## Programma

18.30 uur: Ontvangst & buffet

19.00 uur: Module 3 Diagnosis of prostate cancer

Presentatie en interactieve discussie

20.00 uur: Pauze

20.15 uur: Module 4 Biochemical recurrence after radical treatment

Presentatie en interactieve discussie

Spreker: Prof. dr. R.C.M. Pelger, uroloog LUMC, Leiden

21.30 uur: Afsluiting





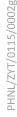
An online program that helps discover the best available evidence at the patient-specific level



Combining the best of two worlds....

### Mirrors of Medicine

- "Translating scientific evidence into everyday practice"
- Developed by scientific society ISSECAM
  - International Society for the Study and Exchange of evidence from Clinical research And Medical experience
- Focus on education and research in uro-oncology (starting PCa)
  - Urologists
  - Oncologists
  - Radiation oncologists



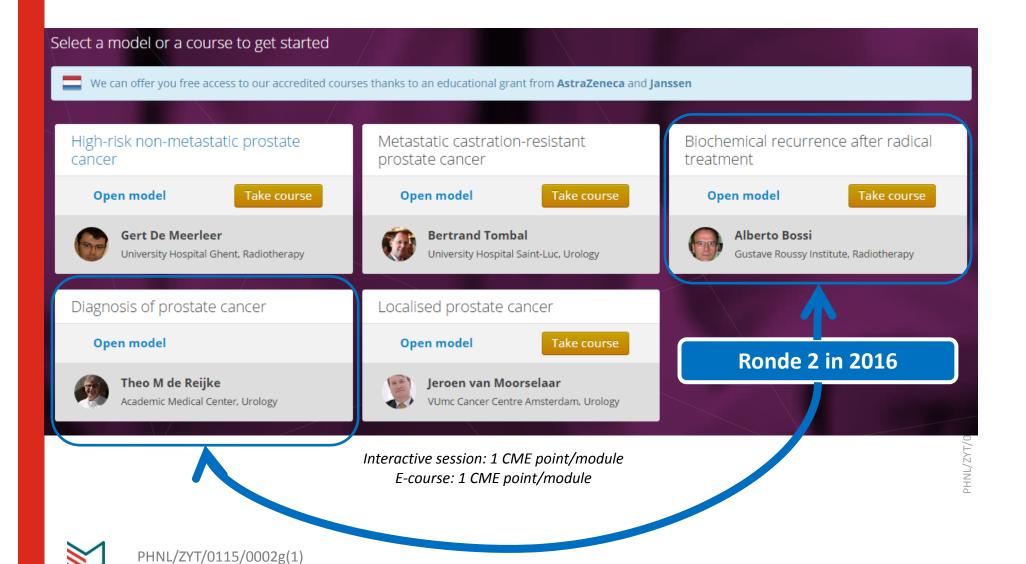


### Mirrors of Medicine models

- Five prostate cancer modules
  - High risk M0, mCRPC, Localised, Biochemical recurrence, Diagnosis
- Treatment recommendations for hundreds of different profiles
  - Updated every 6 months with evidence and guidelines
- Developed using the RAND/UCLA appropriateness method<sup>1</sup>
  - Systemic approach to develop patient-specific recommendations by combining evidence from RCT with the collective judgement of experts
  - Produces reliable, internally consistent and clinically valid results<sup>2</sup>



### **Mirrors of Medicine**



### Mirrors of medicine is...

selecting a patient profile.....



see panel recommendations.....

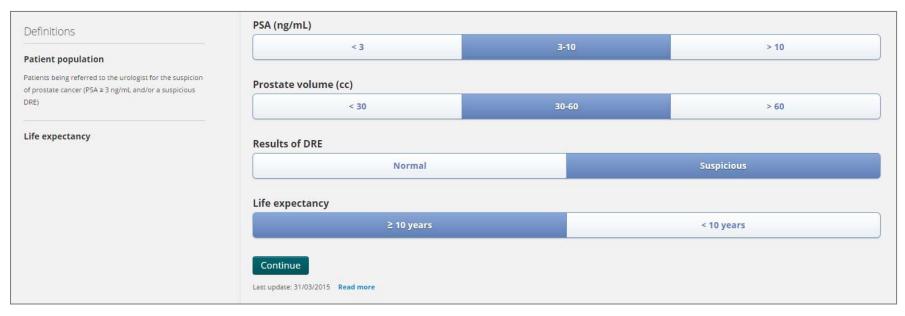


and an overview of underlying evidence + guidelines



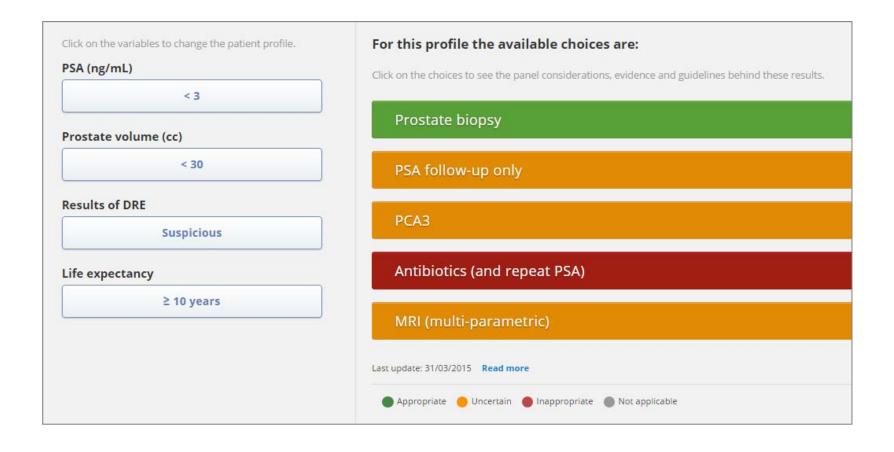


### Selecting a profile





### see panel recommendations.....





# PHNL/ZYT/0115/0002g(1)

### ... with underlying evidence and guidelines

**Prostate biopsy** 

Close

Appropriate

#### Panel considerations

The panel considered prostate biopsy to be an appropriate option in all patients without a previous biopsy and a life expectancy  $\geq 10$  years.

Don't agree? Tell us why.

Share this recommendation \*

#### **Evidence**

Transrectal ultrasound-guided biopsy is the current standard for diagnosing prostate cancer. Suspicion of prostate cancer is based on an elevated PSA value and/or abnormal findings found during digital rectal examination.

Higher PSA levels are associated with a higher risk of having PCa. In a screening study, the proportion of men with PCa on first biopsy was 2% in men with a PSA 0-0.9 ng/mL, 9% in men with a PSA 1.0-1.9 ng/mL, 14% in men with a PSA 2.0-2.9 ng/mL, 23% in men with a PSA 3.0-3.9 ng/mL, 26% in men with a PSA of 4.0-10.0 ng/mL and 57% in men with a PSA > 10 ng/mL [1].

Read in summary

### Guidelines

The EAU guidelines state that the decision to biopsy should be based on PSA testing and DRE [13]. The patient's age, potential co-morbidities and the therapeutic consequences should also be considered.

#### Read in summary

The NCCN guidelines recommend that a biopsy should be considered in men aged 50 to 70 years with a positive DRE and/or a serum PSA > 3.0 ng/mL. However, the decision to perform a biopsy should not be based on a PSA cut-off point alone, but should incorporate other important clinical variables including age, family history, PSA kinetics, ethnicity, health status and patient preference [14].

Read in summary



### ... and all references

References Pub Med

- 1. Postma R, Schröder FH. Screening for prostate cancer. Eur J Cancer 2005;41:825-33.
- 2. Harvey P, Basuita A, Endersby D, et al. A systematic review of the diagnostic accuracy of prostate specific antigen. MBC Urology 2009;9:14.
- 3. Partin AW, Yoo J, Carter HB, et al. The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J Urol 1993;150:110-4.
- 4. Partin AW, Carter HB, Chan DW, et al. Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. J Urol 1990;143:747-52.
- 5. Sajadi KP, Kim T, Terris MK, et al. High yield of saturation prostate biopsy for patients with previous negative biopsies and small prostates. Urology 2007;70:691-5.
- 6. Briganti A, Chun FKH, Suardi N, et al. Prostate volume and adverse prostate cancer features: fact not artifact. Eur J Cancer 2007;43:2669-77.
- 7. Okotie OT, Roehl KA, Han M, et al. Characteristics of prostate cancer detected by digital rectal examination only. Urology 2007;70:1117-20.
- 8. Richie JP, Catalona WJ, Ahmann FR, et al. Effect of patient age on early detection of prostate cancer with serum prostate-specific antigen and digital rectal examination. Urology 1993;42:365-74.
- 9. Schröder FH, van der Maas P, Beemsterboer P, et al. Evaluation of the digital rectal examination as a screening test for prostate cancer. Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 1998;90:1817-23.
- 10. Smith DS, Catalona WJ. Interexaminer variability of digital rectal examination in detecting prostate cancer. Urology 1995;45:70-4.



### ... and NVU guideline for Dutch participants

### NVU richtlijn prostaatcarcinoom 2014



De NVU richtlijn geeft aan dat klinische factoren zoals leeftijd (comorbiditeit), het rectaal toucher en in het bijzonder de aanwezigheid van BPH moeten worden meegenomen in de beslissing over het nemen van prostaatbiopten bij mannen met een PSA ≥ 3.0 ng/mL.

