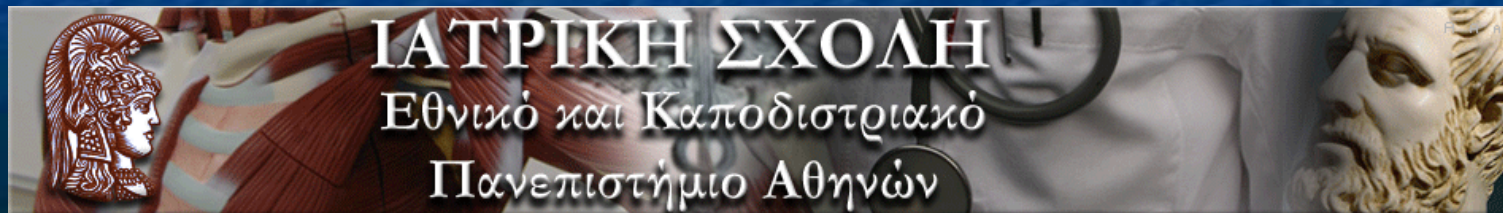# Βιοδείκτες στους καρκίνους του ουροποιητικού:
Υπάρχουν χρήσιμες εφαρμογές στην κλινική πράξη ;

Διονύσιος Ν. Μητρόπουλος

Καθηγητής Ουρολογίας

Σύγκρουση συμφερόντων

Travel grants and/or advisor/lecturer:

Astellas, Amgen, Ferring, GSK, Genekor, Eli
Lilly, Sanofi-Aventis, Specifar, Pfizer,
Pharmanel, Janssen, Rafarm, Takeda,
Ipsen, BMS, Coloplast

12:30 - 13:30	UroSecrets I: Βιοδείκτες στους καρκίνους του ουροποιητικού: υπάρχουν χρήσιμες εφαρμογές στην κλινική πράξη;

Οι υποψίες για παρουσία καρκίνου είναι συχνές. Όπως επίσης και οι θετικές βιοψίες. Πάντα τόσο ο Ουρολόγος όσο και ο ασθενής θέλουν να ξέρουν πόσο επικίνδυνος είναι ο καρκίνος, πόσο γρήγορα θα εξελιχθεί, πότε θα υποτροπιάσει. Τελικά πότε και πώς θα πρέπει να τον αντιμετωπίσει; Υπάρχουν ήδη διαθέσιμοι βιοδείκτες αλλά πόσο χρήσιμοι είναι; Και πότε αξίζει να χρησιμοποιηθούν;

Η εκτίμηση της πορείας ενός νεοπλάσματος αποτελεί βασικό στοιχείο γιά την λήψη των σχετικών θεραπευτικών παρεμβάσεων από τον γιατρό και τον ασθενή.

Οι συνεχείς εξελίξεις στην ιατρική συχνά δημιουργούν περισσότερες της μιάς θεραπευτικές επιλογές, γεγονός που συμβάλλει στην δυσκολία κατανόησης των σχετικών πληροφοριών από τους ασθενείς και το περιβάλλον τους.

Τα νομογράμματα και οι βιοδείκτες σκοπό έχουν να συμβάλλουν στην ορθότερη εφαρμογή της σύγχρονης, ασθενοκεντρικής ιατρικής, που έχει σαν άξονα το "shared decision making"

Nomogram for predicting 1-, 2-, and 5-year survival (HRPC) incorporating PSA kinetics
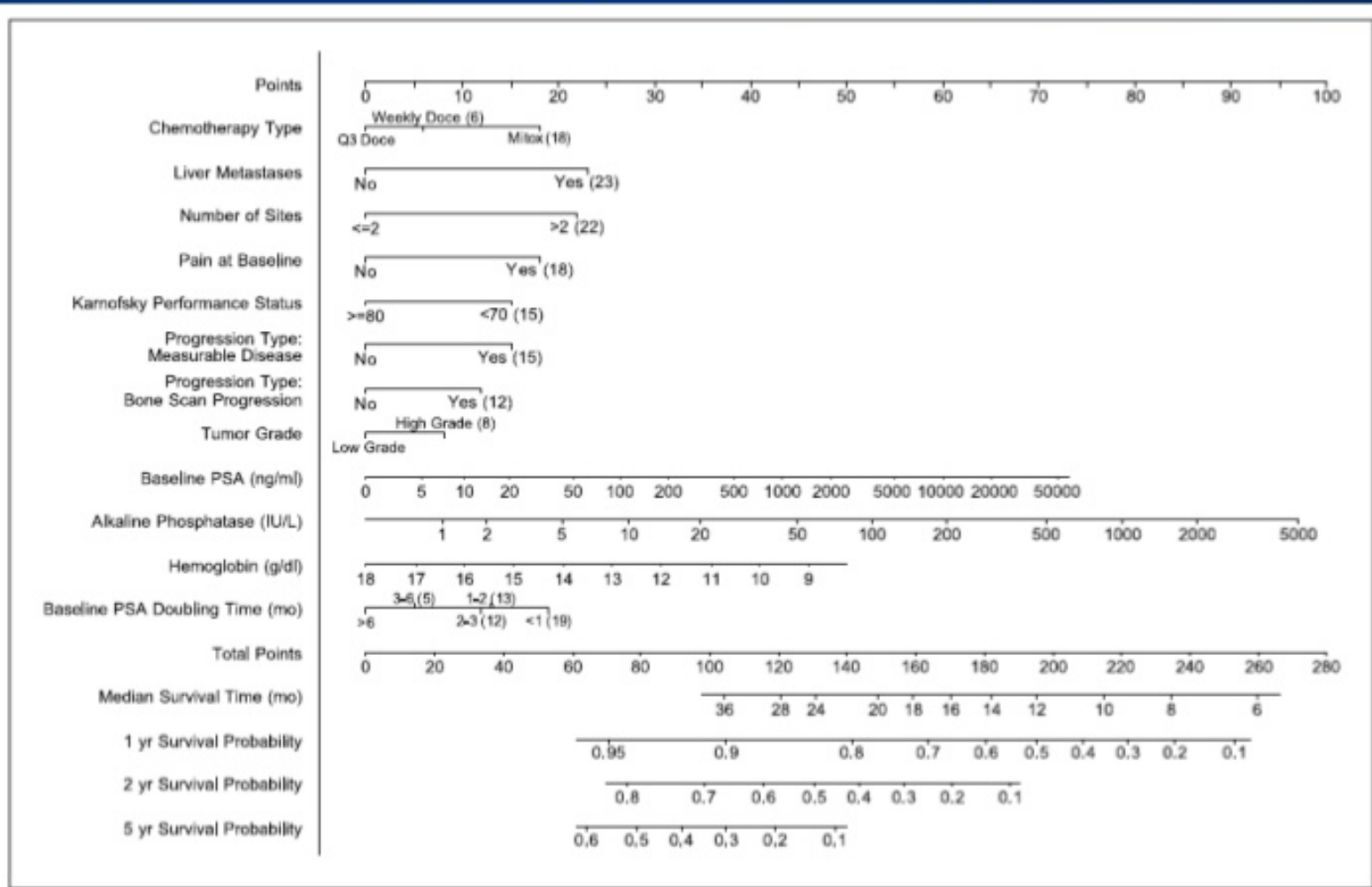
Predictive model for survival in patients with metastatic RCC based on risk stratification utilizing the MSKCC criteria

High Lactate Dehydrogenase?
(> 1.5 times upper limit of normal)   ◯ No   ⦿ Yes

Low Serum Hemoglobin?
(< lower limit of normal)   ◯ No   ⦿ Yes

High Corrected Serum Calcium?
(> 10 mg/dL)   ◯ No   ⦿ Yes

Low Karnofsky Performance Status?
(< 80%)   ◯ No   ⦿ Yes

Disease Free Interval < 1 year?   ◯ No   ⦿ Yes

Please Note: Karnofsky performance status is a scale that allows a physician to rate the patient's ability to perform activities of daily living. Patients who are unable to work or perform normal activity due to their illness are assigned a Karnofsky performance status of less than 80%
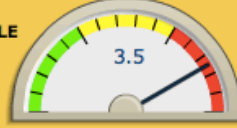
FOX CHASE
CANCER CENTER

