of 25 Vietnam Veterans were surveyed with the LURN SI-10. Twelve had Qualitative and Quantitative Presumed AOE of 0 with a mean age of 82.0±7.9 years, range 68-95, versus 15 Veterans with some presumed AOE (Qualitative OR Quantitative > 0) with a mean age of 76.9 ± 4.4 years, range 74-91 (p not significant). Comparison of the LUTS scores was statistically analyzed using Excel, and values of $p < 0.05$ were considered statistically significant.

There were statistically significantly lower LURN SI-10 scores in Veterans with negative Qualitative AND Quantitative AOE risk **(see figures 3 & 4)** versus Veterans with presumed risk of AOE. We also compared the same exposure categories to the specific response scores on the 1st two questions that reflect LUTS related to an Overactive Bladder (OAB).

Question 1: In the past 7 days, how often did you feel the sudden need to urinate, and

Question 2: In the past 7 days, how often did you leak urine or wet a pad while laughing, sneezing, or coughing.

Figure:3

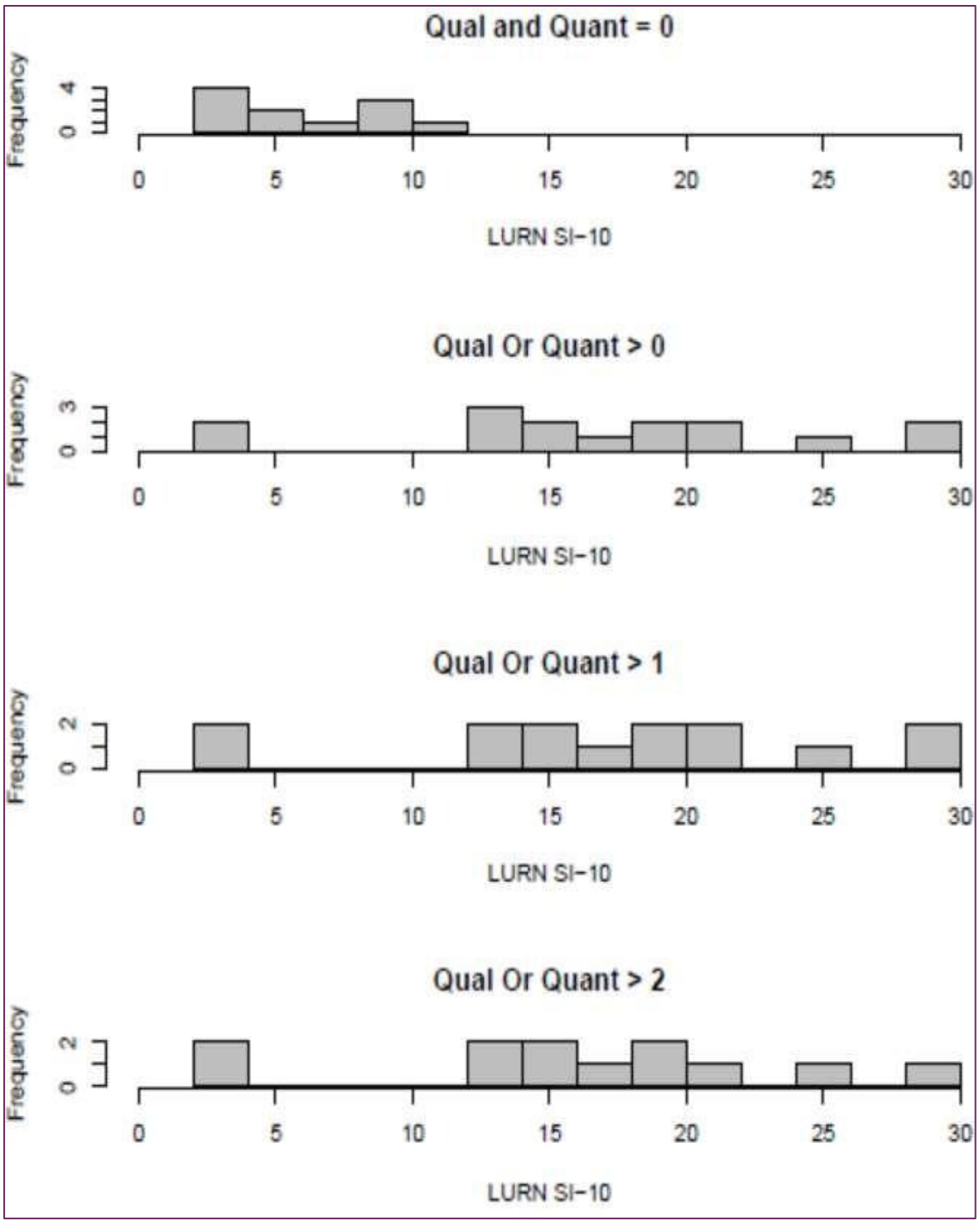
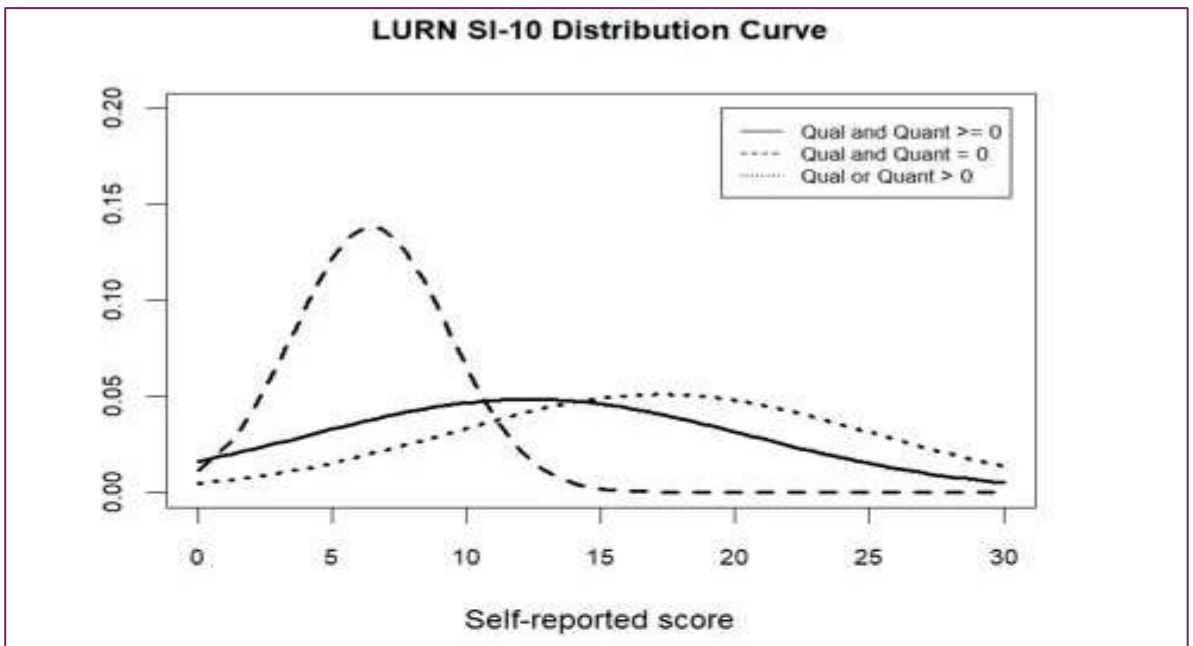