Het is aannemelijk dat risicowijzers en nomogrammen de efficiëntie van de besluitvorming tot het nemen van prostaatbiopten op basis van de PSA test verbeteren. Een voorwaarde is dat het model informatie bevat over het prostaatvolume en het model met acceptabel resultaat is gevalideerd.

Bekijk de volledige richtlijn



### All European MoM panel members

- Alberto Bossi
- Alberto Briganti
- Alessandro Volpe
- Alex Mottrie
- Alexander Govorov
- Alexander Haese
- Alexandre de la Taille
- Amit Bahl
- Andreas Blana
- Andrew Stephenson
- Antonio Alcaraz
- Arnoud Templeton
- Ash Tewari
- Bertrand Tombal
- Bradley Pieters
- Christophe Massard
- Dominik Berthold
- Filip Ameye
- François Cornud

- Frédéric Lecouvet
- Geert Villeirs
- Gert De Meerleer
- Hein Van Poppel
- Inge van Oort
- Jack Schalken
- Jacques Irani
- James Eastham
- Jelle Barentsz
- Jeroen van Moorselaar
- Joaquim Bellmunt
- Jochen Walz
- Johan Braeckman
- Jonas Hugosson
- Jorg Oddens
- Jörg Schröder
- Karim Fizazi
- Karin Haustermans
- Malcolm Mason
- Marco van Vulpen
- Maria De Santis

- Mark Speakman
- Markus Graefen
- Martin Spahn
- Mesut Remzi
- Monique Roobol
- Nicholas Van As
- Nicolas Mottet
- Noel Clarke
- Paolo Gontero
- Paul Kil
- Paul Perrin
- Piet Ost
- Scott Eggener
- Sergio Villa
- Srinivas Samavedi
- Steven Joniau
- Theo de Reijke
- Thomas Wiegel
- Vincent Khoo
- Vip Patel
- Xavier Maldonado





Theo M de Reijke Academic Medical Center, Urology Amsterdam Netherlands

View biography

Model

Panel



Alberto Briganti Vita-Salute University San Raffaele, Urology Milan Italy



Martini-Klinik, Urology Hamburg Germany View biography



**Guillaume Ploussard** CHU Saint-Louis, Urology Paris France View biography

View biography





Paul Kil St. Elisabeth Hospital, Urology Tilburg Netherlands View biography



**Alexander Haese** 



Jochen Walz Paoli-Calmettes Institute Cancer Centre, Urology Marseille France View biography



Mesut Remzi Regional Hospital of Weinviertel-Korneuburg, Urology Korneuburg Austria View biography



Authors



Alexandre de la Taille Henri Mondor Hospital, Urology France View biography



Ash Tewari Mount Sinai Hospital, Urology New York United States View biography



François Cornud Centre d'Imagerie Medicale Tourville, Radiology Paris France View biography



Jack A Schalken Radboud University Nijmegen Medical Centre, Urology Nijmegen Netherlands View biography



Jelle Barentsz Radboud University Medical Centre, Radiology Nijmegen Netherlands View biography



Johan Braeckman University Hospital Brussels, Urology Brussels Belgium View biography



Jonas Hugosson Sahlgrenska University Hospital, Urology Göteborg Sweden View biography



Monique J Roobol Erasmus MC, Urology Rotterdam Netherlands View biography



Theo M de Reijke Academic Medical Center, Urology

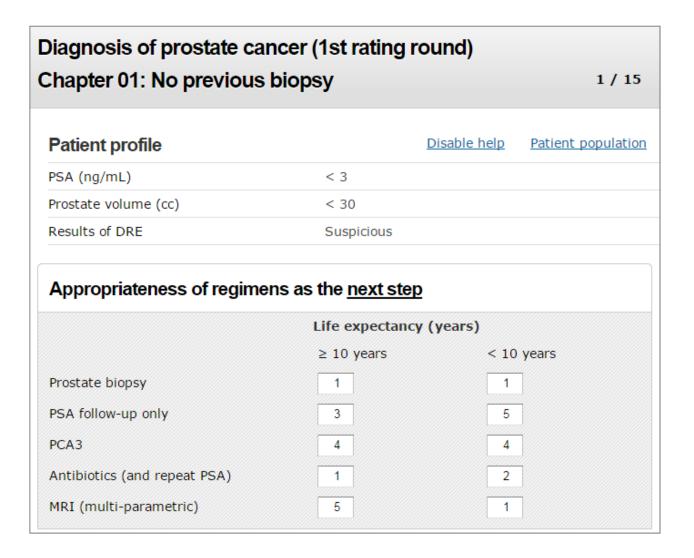
Amsterdam Netherlands View biography



PHNL/ZYT/0115/0002e(1)



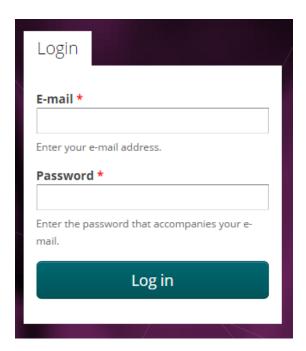
### Panel ratings: appropriateness assessments

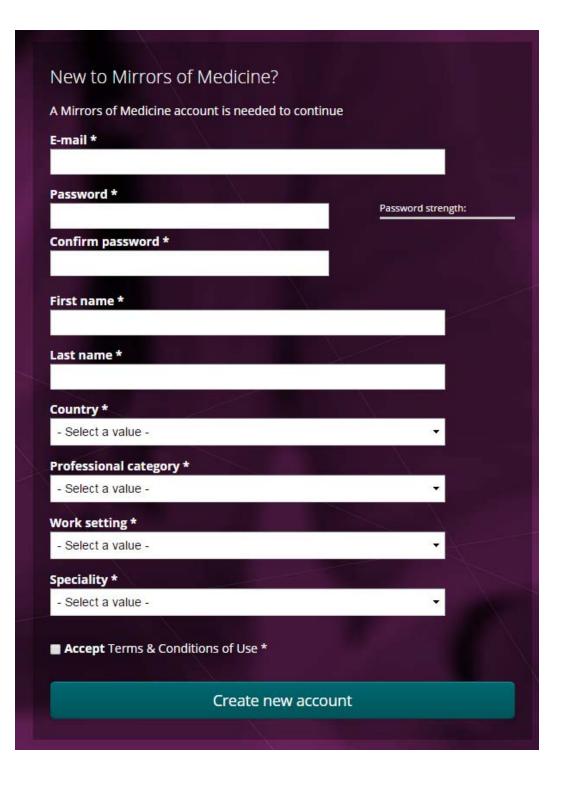




## Registration

pca.mirrorsmed.org



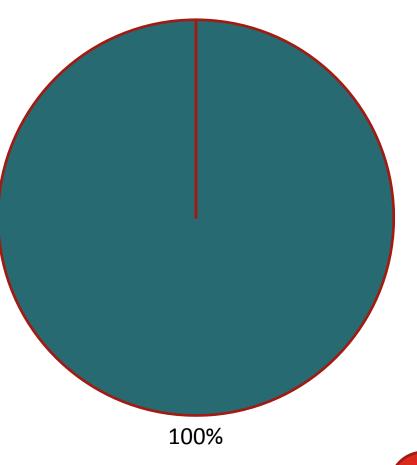






## Wie zijn er aanwezig?

- uroloog
- aios urologie
- radiotherapeut
- aios radiotherapeut
- oncologieverpleegkundige/verpleegkundig specialist
- physician assistant
- radioloog
- nucleair geneeskundige





PHNL/ZYT/0115/0002g(1)

CME accredited educational module

# Diagnosis of prostate cancer

### Subject of this meeting

Diagnostic evaluation of patients who have been referred to the urologist for the suspicion of prostate cancer

• PSA ≥ 3 ng/mL

and/or

suspicious digital rectal examination (DRE)



# PHNL/ZYT/0115/0002g(1

### **Science and practice**



How to translate evidence from clinical studies to individual patients?



### Select a module and compose a patient profile

6	Diagnosis of prostate cancer	>
6	Localised prostate cancer	>
6	High-risk non-metastatic prostate cancer	>
6	Biochemical recurrence after radical treatment	>
6	Metastatic castration-resistant prostate cancer	>

Please select a model



No previous biopsy patient case 1

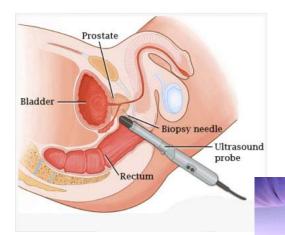
Negative first biopsy



patient case 2



### **Diagnostic options**











PHNL/ZYT/0115/0002g(1)



### **Diagnostic options**

No previous biopsy	Negative first biopsy	
	No further action	
Prostate biopsy (short term)	Repeat biopsy (6-12 weeks)	
PSA follow-up only	Repeat PSA (12-24 weeks)	
PCA3 test	PCA3 test	
Antibiotics + PSA follow-up	Antibiotics + PSA follow-up	
MRI (multiparametric)	MRI (multiparametric)	



# Clinical variables used for the construction of patient profiles

### 



# Patient case 1 No previous biopsy

### Patient case 1 - No previous biopsy

- 68 yr old, retired fireman
- Complaints of fatigue due to nocturia, is afraid of cancer
- GP consultation: PSA 3.2 ng/mL, DRE: enlarged, not suspicious
- PSA at urologist consultation: 3.7 ng/mL
- Prostate examination:

Volume: 40 cc

DRE: normal

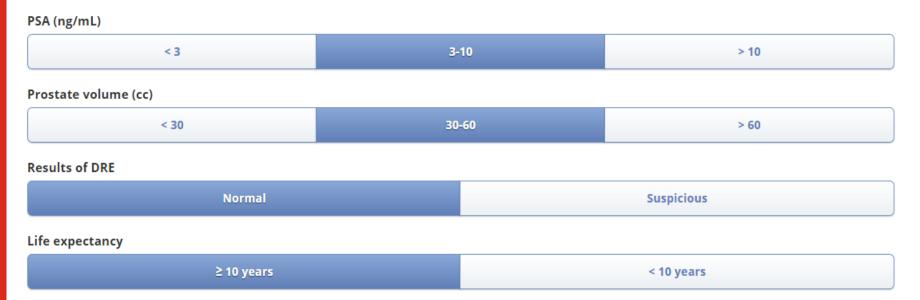
No comorbidities

Previous biopsy	No	
PSA	3-10 ng/mL	
Prostate volume	30-60 cc	
DRE	Normal	
Life expectancy	≥ 10 years	

What would be the most appropriate next step?