Results

My expected survival if I have metastatic renal cell carcinoma and I receive traditional immunotherapy treatment is:
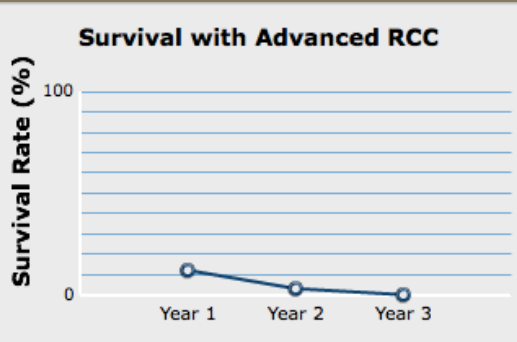
[Hide Results]   [Print]

My overall risk is:

INTERMEDIATE

FAVORABLE   3.5   POOR

My three year survival expectation is:

Year 1	Year 2	Year 3
12%	3%	0%

Survival with Advanced RCC

Survival Rate (%)   100 — 0

Year 1   Year 2   Year 3

[Methodology]   [Source]

Ουροθηλιακός καρκίνος

Upper Tract Urothelial Cancer Predictive Tools

1. *Yates - British Journal of Cancer, 2012:* What are my 3- and 5- year chances for survival following radical nephroureterectomy for my upper urinary tract urothelial carcinoma?

Bladder Cancer Predictive Tools

1. *International Bladder Cancer Nomogram Consortium - Journal of Clinical Oncology, 2006:* Postoperative Nomogram Predicting 5-year Risk of Bladder Cancer Recurrence after Radical Cystectomy

2. *Karakiewicz PI - Journal of Urology, 2006:* Postoperative Nomogram Predicting 2,5, and 8-year Risk of Bladder Cancer Recurrence after Radical Cystectomy

3. *Shariat SF - Clinical Cancer Research, 2006:* Postoperative Nomogram Predicting 2,5, and 8-year Overall Survival after Radical Cystectomy

4. *Karakiewicz P - European Urology, 2006:* Nomogram Predicting the Probability of Identifying Extravesical Spread of Bladder Cancer at Radical Cystectomy

5. *Sylvester RJ - European Urology, 2006:* Likelihood of 1 and 5 year recurrence or progression after transurethral resection

6. *Lughezzani G - Cancer, 2006:* Competing risks of death calculator in patients with Radical Cystectomy for Bladder Cancer

7. *Cambier S, et al. Eur Urol, 2015:* EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Gue'rin.

Prognostic Impact of a 12-gene Progression Score in Non–muscle-invasive Bladder Cancer: A Prospective Multicentre Validation Study
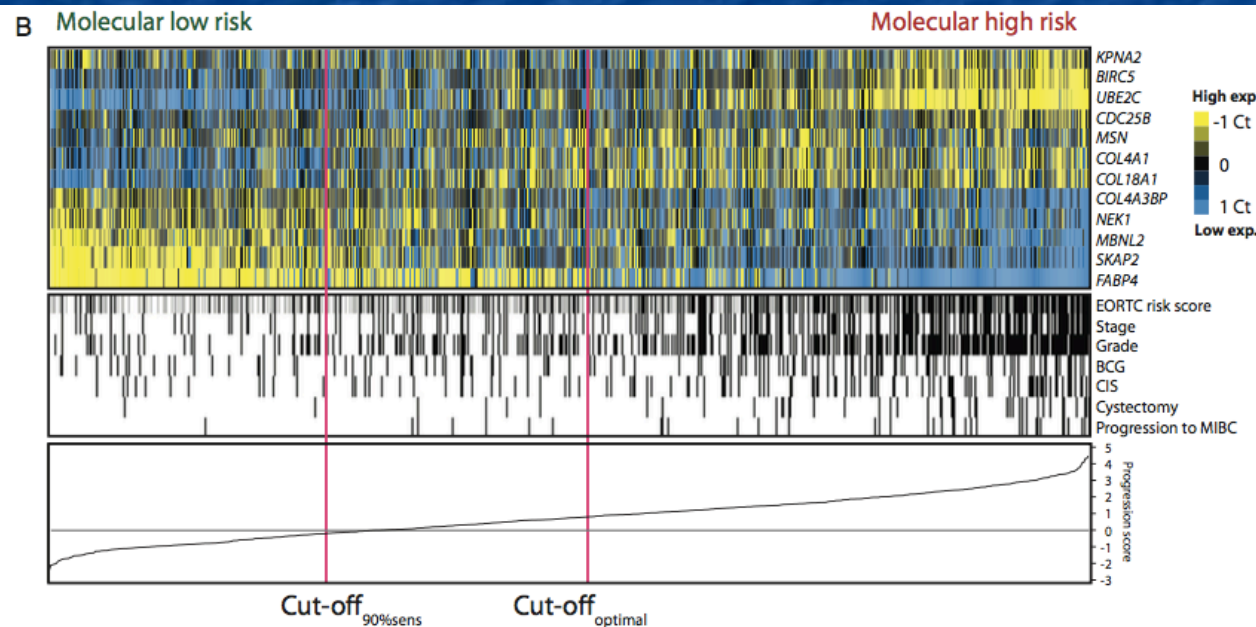
Fig. 1 – Patient enrolment and 12-gene expression assay performance. (A) Flow chart of patient enrolment and exclusion. (B) Heat map of the expression of the 12 genes included in the assay for the first tumours included from each patient (*n* = 750) together with clinical and histopathological characteristics. The distribution of the continuous progression score and associated cut-off values are shown in the bottom panel. Samples are sorted according to the progression score. Colour coding: Stage: Ta, white; T1 + CIS, black. Grade: low grade + PUNLMP, white; high grade, black. BCG treatment: no, white; yes, black. CIS any time in disease course: no, white; yes, black. Cystectomy: no, white; yes, black. Progression to MIBC: no (white), yes (black); EORTC risk score: low (white), intermediate (grey), high (black). MIBC = muscle-invasive bladder cancer; CIS = carcinoma in situ; PUNLMP = papillary urothelial neoplasm of low malignant potential; MIBC = muscle-invasive bladder cancer; EORTC = European Organisation for Research and Treatment of Cancer; RT-qPCR = real-time qualitative polymerase chain reaction; pts = patients; Ct = cycle threshold.

Prognostic Impact of a 12-gene Progression Score in Non–muscle-invasive Bladder Cancer: A Prospective Multicentre Validation Study

Combining the progression and EORTC risk scores significantly increased the predictive accuracy from 0.78 to 0.82 (p < 0.001).
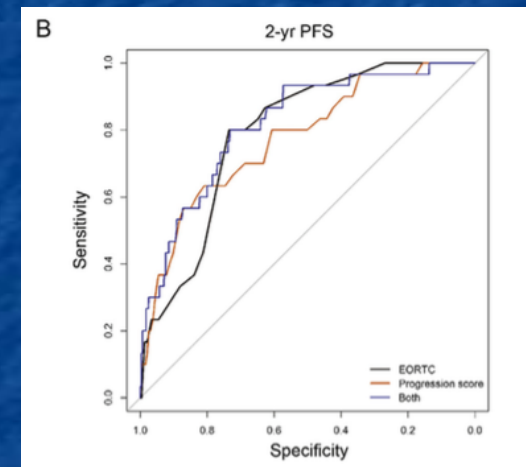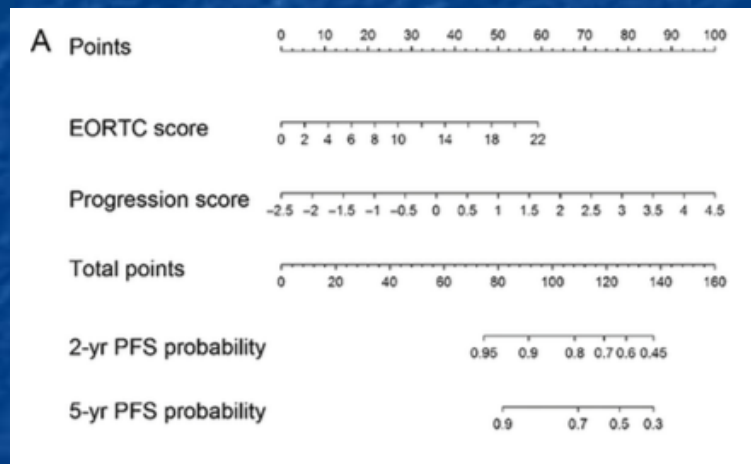
Combined analysis of continuous EORTC risk score and 12-gene progression score. (A) Nomogram for 2-yr and 5-yr PFS probability according to combined EORTC risk and progression scores. (B) Receiver operating characteristic curves depicting sensitivity and specificity for two-year PFS estimates for continuous EORTC risk score and progression score separately and in combination.