Figure: 4



Qual and Quant >= 0

t	p-value	95% confidence interval	Mean
7.751	3.184e-08	9.048966, 15.580664	12.31481

Qual and Quant = 0

t	p-value	95% confidence interval	Mean
7.4204	2.261e-05	4.516434, 8.392657	6.454545

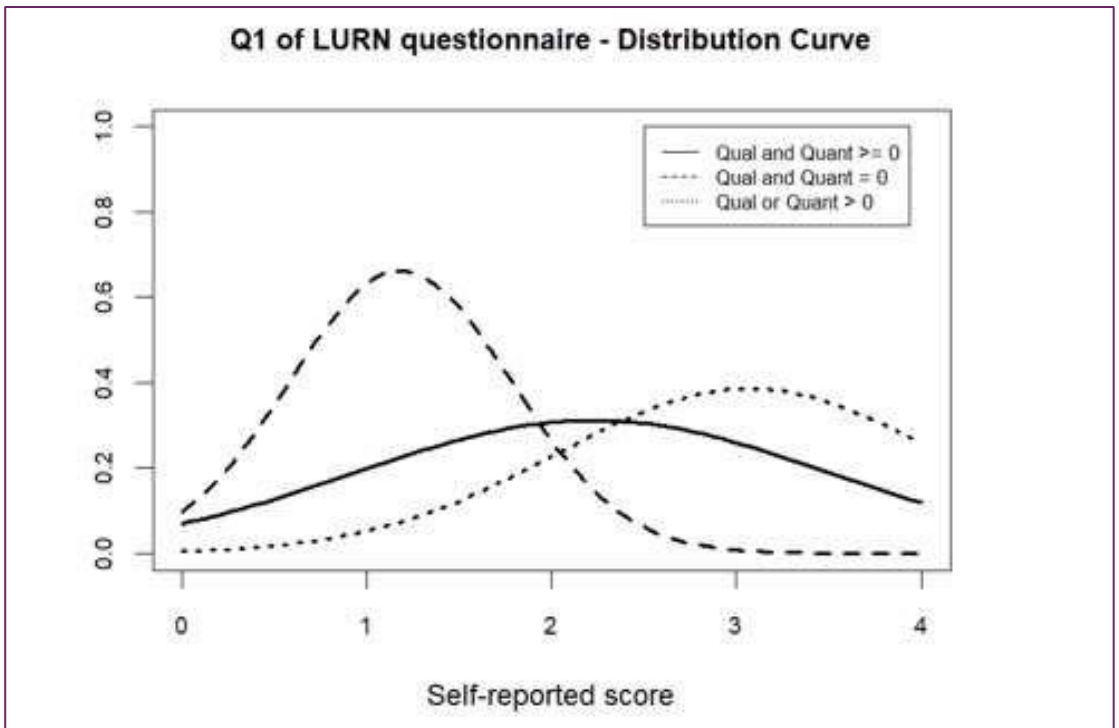
Qual and Quant > 0

t	p-value	95% confidence interval	Mean
8.5088	6.633e-07	12.88938 21.57729	17.23333

We found significantly lower scores in the Qualitative AND Quantitative presumed negative exposure group versus any presumed exposure **(See figures 5-6)**.

Ethics-Gerofit studies are reviewed and approved by the VA Greater Los Angele IRB as QI/QA projects.

Figure: 5



Qual and Quant >= 0

t	p-value	95% confidence interval	Mean
9.0139	1.759e-09	1.715466, 2.728979	2.222222

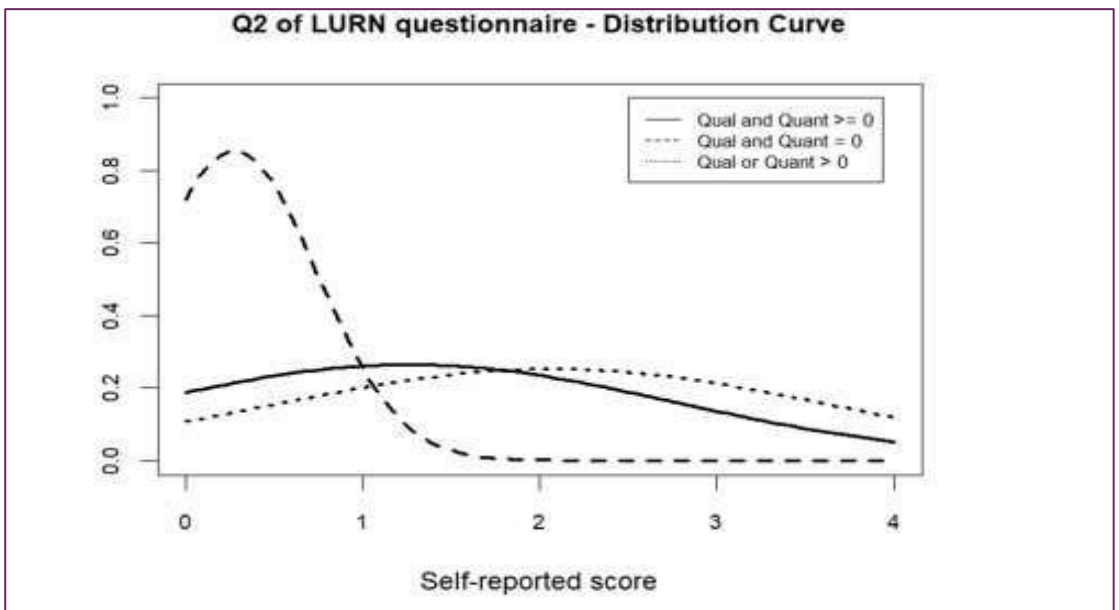
Qual and Quant = 0

t	p-value	95% confidence interval	Mean
6.5	6.895e-05	0.776702, 1.586934	1.181818

Qual and Quant > 0

t	p-value	95% confidence interval	Mean
11.5	1.612e-08	2.494724, 3.638610	3.066667

Figure: 6



Qual and Quant >= 0

t	p-value	95% confidence interval	Mean
4.3369	0.0001933	0.6624141, 1.8561044	1.259259

Qual and Quant = 0

t	p-value	95% confidence interval	Mean
1.9365	0.08155	-0.04107435, 0.58652890	0.2727273

Qual and Quant > 0

t	p-value	95% confidence interval	Mean
5.0671	0.0001718	1.191895, 2.941438	2.066667

Conclusion

The conclusion is that presumed AOE/Dioxin Exposure of Veterans is having a lasting impact on LUTS with what appears to be OAB. What we plan to do next is first teach the Veterans' pelvic floor strengthening exercise, and if LURN SI-10 does not improve, then a referral to Urology for a possible medication trial.

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