# Clinical variables: patient case 1





# Stemronde geopend

# What would be the most appropri treatment for this patient?

1. Prostate biopsy

50%

2. PSA follow-up only

50%

3. PCA3

0%

4. Antibiotics (and repeat PSA)

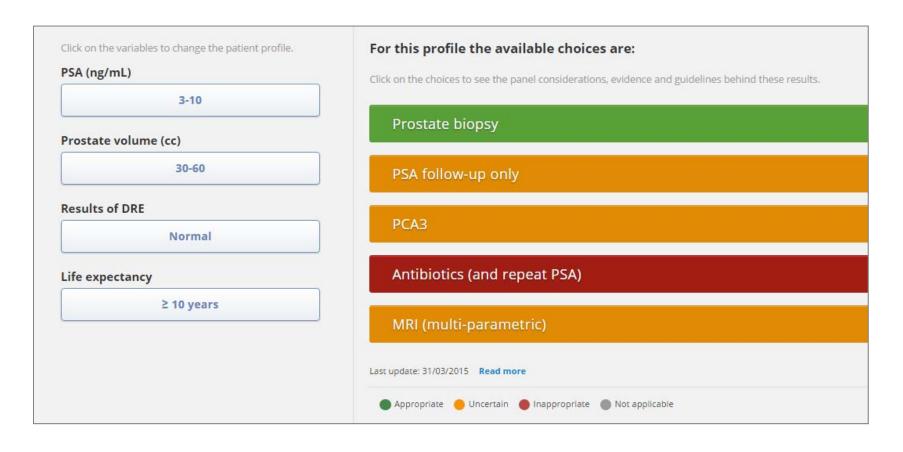
0%

5. MRI (multi-parametric)

0%



### What do the MoM experts recommend?





# Prostate biopsy



# PHNL/ZYT/0115/0002g(1)

# Is prostate biopsy the best option for this patient?

#### Appropriate

### Panel considerations

The panel considered prostate biopsy to be an appropriate option in all patients without a previous biopsy and a life expectancy  $\geq 10$  years.

Don't agree? Tell us why.

Share this recommendation \*

#### **Evidence**

Transrectal ultrasound-guided biopsy is the current standard for diagnosing prostate cancer. Suspicion of prostate cancer is based on an elevated PSA value and/or abnormal findings found during digital rectal examination.

Higher PSA levels are associated with a higher risk of having PCa. In a screening study, the proportion of men with PCa on first biopsy was 2% in men with a PSA 0-0.9 ng/mL, 9% in men with a PSA 1.0-1.9 ng/mL, 14% in men with a PSA 2.0-2.9 ng/mL, 23% in men with a PSA 3.0-3.9 ng/mL, 26% in men with a PSA of 4.0-10.0 ng/mL and 57% in men with a PSA > 10 ng/mL [1].

Read in summary

#### Guidelines

The EAU guidelines state that the decision to biopsy should be based on PSA testing and DRE [13]. The patient's age, potential co-morbidities and the therapeutic consequences should also be considered.

#### Read in summary

The NCCN guidelines recommend that a biopsy should be considered in men aged 50 to 70 years with a positive DRE and/or a serum PSA > 3.0 ng/mL. However, the decision to perform a biopsy should not be based on a PSA cut-off point alone, but should incorporate other important clinical variables including age, family history, PSA kinetics, ethnicity, health status and patient preference [14].

Read in summary

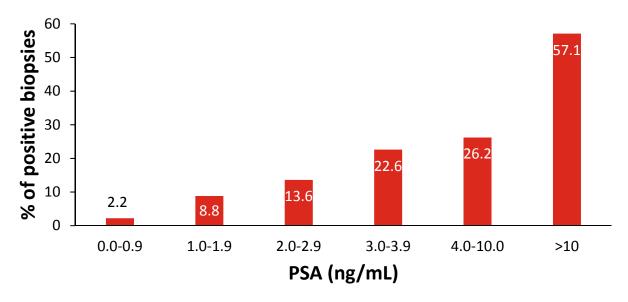


# HNL/ZYT/0115/0002g(1)

### **PSA** and the risk of prostate cancer

### ELEVATED PSA

• 1<sup>st</sup> screening round of ERSPC<sup>1</sup>: N = 19.970



Systematic review of 10 studies<sup>2</sup>:

	Sensitivity	Specificity
tPSA	78-100%	6-66%



### Prostate volume and the risk of prostate cancer

- The PSA level has to be considered in light of the prostate volume (PV) as the PSA level is also increased in patients with a large prostate due to BPH
- In men with a mean PSA level of 9 ng/mL undergoing a saturation biopsy, PV was negatively associated with the probability of PCa<sup>1</sup>
- Among men with a mean PSA level of 11 ng/mL undergoing radical prostatectomy for localised PCa, cancers in small glands were more aggressive than those in large glands<sup>2</sup>

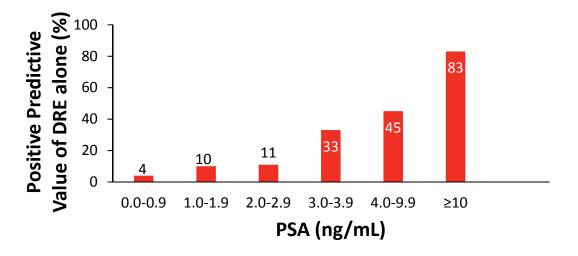


# PHNL/ZYT/0115/0002g(

### DRE and the risk of prostate cancer

### SUSPICIOUS DRE

Rotterdam section of ERSPC¹: N = 10,523



- PCa screening study<sup>2</sup>: N = ±36,000: 14% detected by DRE alone
  - 20% non-organ-confined
  - 20% Gleason sum ≥ 7
- Low sensitivity poor reproducibility



# What do the guidelines say?

- EAU guidelines (2016): Decision to biopsy should be based on:
  - PSA
  - DRE
  - Other important variables: age, potential co-morbidities, therapeutic consequences
- NCCN guidelines (2016): Biopsy should be considered in men:
  - 45-75 years old
  - Serum PSA > 3.0 ng/mL
  - Other important variables: family history, PSA kinetics, ethnicity, health status and patient preference
- ESMO guidelines (2016): Decision to biopsy should be based on:
  - DRE findings
  - PSA
  - Other important variables: ethnicity, age, co-morbidities, family history, free/total PSA and history of previous biopsy



### Wat zegt de NVU richtlijn over prostaatbiopsie?

 Klinische factoren zoals leeftijd (comorbiditeit), het rectaal toucher en in het bijzonder de aanwezigheid van BPH moeten worden meegenomen in de beslissing over het nemen van prostaatbiopten bij mannen met een PSA ≥ 3.0 ng/mL



 Het is aannemelijk dat risicowijzers en nomogrammen de efficiëntie van de besluitvorming tot het nemen van prostaatbiopten op basis van de PSA test verbeteren. Een voorwaarde is dat het model informatie bevat over het prostaatvolume en het model met acceptabel resultaat is gevalideerd





# PSA follow-up



# PHNL/ZYT/0115/0002g(1)

## Could PSA follow-up (only) be an appropriate option for this patient?

PSA follow-up only

Hide evidence

Uncertain

#### Panel considerations

PSA follow-up only may be considered in the case of doubt about the appropriateness (benefit-risk balance) of prostate biopsy. The panel did (generally) not determine specific arguments in favour or against this option.

Don't agree? Tell us why.

Share this recommendation 🛧

#### **Evidence**

In men suspicious of prostate cancer, the decision to biopsy requires a careful balance of potential benefits and risks. In particular situations, PSA follow-up (12-24 weeks) may be favoured over immediate biopsy. However, there are no clinical or epidemiological studies that allow selection of specific patients benefiting most from a deferred biopsy decision.