- **Title:** A study to evaluate the prognostic and predictive utility of CCP and HRD assays and genetic sequencing in patients undergoing neoadjuvant chemotherapy in bladder cancer.
  Date: Sunday, May 8, 2016: 1:00—3:00 p.m. PT.
  Location: Poster MP49.
 **Presenter:** Hristos Kaimakliotis, M.D., Indiana University.

This exploratory study evaluated three molecular assays to determine if they were able to predict response to neoadjuvant chemotherapy with cisplatin in patients with urothelial bladder cancer (UBC). The assays included 1) a cell cycle progression score, 2) the homologous recombination deficiency (HRD) score, and 3) genetic sequencing of a set of 80 genes associated with UBC. The results showed that RB1 mutations were associated with response to cisplatin neoadjuvant chemotherapy, and the predictive ability was improved by the addition of either the CCP or HRD scores. Additionally, HRD could be used to predict risk of disease recurrence in patients after neoadjuvant chemotherapy followed by cystectomy. If validated, these tests may help identify chemo-responsive patients.

Myriad's myChoice Homologous Recombination Deficiency (HRD) is the first homologous recombination deficiency test that can detect when a tumor has lost the ability to repair double-stranded DNA breaks, resulting in increased susceptibility to DNA-damaging drugs such as platinum drugs or PARP inhibitors.

Review article

Novel neoadjuvant therapy paradigms for bladder cancer: Results from the National Cancer Center Institute Forum

clinical trial to compare the clinical efficacy of the two frontline chemotherapy regimens (gemcitabine plus cisplatin versus MVAC) and the ability of a gene expression profiling-based algorithm (CoXEN) to predict complete pathological response.
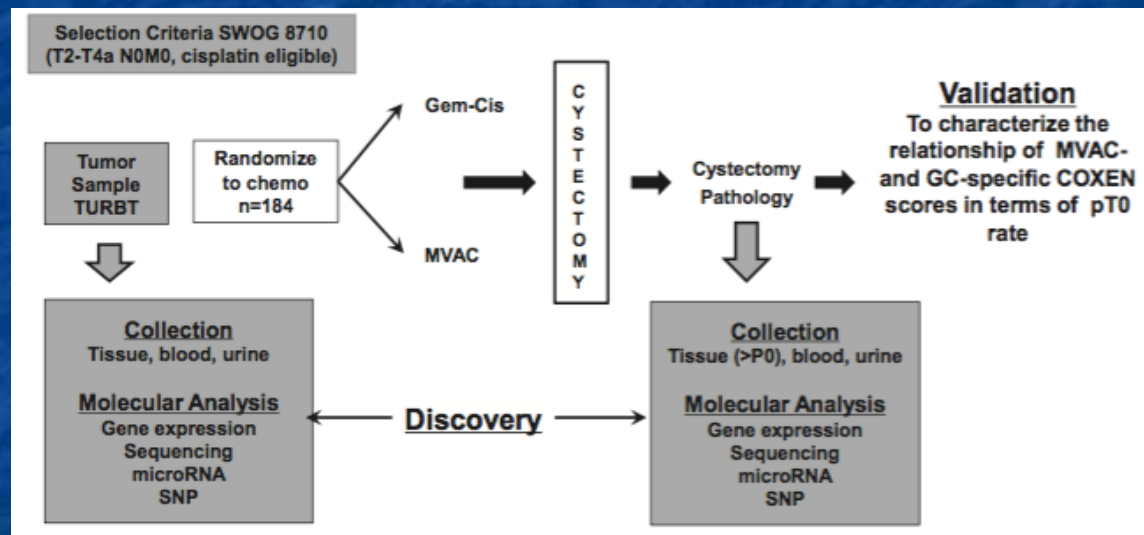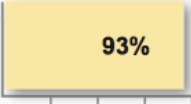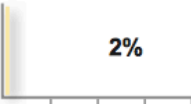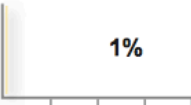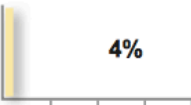

A second clinical trial was planned that will examine the relationship between expression of the DNA repair protein MRE11 and complete response in patients treated with concurrent 5-flurouracil/mitomycin C plus radiation.

Decipher Bladder determines the molecular subtype with high accuracy for an individual patient tumor and informs which patients with muscle invasive bladder cancer may benefit from neoadjuvant chemotherapy.

Decipher Bladder classifies into one of four molecular subtypes to guide personalized therapeutic decision making

Subtype	Interpretation
Luminal	• Limited benefit from neoadjuvant chemotherapy • May be considered for immediate radical cystectomy
Luminal Infiltrated	• Limited benefit from neoadjuvant chemotherapy • May be considered for immediate radical cystectomy and enrollment into immunotherapy trials
Basal	• Substantial benefit from neoadjuvant chemotherapy • May be prioritized to neoadjuvant chemotherapy
Basal Claudin-Low	• May benefit from neoadjuvant chemotherapy • May be considered for neoadjuvant chemotherapy and enrollment into clinical trials of novel agents

Bladder

Your Decipher Result – **Luminal Subtype**

Subtype	Subtype Probability	Interpretation
Luminal	93%	**Patients may be considered for immediate radical cystectomy** • **Favorable prognosis** following surgery and may have limited benefit from cisplatin-based neoadjuvant chemotherapy[1,2] • 3-year overall survival for these patients with cisplatin-based neoadjuvant chemotherapy was similar to those with surgery alone[2]
Luminal Infiltrated	2%	**Patients may be considered for immediate radical cystectomy and enrollment into immunotherapy clinical trials** • **Unfavorable prognosis** and may have limited benefit from cisplatin-based neoadjuvant chemotherapy[2,3] • 3-year overall survival for these patients with cisplatin-based neoadjuvant chemotherapy was similar to those with surgery alone[2] • Patients with this subtype have been shown to most likely benefit from anti-PD-L1 immunotherapy in the locally advanced and metastatic setting[4]
Basal	1%	**Patients may be prioritized to cisplatin-based neoadjuvant chemotherapy** • **Unfavorable prognosis** but may receive substantial benefit from cisplatin-based neoadjuvant chemotherapy[1,2] • 3-year overall survival for these patients with cisplatin-based neoadjuvant chemotherapy was substantially higher than those with surgery alone[2]
Basal Claudin-Low	4%	**Patients may be considered for cisplatin-based neoadjuvant chemotherapy and enrollment into clinical trials of novel agents** • **Unfavorable prognosis** and may benefit from cisplatin-based neoadjuvant chemotherapy[2,5] • 3-year overall survival for these patients with cisplatin-based neoadjuvant chemotherapy was moderately higher than those with surgery alone[2]

Νεφροκυτταρικό καρκίνωμα

FOX CHASE CANCER CENTER
TEMPLE HEALTH

Competing Risk Analyses for RCC

1. *Kutikov, Journal of Clinical Oncology, 2010* Competing risks of death calculator in patients with localized RCC

2. *Kutikov, Journal of Urology, 2012* Competing risks of death calculator in patients with localized RCC, adjusted for comorbidities

Prognostic models before surgery

1. Benign vs Malignant Calculator

2. Preoperative Recurrence Calculator

3. What is the likelihood that my enhancing renal mass is malignant or high grade?

Prognostic models after surgery

1. Postoperative 1,2,5, and 10-year Disease-Specific Survival Calculator (2007 Karakiewicz Nomogram)

2. Postoperative 5-year Recurrence-Free and Overall Survival Calculator Based on UCLA Risk Group Stratification

3. Postoperative 5-year Recurrence-Free Survival Calculator for Clear Cell RCC (2005 MSKCC Nomogram)

4. Postoperative Cancer Specific Survival following Radical Nephrectomy for Clear Cell Renal Cell Carcinoma (Mayo SSIGN/DSSIGN)

Prognostic models - recurrent / advanced / metastatic disease

1. Survival in Patients with Metastatic RCC (MSKCC criteria)

2. Survival in the Setting of a Recurrence Following Nephrectomy (MSKCC criteria)

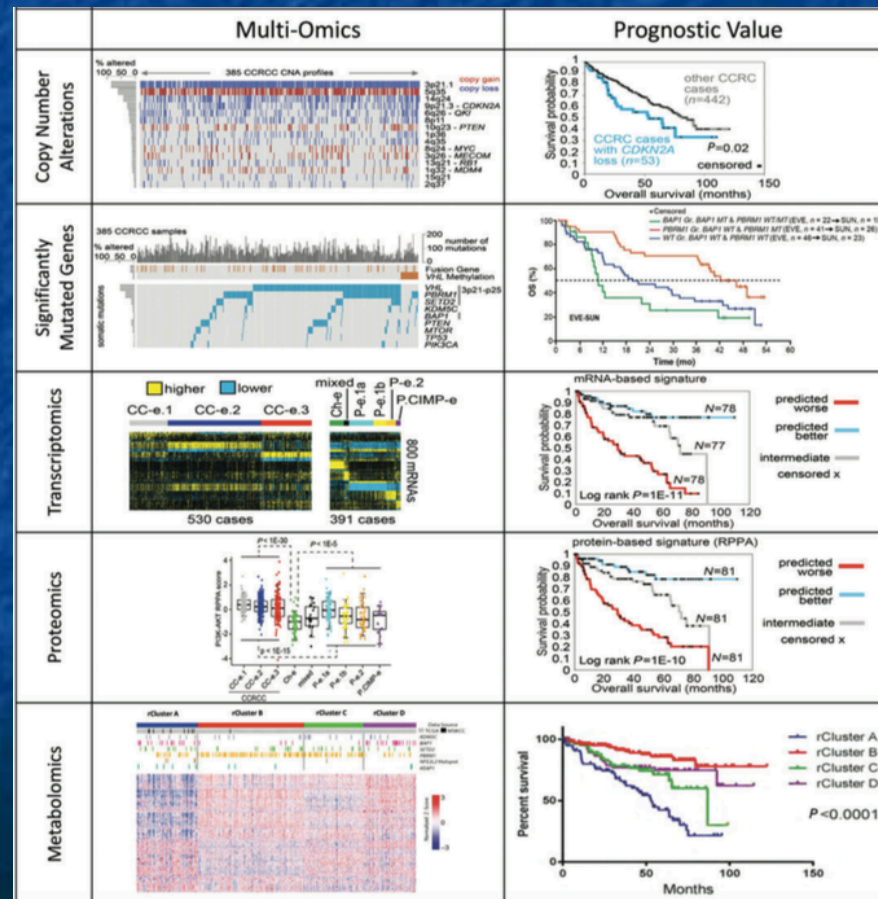**3. Progression-Free Suvival in Patients Receiving Sunitinib**

Αναγκαιότητα γιά προγνωστικά μοντέλα σε:

➢ Όγκους υψηλού κινδύνου γιά υποτροπή/μετάσταση που θα μπορούσαν να ωφεληθούν από επικουρική θεραπεία

➢ Μεταστατικούς όγκους υποψήφιους γιά κυτταρομειωτική χειρουργική

➢ Αντικειμενοποίηση των θεραπευτικών επιλογών/γραμμών/συνδυασμών σε μεταστατικό καρκίνο

Genomic classifications of renal cell carcinoma: a critical step towards the future application of personalized kidney cancer care with pan-omics precision

James J Hsieh[1]*, Valerie Le[1], Dengfeng Cao[2], Emily H Cheng[3] and Chad J Creighton[4]

- **Title:** Prognostic utility of a multi-gene signature (the cell cycle proliferation score) in patients with renal cell carcinoma (RCC) after radical nephrectomy.
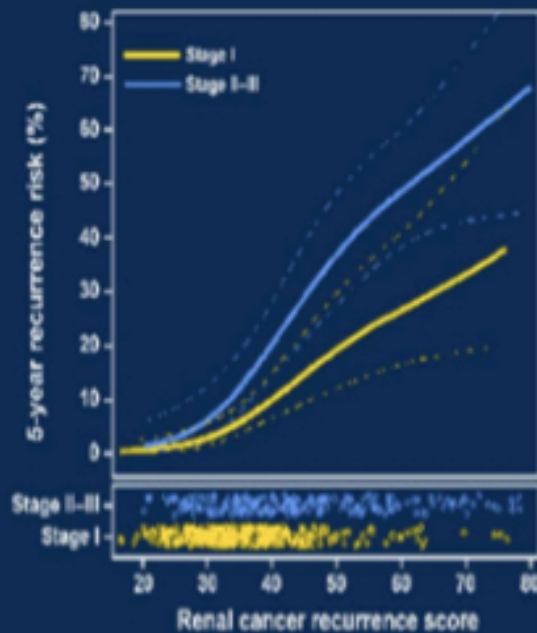 **Date:** Monday, May 9, 2016: 3:30—5:30 p.m. PT.
  Location: Poster MP78.
  Presenter: Adam Feldman, M.D., Massachusetts General Hospital.

The objective of this study was to assess the ability of the Myriad myPlan® Renal Cancer cell cycle progression test to predict long-term oncologic outcomes in patients with surgically-resected renal cell carcinoma (RCC). Outcomes were defined as disease recurrence (local or metastatic) or disease-specific survival (DSS). Patient data were censored at five-years of follow-up. In the training cohort (N= 305), the myPlan Renal Cancer test was a significant prognostic predictor for recurrence (HR: 1.74; $p = 0.02$) and DSS (HR: 2.59; $p < 0.001$) after adjusting for clinical variables. The validation cohort (N=262) demonstrated a consistent and significant prediction of recurrence and DSS, with the strongest association being for DSS (HR: 2.2; $p < 0.001$) after adjusting for clinical variables. Based on these data, the myPlan Renal Cancer test appears to be a significant and independent predictor of key long-term oncologic outcomes in patients who have undergone nephrectomy for RCC, providing prognostic information beyond what is available from clinical parameters. Additional studies are underway to evaluate the utility of the score when derived from diagnostic biopsy.