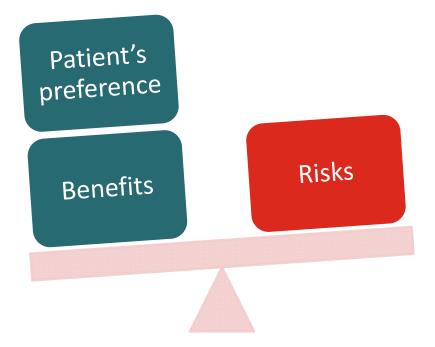
#### Guidelines

The NCCN guidelines recommend that patients aged 45-75 years with a PSA > 3.0 ng/mL can either receive a biopsy, be followed with DRE and PSA measurements in 6-12 months (with a biopsy based on the results) or can be offered further risk assessment using %free PSA, 4Kscore or PHI [2]



### PSA follow-up only versus immediate biopsy

**BIOPSY** 





PHNL/ZYT/0115/0002g(1)



### What do the guidelines say?

- EAU guidelines (2016): No recommendations
- NCCN guidelines (2016):
  - Patients aged 45-75 years with a PSA > 3.0 ng/mL:
    - 1) Biopsy followed with DRE and PSA in 6-12 months
    - Or 2) Risk assessment using %free PSA, 4Kscore or PHI
- ESMO guidelines (2016): No recommendations

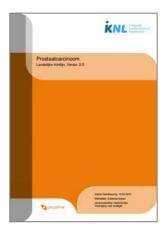


# PHNL/ZYT/0115/0002g(

### Wat zegt de NVU richtlijn over PSA opvolging?

 Geen specifieke aanbevelingen over PSA opvolging als initiële keuze bij mannen die doorverwezen zijn naar de uroloog met een verdenking van prostaatkanker (PSA ≥ 3 ng/mL en/of verdacht rectaal toucher)



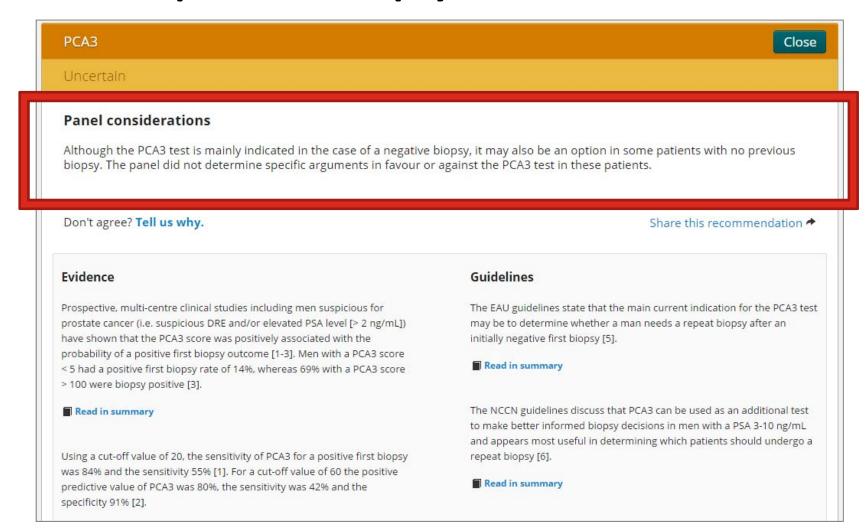




### PCA3 test



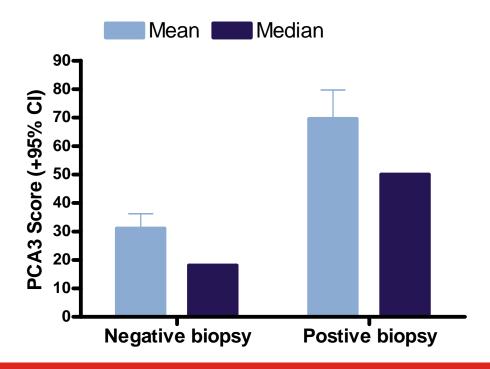
## Is PCA3 an appropriate option in patients without a previous biopsy?





#### PCA3 in men with an initial biopsy

516 European men with PSA 2.5-10 ng/mL scheduled for initial biopsy<sup>1</sup>
 99% of urine samples had sufficient mRNA for analysis
 207 men (40%) had a positive initial biopsy



The higher the PCA3 score, the higher the probability of a positive biopsy



#### PCA3 in men with an initial biopsy

- Study in 516 men with PSA 2.5-10 ng/mL scheduled for initial biopsy; 40% had a positive first biopsy<sup>1</sup>
- National Cancer Institute Early Detection Research Network (NCI EDRN) validation trial in 562 men scheduled for first biopsy<sup>2</sup>

PCA3 score	Sensitivity	Specificity	Positive predictive value
PCA3 score cut-off 20 <sup>1</sup>	84%	55%	
PCA3 score cut-off 35 <sup>1</sup>	64%	76%	
PCA3 score cut-off 60 <sup>2</sup>	42%	91%	80%
Total PSA cut-off 4 ng/mL <sup>1</sup>	91%	16%	
% free PSA cut-off 25% <sup>1</sup>	90%	18%	



## What do the guidelines say?

- EAU guidelines (2016):
  - The main current indication for PCA3 is to determine the need for a repeat biopsy
- NCCN guidelines (2016):
  - PCA3 test is not recommended in men who did not have a prior biopsy
- ESMO guidelines (2016): No recommendation



## PHNL/ZYT/0115/0002g

### Wat zegt de NVU richtlijn over PCA3?

 Aangezien PCA3 de uitkomst van het herhalingsbiopt verbetert, kan overwogen worden om na het eerste of tweede negatieve biopt een PCA3 test te verrichten







### Antibiotics + PSA follow-up



## Could antibiotics + repeat PSA be an appropriate option?

Antibiotics (and repeat PSA) Close Inappropriate Panel considerations The panel considered empiric antibiotic therapy to be inappropriate in patients suspicious of prostate cancer, both in patients without a previous biopsy and in those with a negative first biopsy. Don't agree? Tell us why. Share this recommendation \* Guidelines Evidence One of the causes of an elevated PSA level may be clinical prostatitis due The international guidelines do not give recommendations regarding to bacterial infection. In these cases repeat PSA after treatment with empirical antibiotic therapy and repeat PSA measurement for men with appropriate antibiotics (1-3 months) is indicated [1]. suspicion of prostate cancer who have not had a biopsy. Studies into empiric antibiotic therapy in men with elevated PSA (> 2.5 ng/mL), a normal DRE and no signs of clinical prostatitis, showed no or minimal impact on PSA [2-4].



#### **Prostatitis and PSA**

### Antibiotics 1-3 months

#### **Prostatitis**

- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Chronic pelvic pain syndromes
- Asymptomatic inflammatory prostatitis

#### **↑PSA**

- Leakage into blood stream
- Hypervascularity
- Altered vascular permeability secondary to inflammation

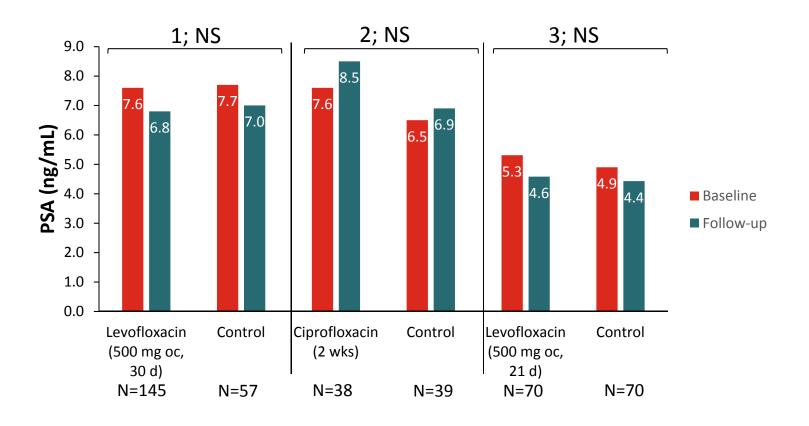
## Normalised PSA



# PHNL/ZYT/0115/0002g(1)

#### **Antibiotics and PSA**

 No impact of antibiotics in men with elevated PSA (> 2.5 ng/mL), a normal DRE and no signs of prostatitis<sup>1-4</sup>:





## PHNL/ZYT/0115/0002g(

### What do the guidelines say?

- EAU guidelines (2016):
  - Should not be given in asymptomatic patients in order to lower the PSA level
- NCCN guidelines (2016): No recommendations
- ESMO guidelines (2016): No recommendations



# PHNL/ZYT/0115/0002g(

## Wat zegt de NVU richtlijn over empirische behandeling met antibiotica?

 Geen specifieke aanbevelingen over empirische behandeling met antibiotica (en herhaalde PSAmeting) bij mannen die doorverwezen zijn naar de uroloog met een verdenking van prostaatkanker (PSA ≥ 3 ng/mL en/of verdacht rectaal toucher)



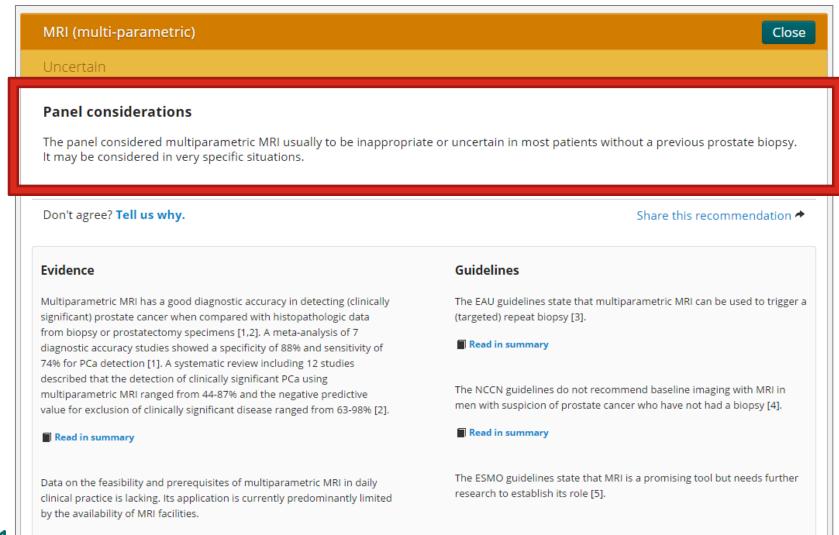




### Multiparametric MRI (mp-MRI)



## Could multiparametric MRI be an appropriate option in men without a previous biopsy?





## PHNL/ZYT/0115/0002g(

#### Diagnostic accuracy of multiparametric (mp)-MRI

 Meta-analysis of 7 diagnostic accuracy studies for PCa detection<sup>1</sup> (N=526):

Specificity: 88% (95% CI: 82-92%)

Sensitivity: 74% (95% CI: 66-81%)

Systematic review of 12 studies<sup>2</sup>:

Using mp-MRI	Range
Detection of clinically significant PCa	44-87%
NPV for exclusion of clinically significant PCa	63-98%

Mp-MRI has a good diagnostic accuracy in detecting PCa BUT data are lacking on:

- Feasibility
- Prerequisites



## What do the guidelines say?

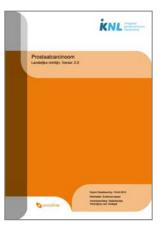
- EAU guidelines (2016):
  - The use of mpMRI before a biopsy in the initial biopsy setting is not recommended.
- NCCN guidelines (2016):
  - MRI is not recommended in men with suspicion of PCa who have not had a biopsy
- ESMO guidelines (2016):
  - mp-MRI is recommended before a repeat biopsy with the intention to perform an MRI-guided or MRI-TRUS fusion biopsy



### Wat zegt de NVU richtlijn over mp-MRI?

 Bij patiënten met blijvende of sterke klinische verdenking op prostaatcarcinoom wordt multiparametrische MRI (indien beschikbaar) aanbevolen, met inachtneming van de ESUR consensus based richtlijnen voor techniek en beoordeling (2012)







## What is the first step before you w geopend take prostate biopsies in this patient?

1. MRI

14%

2. No further investigation. Just take biopsies

43%

Gather items for you nomogram for predicting positive biopsies (prostaatwijzer 3)

29%

4. At least one PSA a few weeks later from the PSA of 3.7, to be sure of a rise in PSA

14%





## Recommendations in the NVU guideline regardinuse of the CT-scan in the stagering (TNM) of PCa are:

- 1. Determination of the local status of the prostate (T)
- 2. Identification of skeletal involvement (M)
- 3. Puncture guidance of lymph nodes suspected of metastasis (N)
- 4. Determine the lymph node status (N)



# PHNL/ZYT/0115/0002g(

### Wat zegt de NVU richtlijn over de CT-scan?

Gebruik van een CT-scan wordt niet aanbevolen voor de diagnostiek en lokale- en lymfeklierstagering van het prostaatcarcinoom.



Een CT-scan kan van waarde zijn bij de geleiding van punctie van voor metastase verdachte lymfeklieren.





### Patient case 1 - No previous biopsy

- 68 yr old, retired fireman
- Complaints of fatigue due to nocturia, is afraid of cancer
- GP consultation: PSA 3.2 ng/mL, DRE: enlarged, not suspicious
- PSA at urologist consultation: 3.7 ng/mL
- Prostate examination:

Volume: 40 cc

DRE: normal

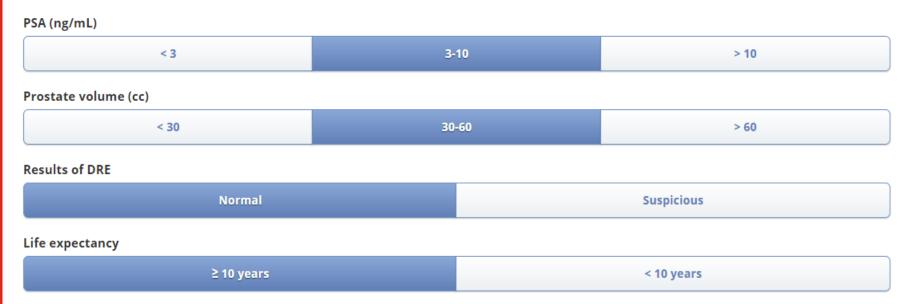
No comorbidities

Previous biopsy	No	
PSA	3-10 ng/mL	
Prostate volume	30-60 cc	
DRE	Normal	
Life expectancy	≥ 10 years	

What would be the most appropriate next step?



## Clinical variables: patient case 1





## Stemronde geopend

## What would be the most appropri treatment for this patient?

1. Prostate biopsy

66,7%

2. PSA follow-up only

33,3%

3. PCA3

0,0%

4. Antibiotics (and repeat PSA)

0,0%

5. MRI (multi-parametric)

0,0%



# 64 (1) BHNI /2VT/0115/0003a(1)

## Comparison of voting results 2st voting 2nd voting

- 1. Prostate biopsy
- 2. PSA follow-up only
- 3. PCA3
- 4. Antibiotics (and repeat PSA)
- 5. MRI (multi-parametric)



# Patient case 1 Case change

### What if the previous patient .....

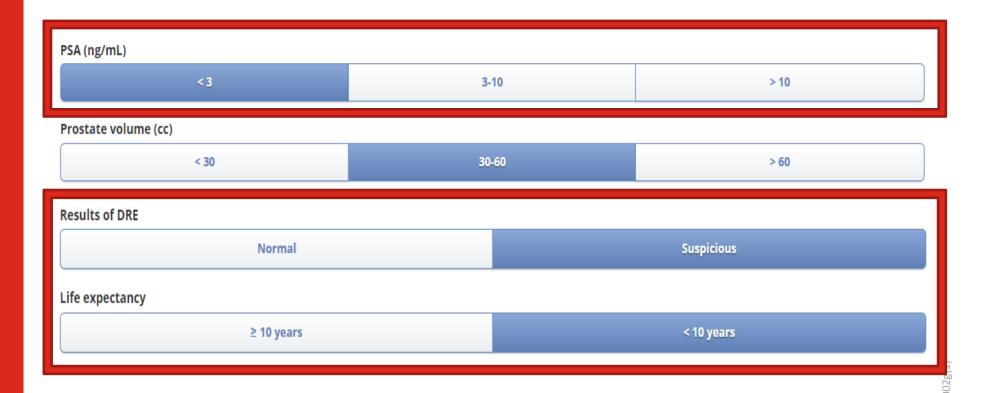
- Bit older: 76 years, retired fireman
- Complaints of fatigue due to nocturia, afraid of cancer
- PSA at consultation: 2.8 ng/mL
- Prostate examination:
  - Volume: 40 cc
  - DRE: irregular shape, suspicious
- Hypertension (not well controlled)

Previous biopsy	No
PSA	< 3 ng/mL
Prostate volume	30-60 cc
DRE	Suspicious
Life expectancy	< 10 years

What would be the most appropriate diagnostic option for this patient?

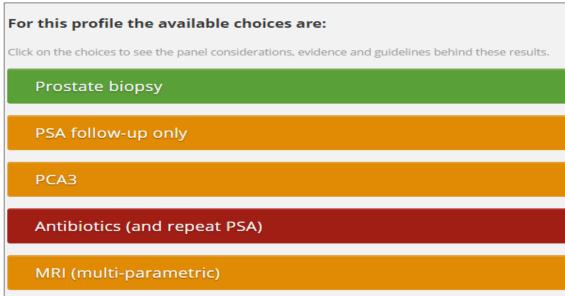


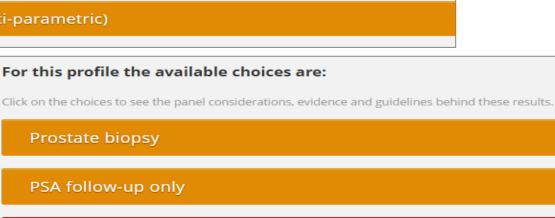
## Clinical variables: pt 1 case change





### What have we learned from this patient case?





Antibiotics (and repeat PSA)

MRI (multi-parametric)

PCA3





## When will you perform prostate biopsy in this patient?

1. Immediately, there is a suspicious DRE

29%

- 2. Only if PSA will increase over time 0%
- 3. After informing the patient well about the pro's and con's of prostate biopsies in this specific case

71%

4. Not anymore, because this patient will not die from prostate cancer

0%



DHNI /7VT/0115/0002

#### **Key messages - No previous biopsy**

- Prostate biopsy is the current standard for men with elevated PSA and/or suspicious DRE
- PSA follow-up only may be an option in selective patients
- Role of PCA3 predominantly in patients with a negative biopsy, but it may also be an option in some patients without a previous biopsy and PSA 3-10 ng/mL
- Antibiotics + repeat PSA is never an appropriate option
- MRI (multiparametric) is a promising technique, but in patients without a previous biopsy currently advised only in very specific cases



# Patient case 2 Negative first biopsy

#### Patient case 2 - Negative first biopsy

- 58 years old, school teacher
- Recent (first) prostate biopsy because of elevated PSA (case finding)
- Findings at the time of the first biopsy