# of IMDC Criteria Met	No CN OS months (N)	CN OS months (N)	P value
0	92% (65/71) patients had CN, insufficient number to compare		
1	22.5 (n=72)	30.4 (n=178)	0.0024
2	10.2 (n=143)	20.2 (n=253)	<0.0001
3	10.0 (n=113)	15.9 (n=106)	<0.0001
4	5.4 (n=103)	6.0 (n=67)	0.1664
5	3.6 (n=36)	2.8 (n=14)	0.5044
6	25% (3/12) patients had CN, insufficient number to compare		

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria: hemoglobin less than the LLN, serum corrected calcium greater than the ULN, Karnofsky performance status less than80%, time from initial diagnosis to initiation of therapy of less than 1 year, absolute neutrophil count greater than ULN and platelets greater than ULN

Καρκίνος του όρχι

Καρκίνος προστάτη

Αποφυγή μη απαραίτητων βιοψιών
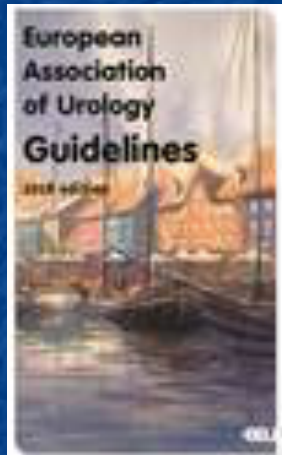
Recommendation	LE	Strength rating
In order to avoid unnecessary biopsies, offer further risk-assessment to asymptomatic men with a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level between 2-10 ng/mL prior to performing a prostate biopsy. Use one of the following tools: • risk-calculator; • an additional serum or urine-based test (e.g. Prostate Health Index test [PHI], four kallikrein [4K]score, Prostate cancer gene 3 [PCA3], *HOXC6/DLX1*) or; • imaging.	3	Strong

Risk calculators may be useful in helping to determine (on an individual basis) what the potential risk of cancer may be, thereby reducing the number of unnecessary biopsies. Several tools developed from cohort studies are available including:

- the PCPT cohort: PCPTRC 2.0 http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp;
- the ERSPC cohort: http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-riskcalculators; An updated version was presented in 2017 including prediction of low and high risk now also based on the ISUP grading system and presence of cribriform growth in histology [99].
- a local Canadian cohort: http://sunnybrook.ca/content/?page=occ-prostatecalc (among others).

Since none of these risk calculators has clearly shown superiority, it remains a personal decision as to which one to use [100].

A few prospective multicentre studies demonstrated that both the PHI and 4K test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa in men with a PSA between 2-10 ng /mL. In a head to head comparison both tests performed equally.

PCA3 marker/SelectMDX

1. DRE (3 STROKES PER LOBE)
2. FIRST CATCH URINE SPECIMEN (20-30 mL)
3. TRANSFER URINE TO TRANSPORT TUBE — FOLLOW INSTRUCTIONS FOR STORING AND SHIPPING CONDITIONS
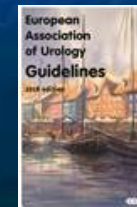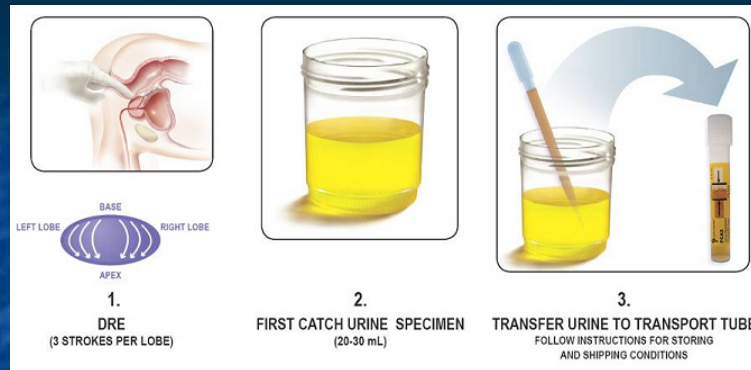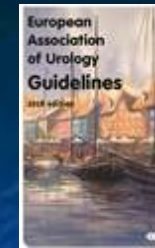
➢ Prostate cancer gene 3 (PCA3) is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA as it shows significant increases in the area under the receiver-operator characteristic curve for positive biopsies.

➢ The SelectMDX test is similarly based on mRNA biomarker isolation from urine. The presence of HOXC6 and DLX1 mRNA levels is assessed to provide an estimate of the risk of both presence of PCa on biopsy as well as presence of high-risk cancer.
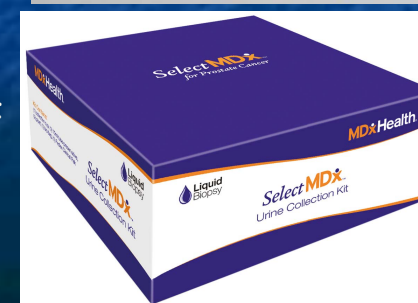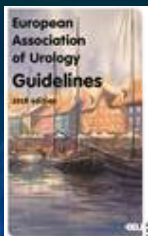
Απόφαση γιά επαναληπτική βιοψία

➢ The role of PHI, Progensa PCA3, and SelectMDX in deciding whether to take a repeat biopsy in men who had a previous negative biopsy is uncertain and probably not cost-effective.

➢ The ConfirmMDx test is based on the concept that benign prostatic tissue in the vicinity of a PCa focus shows distinct epigenetic alterations. If the PCa is missed at biopsy, demonstration of epigenetic changes in the benign tissue would indicate the presence of carcinoma. The ConfirmMDX test quantifies the methylation level of promoter regions of three genes in benign prostatic tissue. A multicentre study found a negative predictive value (NPV) of 88% when methylation was absent in all three markers, implying that a repeat biopsy could be avoided in these men. Given the limited available data, no recommendation can be made regarding its routine application.

Prostate Cancer Predictive Tools

1. Prognostication of Outcomes of Prostate Biopsy

2. Prognostication of Disease Characteristics Based on Pretreatment Data

3. Prognostication of Post-surgical Outcomes

4. Prognostication of Post-radiotherapy Outcomes

5. CALGB 90203

CALGB 90203

1. *Kattan - CALGB:* What is my probability of remaning recurrence free for 60 months following radical prostatectomy?

Απόφαση γιά ενεργό επιτήρηση
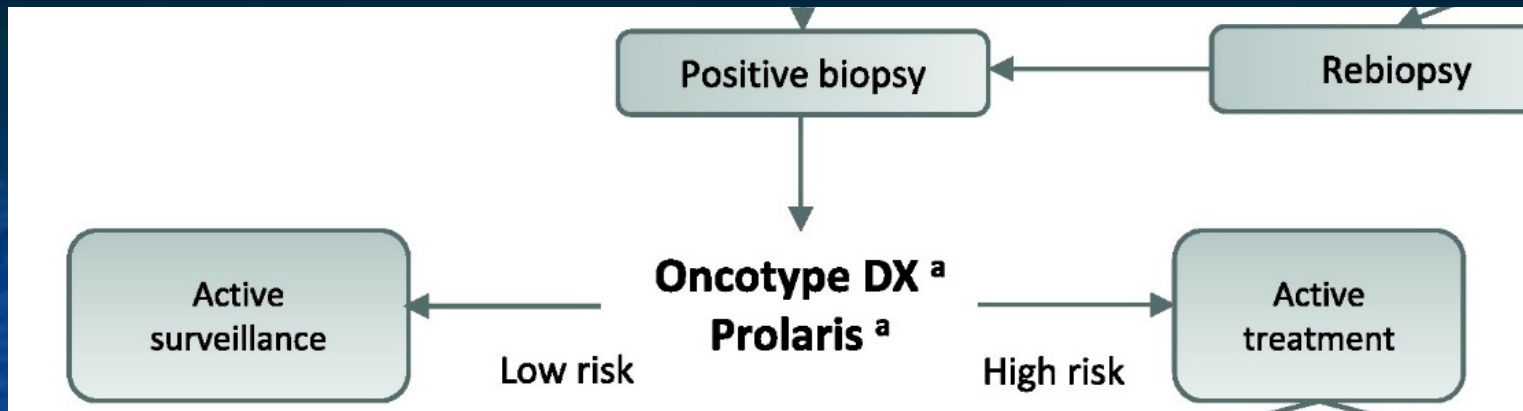
Oncotype Dx Genomic Prostate Score (GPS; Genomic Health Inc., Redwood City, CA, USA) is a quantitative real-time PCR assay performed on small fixed paraffin-embedded tissue samples obtained by needle biopsy. This assay includes 12 cancer-related genes involved in four different biological pathways (androgen pathway, cellular organization, prolif- eration, and stromal response) and five reference house- keeping genes algorithmically combined to calculate the GPS .