- PSA: 10.8 ng/mL

Prostate volume: 40 cc

– DRE: normal

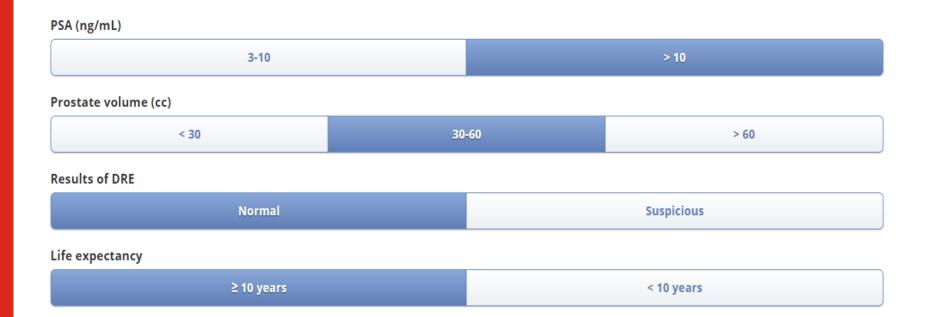
Biopsy: negative

No co-morbidities

Previous biopsy	1 negative
PSA	> 10 ng/mL
Prostate volume	30-60 cc
DRE	Normal
Life expectancy	≥ 10 years



### Clinical variables: patient 2





### Stemronde geopend

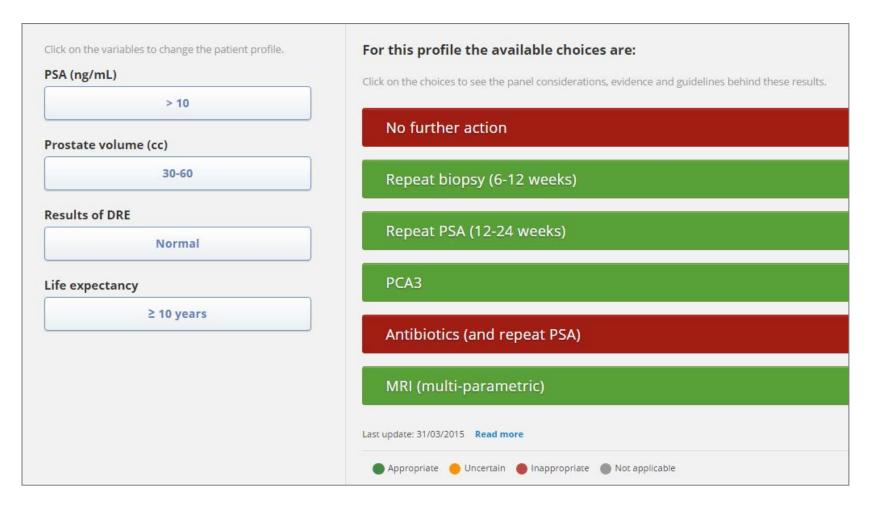
# What would be the most appropri treatment for this patient?

- 1. No further action
  - 0%
- 2. Repeat biopsy (6-12 weeks)
- 3. Repeat PSA (12-24 weeks)
  - 14%
- 4. PCA3
- 5. Antibiotics (and repeat PSA)

  0%
- 6. MRI (multi-parametric)



#### What do the MoM experts recommend?

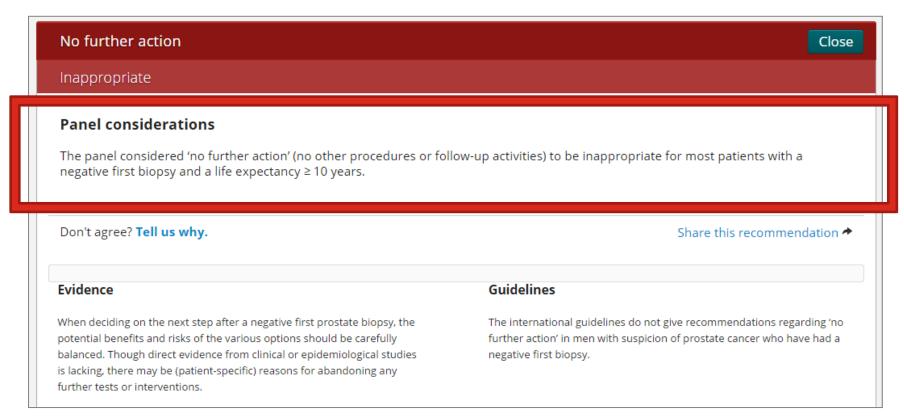




### No further action

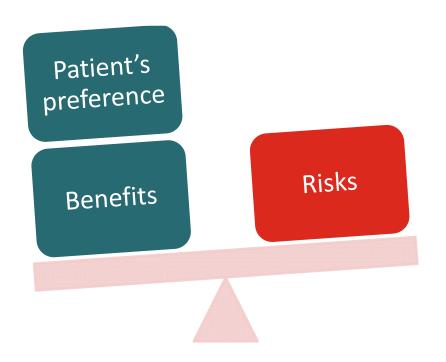


# Why is "no further action" an inappropriate option in this patient?





### "Doing nothing": balancing benefits and risks...







#### What do the guidelines say?

- EAU guidelines (2016): No recommendations
- NCCN guidelines (2016): No recommendations
- ESMO guidelines (2016): No recommendations



### Wat zegt de NVU richtlijn over 'geen actie'?

- Geen expliciete criteria voor het afzien van verdere actie na een negatieve eerste biopsie
- Wel wordt aangegeven dat bij klinische verdenking op maligniteit tenminste één keer de serie biopten dient te worden herhaald, bij voorkeur na (mp)MRI







### Repeat biopsy (6-12 weeks)



#### Repeat biopsy (6-12 weeks)

Repeat biopsy (6-12 weeks)

Close

Appropriate

#### Panel considerations

In patients with a negative first biopsy, repeat biopsy (after 6-12 weeks) was usually considered appropriate in patients with a life expectancy  $\geq$  10 years.

Don't agree? Tell us why.

Share this recommendation \*

#### **Evidence**

The most recent studies into the diagnostic yield of repeat biopsy in men with (persistent) suspicion of prostate cancer who had one or more prior negative biopsies, report a positive outcome in around 17% of patients [1-31.

In a prospective observational study, a positive outcome of repeat biopsy was significantly higher in patients with PSA > 6 ng/mL, PSA density > 0.15 ng/mL/g, free-to-total PSA ratio < 15, and/or prostate volume < 50 mL[2].

In an earlier cohort in this study, 85% of tumours found at repeat biopsy were clinically significant, though most were localized and well-differentiated [1].

#### Guidelines

The EAU guidelines state that the indications for a repeat biopsy are [4]: o a rising and/or persistently elevated PSA level o a suspicious DRE o atypical small acinar proliferation (ASAP) on prior biopsy o extensive (multiple biopsy sites) prostatic intra-epithelial neoplasia (PIN) on prior biopsy.

The NCCN guidelines discuss that a consideration for repeat biopsy may be based on risk stratification (PSA, age, family history, etc.) and/or the use of biomarkers that improve specificity, such as PCA3 and % free PSA. Patients with ASAP and multifocal high-grade PIN on prior biopsy should have a repeat extended biopsy within 3-6 months [5].

The ESMO guidelines recommend that the decision whether or not to have a biopsy should be made in the light of PSA level, DRE findings, history of previous biopsy, prostate size, age, ethnicity, co-morbidities, family history and patient values [6,7].

Read in summary



#### **Outcomes of repeat biopsy**

- Recent studies:
  - ± 17% PCa in patients after prior negative biopsies<sup>1-3</sup>
  - Most tumours: localised and well-differentiated, still 85% clinically significant (tumour volume >0.5 cc, Gleason sum ≥7 and/or pT3)¹
  - Predictive factors of PCa detection based on a prospective, observational study<sup>2</sup> (N=617):

PSA > 6 ng/mL

PSAD > 0.15ng/mL/g

%fPSA > 15

Prostate volume < 50 mL

PHNL/ZYT/0115/0002g(1)



### What do the guidelines say?

- EAU guidelines (2016): Indications for repeat biopsy:
  - Rising or persistently elevated PSA level
  - Suspicious DRE
  - ASAP on prior biopsy
  - Extensive high-grade HGPIN on prior biopsy
  - A few atypical glands immediately adjacent to HGPIN
- NCCN guidelines (2016): Consideration for repeat biopsy:
  - Based on follow-up (6-12 months) with PSA and DRE
  - Use of biomarkers which improve specificity and mp-MRI may be of value
  - → Repeat biopsy within 6 months
  - ASAP on prior biopsy
  - Multifocal HGPIN on prior biopsy
- ESMO guidelines (2016): Indications for repeat biopsy:
  - Rising PSA, suspicious DRE, abnormal MRI, ASAP, multifocal HGPIN



#### Wat zegt de NVU richtlijn over herhaalbiopsie?

 Bij klinische verdenking op maligniteit en een negatieve eerste biopsie dient tenminste één keer de serie biopten te worden wordt herhaald, bij voorkeur na een (multiparametrische) MRI