The GPS, expressed on a scale of 0–100, has been investigated as a risk predictor of adverse pathology at RP in patients diagnosed with low or intermediate disease on biopsy. The GPS may guide clinicians in stratifying patients for active surveillance versus therapeutic intervention.

The commercially available Prolaris test is a 46-gene panel (31 cell-cycle progression [CCP] genes and 15 housekeeping genes) developed by Myriad Genetics (Salt Lake City, UT, USA). The Prolaris assay, performed in prostate biopsy specimens, could help in the decision making between active surveillance and active treatment in low-risk PCa

Genomic Prostate Score (GPS) Report

oncotype DX®
Genomic Prostate Score

PATIENT-LAST-NAME, FIRST-NAME I.

Date of Birth: **01-Jan-1950**　　　Gender: **Male**　　　Report Number: **OR000123456-01**　　　Report Date: **22-May-2017**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

GPS + NCCN®[1] : **Low Risk**

		FAVORABLE / UNFAVORABLE	
VERY LOW	**LOW**	**INTERMEDIATE***	**HIGH**

GPS **21**
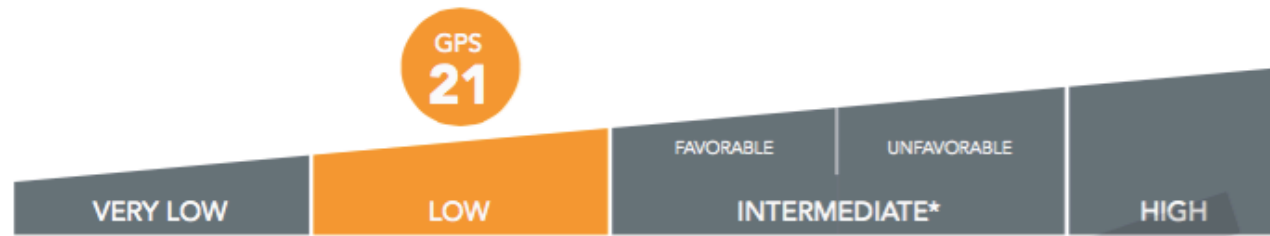
Clinical Interpretation	Clinical Endpoints[†]	Individualized Risk (95% Confidence Interval [CI])
The combination of GPS and clinical features predicts that this patient's risk is consistent with **NCCN Low Risk** disease.[‡]	**Prostate Cancer Death Within 10 Years**	**<1%** (95% CI: <1% - <1%)
	Metastasis Within 10 Years[§]	**1%** (95% CI: <1% - 6%)
	Adverse Pathology (Gleason ≥ 4+3 and/or pT3+)	**22%** (95% CI: 17% - 26%)

Prolaris Biopsy Report
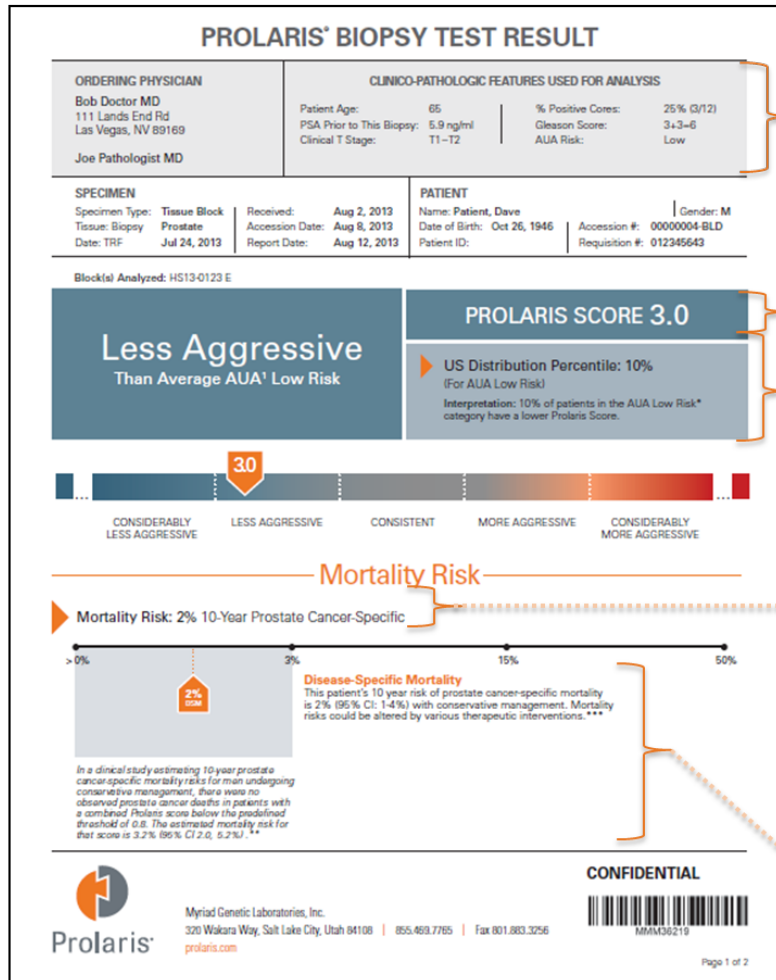
Clinical and pathological features

Prolaris Score – CCP Cancer Aggressiveness is **independent** of clinico-pathologic features.

US Distribution – of score within AUA risk group

Mortality Risk – Prolaris Score combined with clinico-pathologic values

Active Surveillance Threshold – Patients who fall in the gray box, may be candidates for Active Surveillance.

Decipher Classification	Suggested Patient Management Plan
Decipher Biopsy Low Risk	Favorable prognosis - may be suitable candidate for active surveillance and may have excellent outcomes when treated with local therapy alone such as surgery[2,5] or radiotherapy[7]
Decipher Biopsy High Risk	Unfavourable prognosis - may not be suitable candidate for active surveillance and may benefit from intensification with multi-modal therapy[3,5,7]

YOUR DECIPHER RESULT: GENOMIC LOW RISK

DECIPHER SCORE: 0.23	
Risk at RP - Percent Likelihood	
High Grade Disease (primary Gleason grade 4 or 5)	12.5%
5-Year Metastasis	1.0%
10-Year Prostate Cancer Specific Mortality	1.9%

INTERPRETATION

References on reverse

Clinical studies have shown that men with a Decipher low risk score have a favorable prognosis. Men considering active surveillance with a Decipher low risk score may be suitable candidates for active surveillance. Men considering a definitive therapy may have excellent outcomes when treated with local therapy alone.[1-3]

DECIPHER SCORE

1.0

HIGH RISK

0.60

AVG.* RISK

0.45

LOW RISK

YOUR DECIPHER SCORE

0

'Notable Differences' With 3 Prostate Cancer Genomics Tests

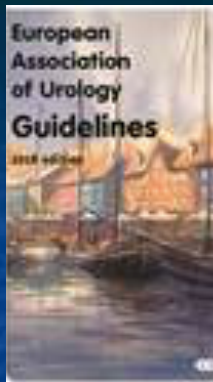**Study Author Admits: 'I Need a Lot of Help'**

Nick Mulcahy

May 20, 2018

"I need a lot of help figuring out how to use these tests," Wagner acknowledged during a meeting press conference.

PD06-09
PROSTATE CANCER GENOMICS: COMPARING DECIPHER, PROLARIS, AND ONCOTYPEDX RESULTS

6.2.1.1.Selection criteria for active surveillance

6.2.1.1.2.Biological markers

Biological markers, including urine PCA3, transmembrane protease, serine 2-TMPRSS2-ERG fusion, or PSA isoforms appear promising, as does genomics on the tissue sample itself [503-505]. However, further data will be needed before such markers can be used in standard clinical practice [132].

132.Lamy, P.J., et al. Eur Urol Focus, 2017.
503.Klein, E.A., et al. Eur Urol, 2014. 66: 550.   504.Berg, K.D., et al. Eur Urol, 2014. 66: 851   505.Cantiello, F., et al. World J Urol, 2016. 34: 485.