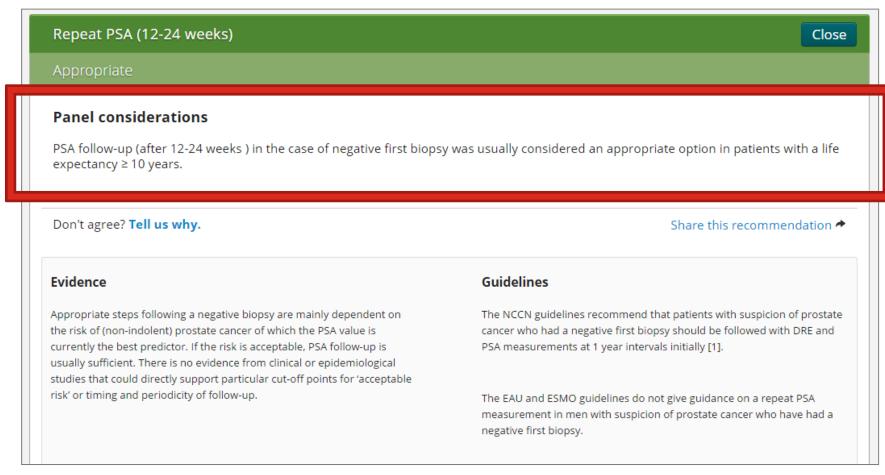




### Repeat PSA (12-24 weeks)

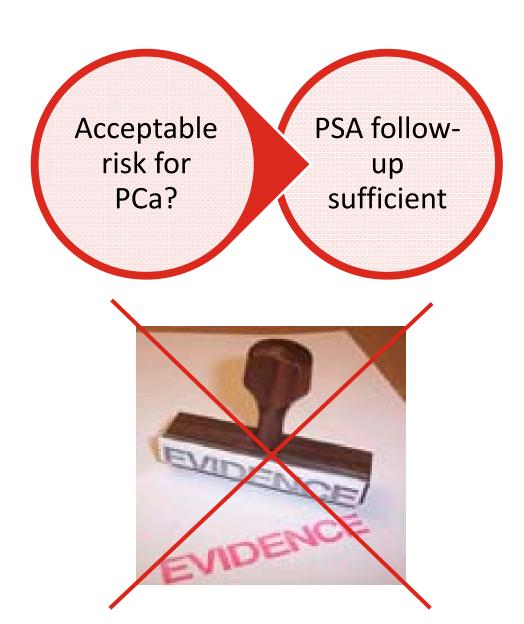


## Is repeat PSA (12-24 weeks) an appropriate option for men with a negative first biopsy?





### Repeat PSA: a matter of risk assessment





### What do the guidelines say?

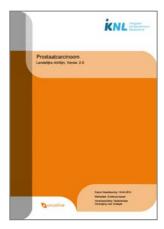
- EAU guidelines (2016):
  - No recommendations
- NCCN guidelines (2016):
  - Patients with suspicion for PCa after a negative first biopsy can be followed with DRE and PSA in 6-12 months (with a repeat biopsy based on the results)
- ESMO guidelines (2016):
  - No recommendations



### Wat zegt de NVU richtlijn over PSA opvolging?

 Geen specifieke aanbevelingen over herhaling van de PSA-meting na een eerste negatieve biopsie



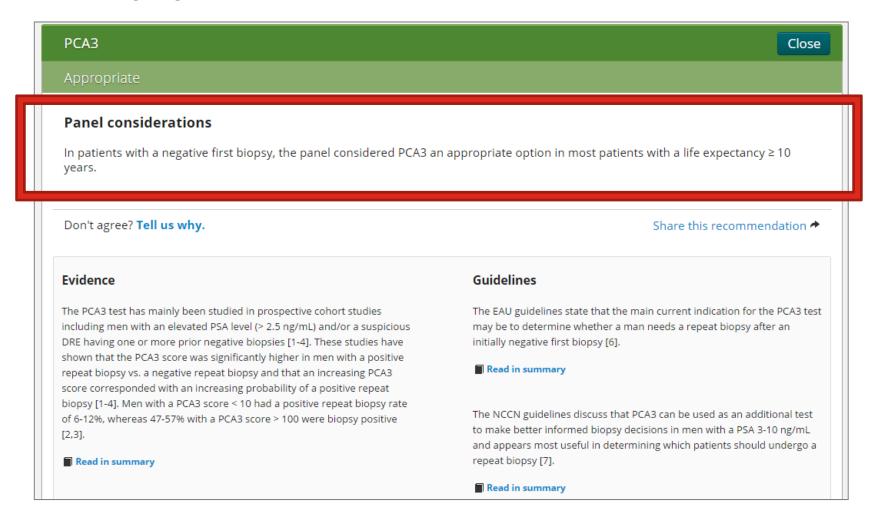




### PCA3 test



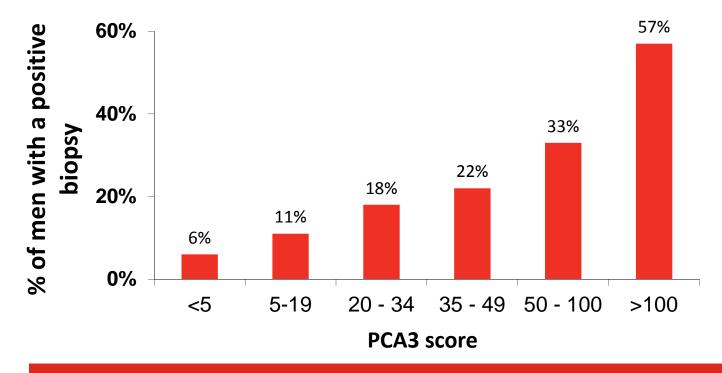
## Is PCA3 a useful option for men with a negative first biopsy?





### PCA3 and repeat biopsy (1)

 Study in 1,072 men scheduled for repeat biopsy; 190 men (17%) had a positive repeat biopsy



The higher the PCA3 score, the higher the probability of a repeat positive biopsy



# PHNI /2YT/0115/00028/

### PCA3 and repeat biopsy (2)

- Study in 466 scheduled for repeat biopsy; 22% had a positive repeat biopsy<sup>1</sup>
- National Cancer Institute Early Detection Research Network (NCI EDRN) validation trial in 562 men scheduled for repeat biopsy<sup>2</sup>
- Study in 470 men with 1-2 prior negative biopsies scheduled for repeat biopsy;
   28% had a positive repeat biopsy<sup>3</sup>

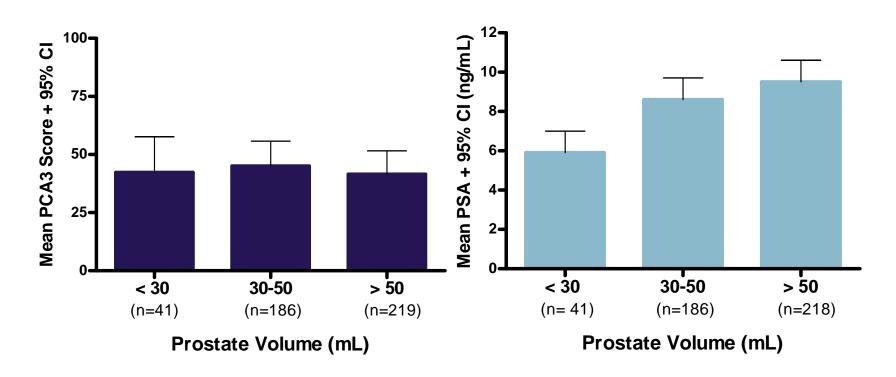
PCA3 score	Sensitivity	Specificity	PPV	NPV
PCA3 score cut-off 25 <sup>1</sup>	78%	57%	34%	90%
PCA3 score cut-off 20 <sup>2</sup>	76%	52%		88%
PCA3 score cut-off 20 <sup>3</sup>	73%	51%		
% free PSA cut-off 25% <sup>3</sup>	83%	23%		

PPV: positive predictive value; NPV: negative predictive value



### PCA3 and repeat biopsy (3)

Study in 445 men with 1-2 previous negative biopsies scheduled for repeat biopsy



The PCA3 score is not affected by prostate volume



### What do the guidelines say?

- EAU guidelines (2016):
  - The main current indication for PCA3 is to determine the need for a repeat biopsy
- ESMO guidelines (2016): No recommendation
- NCCN guidelines (2016):
  - Consideration may be given to PCA3 to inform decisions regarding repeat biopsy despite a negative biopsy



### Wat zegt de NVU richtlijn over PCA3?

 Aangezien PCA3 de uitkomst van het herhalingsbiopt verbetert, kan overwogen worden om na het eerste of tweede negatieve biopt een PCA3 test te verrichten



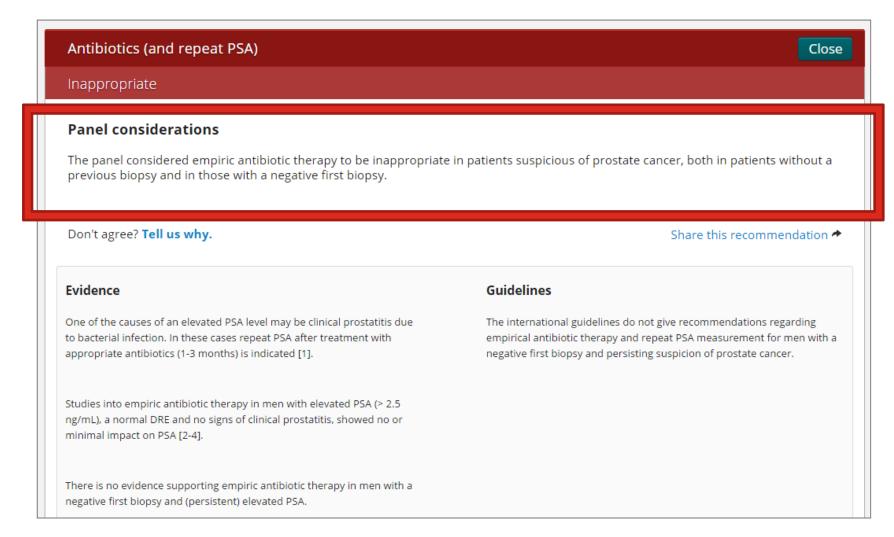




### Antibiotics + repeat PSA



## Antibiotics + repeat PSA also inappropriate in patients with a negative first biopsy





### What do the guidelines say?

- EAU guidelines (2016): AB should not be given
- ESMO guidelines (2016): No recommendation
- NCCN guidelines (2016): No recommendation