In the NCCN guidelines, OncotypeDX and Prolaris are mentioned as a potential tool in the post-biopsy setting in very-low- and low-risk PCa patients with a life expectancy of 10 years or more who are considering active surveillance as preferred treatment option, while Decipher is not mentioned in this setting *(NCCN, 2017)*.

Current AUA guidelines state that OncotypeDX, Prolaris and Decipher have not yet been proven to have a substantial role in the selection of active surveillance candidates (Expert opinion) *(Sanda MG et al., J Urol 2018; 199:990-7).*

Απόφαση γιά επικουρική ακτινοθεραπεία
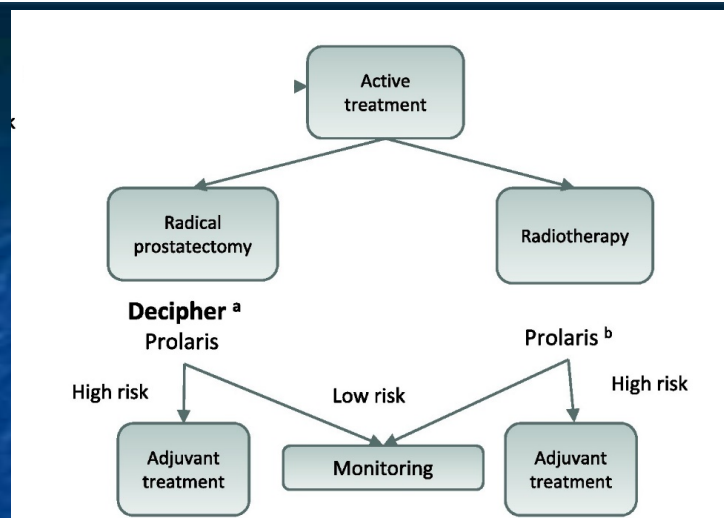
The tissue-based genomic classifier (GC) Decipher was codeveloped and validated by GenomeDx Biosciences (Vancouver, BC, Canada) and Mayo Clinic (Rochester, MN, USA). Based on 22 RNA biomarkers related to cell proliferation, differentiation, motility, immune modulation, and androgen receptor (AR) signaling, GenomeDx continuous risk score (0–1) is able to predict the risk of clinical metastasis development after surgery. GenomeDx GC has also been shown to guide treatment decisions after RP and to identify men who could benefit from adjuvant RT versus initial observation

The Prolaris assay, performed in RP specimens, may suggest the use of adjuvant therapy in high- risk patients with adverse pathological features after surgery

Panel 1 (Top Left)

CLINICAL DETAILS

Pre-operative PSA (ng/mL): **7.78** Specimen Type: **Radical Prostatectomy** Grade Group: **3**

☐ SM+ ☐ EPE ☑ SVI ☑ LNI ☐ BCR ☐ Tertiary Gleason 5
☑ Other: Close margin

YOUR DECIPHER RESULT: GENOMIC LOW RISK

DECIPHER SCORE: 0.36	
Risk at RP - Percent Likelihood	
5-Year Metastasis	**2.3%**
10-Year Prostate Cancer Specific Mortality	**3.2%**

DECIPHER SCORE axis: 1.0 — HIGH RISK; 0.60 — AVG.* RISK; 0.45 — LOW RISK; 0
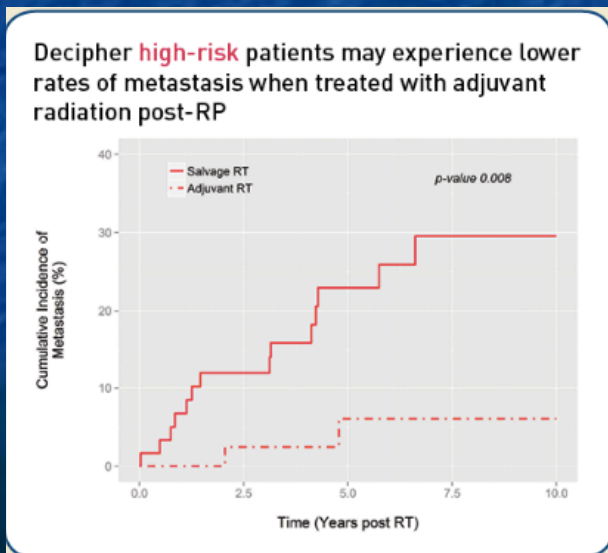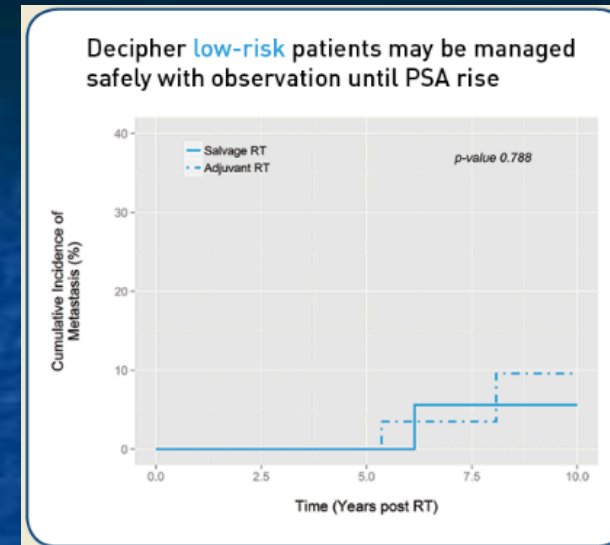
YOUR DECIPHER SCORE

INTERPRETATION
References on reverse

Clinical studies concluded that Decipher low risk results in men with adverse pathology have good prognosis overall and may be optimally managed with observation after surgery.[1-3,8] Upon PSA rise, these patients may be treated with delayed radiotherapy without concurrent hormone therapy.[4,7]

Relevant findings from published clinical studies: Patients with Decipher low risk had > 97% 5-year metastasis free survival and > 94.7% 10-year cause specific survival.[1,2,3] For these patients there were no significant differences in metastasis free survival with adjuvant, early or late salvage post-operative radiotherapy treatment.[5,6,7]

In patients with PSA rise or biochemical recurrence after surgery that received salvage radiotherapy, > 97% 5-year metastasis free survival was observed with or without concurrent hormone therapy.[4]

Additional Comment: Tumor heterogeneity exists in most cancers, including prostate. To ensure that the most aggressive tumor tissue was evaluated, analysis was repeated on two different areas of the tumor. Both samples resulted in a low risk Decipher score. The higher score was reported here.

Panel 2 (Top Right)

Decipher low-risk patients may be managed safely with observation until PSA rise

Salvage RT / Adjuvant RT — p-value 0.788
Cumulative Incidence of Metastasis (%) vs Time (Years post RT)

Panel 3 (Bottom Left)

Decipher high-risk patients may experience lower rates of metastasis when treated with adjuvant radiation post-RP

Salvage RT / Adjuvant RT — p-value 0.008
Cumulative Incidence of Metastasis (%) vs Time (Years post RT)

Panel 4 (Bottom Right)

CLINICAL DETAILS

Pre-operative PSA (ng/mL): **21.8** Specimen Type: **Radical Prostatectomy** Grade Group: **5**

☑ SM+ ☑ EPE ☐ SVI ☐ LNI ☐ BCR ☑ Tertiary Gleason 5
☑ Other: Preoperative PSA (≥ 20ng/mL), Perineural Invasion, Capsular Invasion

YOUR DECIPHER RESULT: GENOMIC HIGH RISK

DECIPHER SCORE: 0.78	
Risk at RP - Percent Likelihood	
5-Year Metastasis	**25.5%**
10-Year Prostate Cancer Specific Mortality	**15.3%**

DECIPHER SCORE axis: 1.0 — HIGH RISK; 0.60 — AVG.* RISK; 0.45 — LOW RISK; 0

YOUR DECIPHER SCORE

INTERPRETATION
References on reverse

Clinical studies concluded that Decipher high risk men with adverse pathology have a poor prognosis overall.[1-3,8] These men may benefit from adjuvant or early salvage radiotherapy and consideration for clinical trials.[4-6]

Relevant findings from published clinical studies: Patients with Decipher high risk had 77.5% 5-year metastasis free survival and 70.0% 10-year cause specific survival.[1,2,3,9] For these patients there was improved metastasis-free survival favoring adjuvant and early salvage post-operative radiotherapy compared to post-operative observation.[5,6,7]

In patients with PSA rise or biochemical recurrence after surgery that received salvage radiotherapy, only 66.9% remained metastasis free after 5 years.[4]

Additional Comment: Tumor heterogeneity exists in most cancers, including prostate cancer. To ensure that the most aggressive tumor tissue was evaluated, analysis was repeated on two different areas of the tumor. The higher Decipher risk score was reported.