## Wat zegt de NVU richtlijn over empirische behandeling met antibiotica?

 Geen specifieke aanbevelingen over empirische behandeling met antibiotica (en herhaalde PSAmeting) na een eerste negatieve biopsie



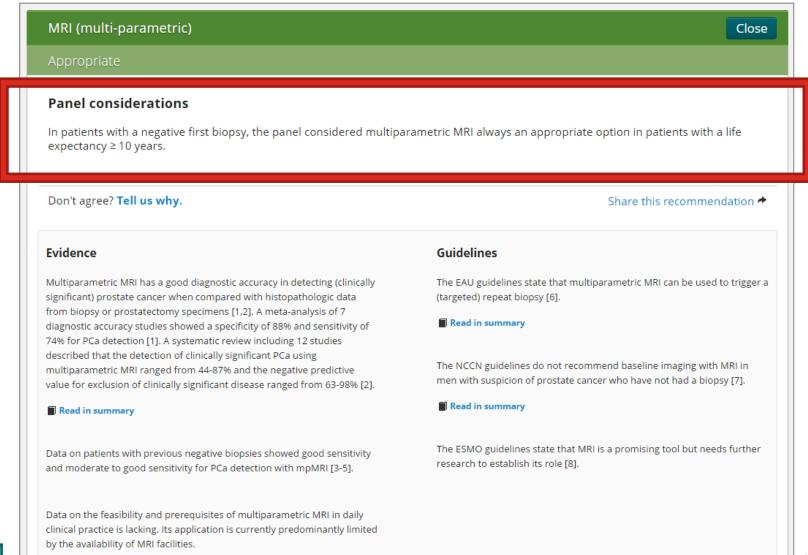




### Multiparametric MRI (mp-MRI)



## What is the role of multiparametric MRI in men with a negative first biopsy?





#### Diagnostic accuracy of multiparametric (mp)-MRI (1)

 Meta-analysis of 7 diagnostic accuracy studies for PCa detection<sup>1</sup> (N=526):

Specificity: 88% (95%CI: 82-92%)

Sensitivity: 74% (95%CI: 66-81%)

Systematic review of 12 studies<sup>2</sup>:

Using mp-MRI	Range
Detection of clinically significant PCa	44-87%
NPV for exclusion of clinically significant PCa	63-98%

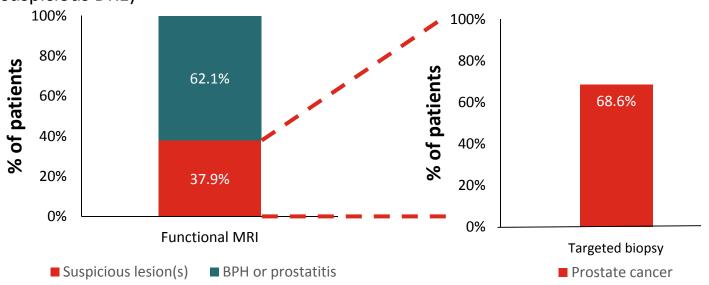
Mp-MRI has a good diagnostic accuracy in detecting PCa. BUT data are lacking on:

- Feasibility
- Prerequisites



### Diagnostic accuracy of mp-MRI (2)

 Pilot study in 58 patients¹ (≥1 previous negative biopsy, persistently increased PSA, unsuspicious DRE)



Accuracy of mp-MRI in 2 prospective studies:

Study	N	Sensitivity	Specificity
Labanaris AP <sup>2</sup>	260	80.8	73.9
Panebianco V <sup>3</sup>	150	93.7	90.7



### What do the guidelines say?

- EAU guidelines (2016):
  - Mp-MRI may be useful in the repeat biopsy setting
  - Inter-reader variability remains a concern
- NCCN guidelines (2016):
  - Mp-MRI should be considered in selected cases after ≥ 1 negative biopsy
- ESMO guidelines (2016):
  - Mp-MRI is recommended before a repeat biopsy with the intention to perform a MRI-guided or MRI-TRUS fusion biopsy



#### Wat zegt de NVU richtlijn over mp-MRI?

 Bij patiënten met een negatieve echogeleide biopt sessie en blijvende klinische verdenking op prostaatcarcinoom dient men bij voorkeur een multi-parametrisch MRI onderzoek toe te passen, met inachtneming van de richtlijnen voor techniek en beoordeling die daartoe door Europese prostaat MRI-experts zijn opgesteld (ESUR consensus based richtlijnen 2012)









# What would be the most appropriate treatment for this patient?

1. No further action

0%

2. Repeat biopsy (6-12 weeks)

3. Repeat PSA (12-24 weeks)

4. PCA3

0%

5. Antibiotics (and repeat PSA)

6. MRI (multi-parametric)

PHNL/ZYT/0115/0002g(1)



### 1st voting 2nd voting

### Comparison of voting results

1. No further action

0% 0%

2. Repeat biopsy (6-12 weeks)

0% 0%

3. Repeat PSA (12-24 weeks)

0%

4. PCA3

0% 0%

5. Antibiotics (and repeat PSA)

0% 0%

6. MRI (multi-parametric)

86%

100%



# Patient case 2 Case change

## What if the previous patient would have a lower PSA but larger prostate?

- 58 years old, school teacher
- Recent (first) prostate biopsy because of elevated PSA (case finding)
- Findings at the time of the first biopsy

- PSA: 4.2 ng/mL

Prostate volume: 65 cc

DRE: normal

Biopsy: negative

No co-morbidities

Previous biopsy	1 negative	
PSA	3-10 ng/mL	
Prostate volume	> 60 cc	
DRE	Normal	
Life expectancy	≥ 10 years	

#### What would be the most appropriate diagnostic option?



### Clinical variables: pt 2 case change

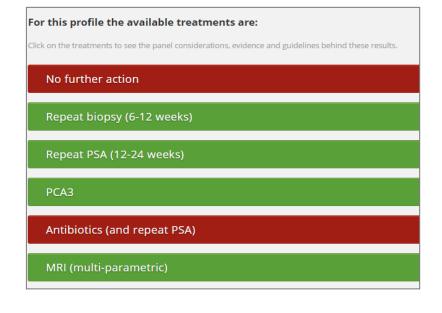


#### Results of DRE





#### What have we learned from this patient case?





For this profile the available choices are:

+ No further action View evidence

+ Repeat biopsy (6-12 weeks) View evidence

+ Repeat PSA (12-24 weeks) View evidence

+ PCA3 View evidence

+ Antibiotics (and repeat PSA) View evidence



+ MRI (multi-parametric)

View evidence

113



#### **Next: longer follow-up on PSA**

After 12 months PSA has increased to 5.1 ng/mL PSA was 4.2 ng/mL before What will be your approach?

1. 1. No further action

0%

2. 2. Repeat biopsy

0%

3. 3. MRI

100%

4. 4. MRI and PCA3 cq quattro

0%





#### **Next: longer follow-up on PSA**

You decided on MRI combined with PCA3 Outcome: both tests show normal results What will be your approach?

- 1. 1. No further action 0%
- 2. 2. Repeat PSA after 3 months

100%

3. 3. Repeat biopsy nevertheless





## Stemronde geopend

# If you perform an mp-MRI of the prostate what will be the next step?

- MRI guided biopsies of lesions PIRAD score 4 or 5
- MRI guided biopsies of lesions PIRAD score 4 or 5 and random biopsies

100%

3. Fusion biopsies with ultrasound of lesions PIRAD score 4 or 5

0%

4. Fusion biopsies with ultrasound of lesions PIRAD score 4 or 5 and random biopsies

0%



 $^{116}$ 

#### **Key messages - Negative first biopsy**

- In patients with a negative first biopsy, benefits and risks of different of further diagnostic tests should be carefully balanced, also in relation to patient preferences
- Repeat biopsy and PSA follow-up are both appropriate options in men with a life expectancy ≥ 10 years, but should be considered in the light of DRE, PSA, and ASAP/PIN findings in the first biopsy
- PCA3 and mp-MRI are both useful (additional) tests for determining the need for repeat biopsy



## Thank you



### **Evaluatie**

1. Hoe waardeert u de inhoud?	12345
2. Module 3: Diagnosis of prostate cancer	12345
3. Module 4: Biochemical recurrence after radical treatment	12345
4. Door de nascholing heb ik meer inzicht gekregen in de behandeling prostaatkanker en mijn kennis ervan vergroot	van <b>1234</b> 5
5. Ik wil graag een persoonlijk account aanmaken	12345
6. Hoe waardeert u de locatie?	12345
7. Sluit de gevolgde nascholing Mirrors of Medicine voldoende aan bij klinische praktijk?	de <b>1234</b> 5
8. Vond u dat er voldoende tijd was voor het stellen van vragen?	12345
9. Zou u op basis van deze nascholing Mirrors of Medicine aanbeveler collega's?	n bij uw <b>1234</b> 5
10. Vond u de rol van Janssen en AstraZeneca passend tijdens de nasc	holing
Mirrors of Medicine? 1=Ja 2=	:Nee