Validation of a Cell-Cycle Progression Gene Panel to Improve Risk Stratification in a Contemporary Prostatectomy Cohort

Matthew R. Cooperberg, Jeffry P. Simko, Janet E. Cowan, Julia E. Reid, Azita Djalilvand, Satish Bhatnagar, Alexander Gutin, Jerry S. Lanchbury, Gregory P. Swanson, Steven Stone, and Peter R. Carroll
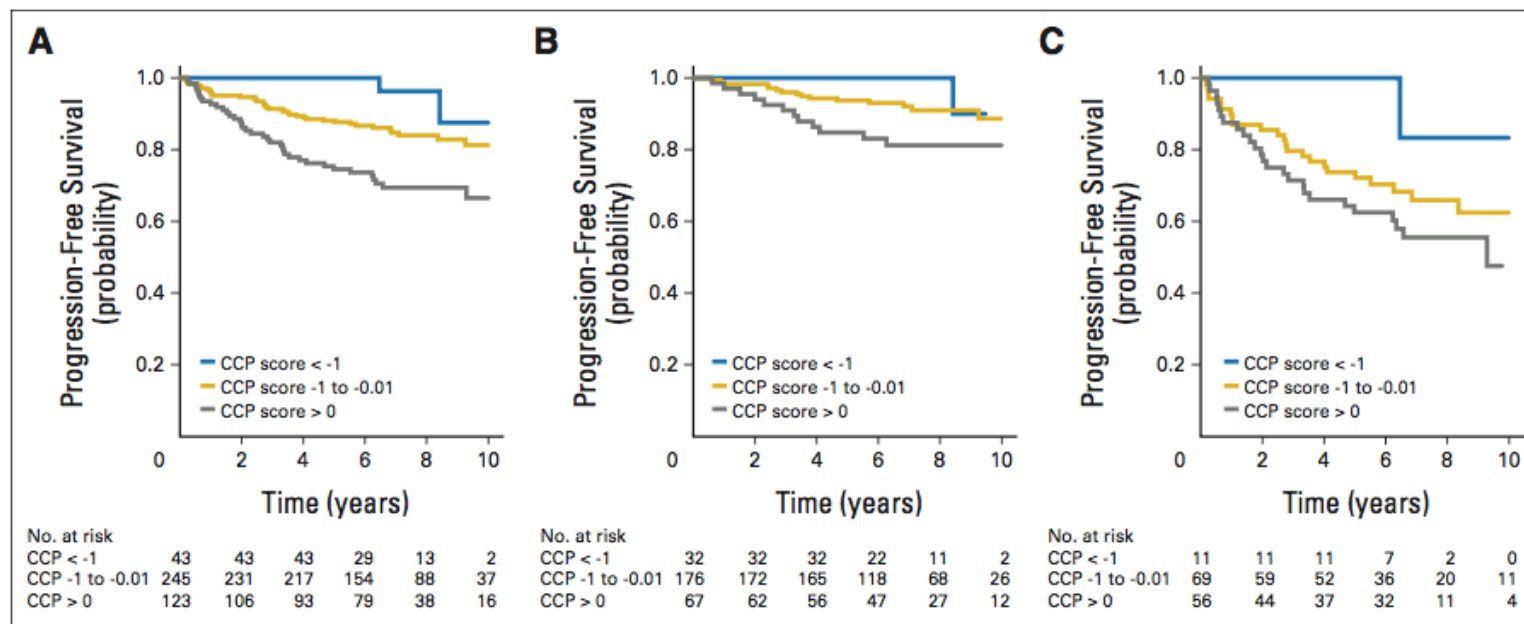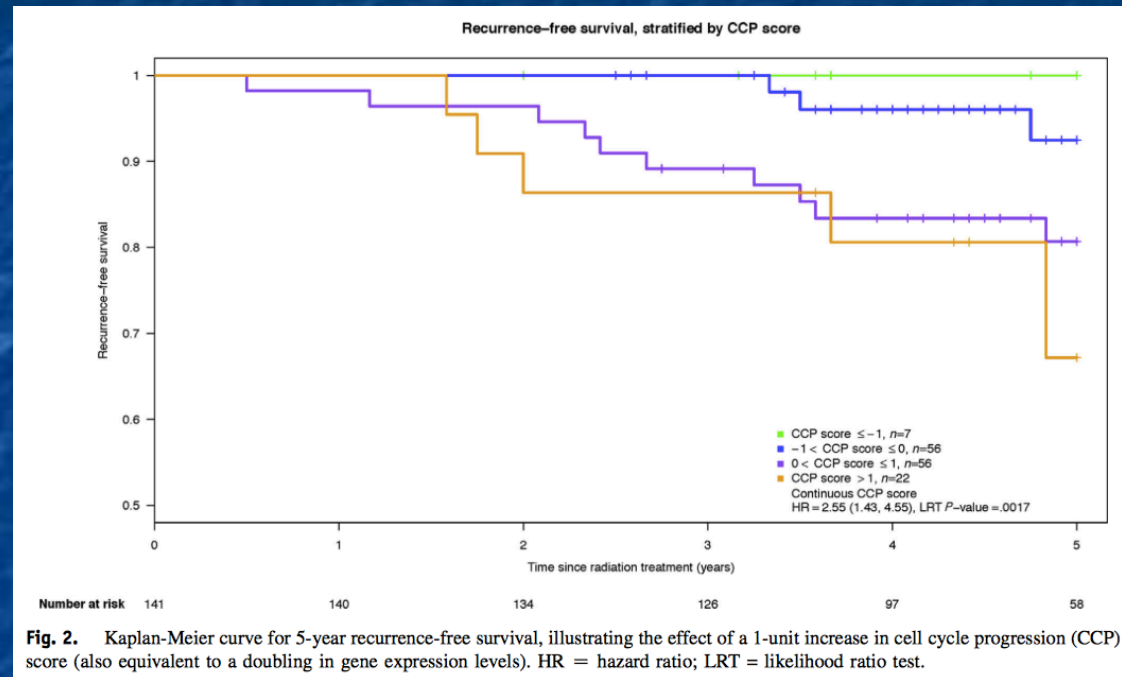
Fig 1. Kaplan-Meier plots of biochemical progression-free probability by cell-cycle progression (CCP) scores grouped by integers for (A) the overall cohort, (B) the subset of patients who were low risk by clinical criteria defined by Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score of 0 to 2, and (C) the subset of patients who were intermediate or high risk by clinical criteria defined by CAPRA-S score ≥ 3.

Πρόγνωση της εξέλιξης μετά από ακτινοθεραπεία

Prognostic Utility of Cell Cycle Progression Score in Men With Prostate Cancer After Primary External Beam Radiation Therapy

Fig. 2. Kaplan-Meier curve for 5-year recurrence-free survival, illustrating the effect of a 1-unit increase in cell cycle progression (CCP) score (also equivalent to a doubling in gene expression levels). HR = hazard ratio; LRT = likelihood ratio test.

This study evaluated whether an mRNA-based diagnostic assay (CCP score) can be used as a prognostic indicator in EBRT-treated prostate cancer patients.

The CCP score was significantly predictive of biochemical recurrence even after adjustment for standard clinical parameters.

Επιλογή Θεραπείας σε mCRPC
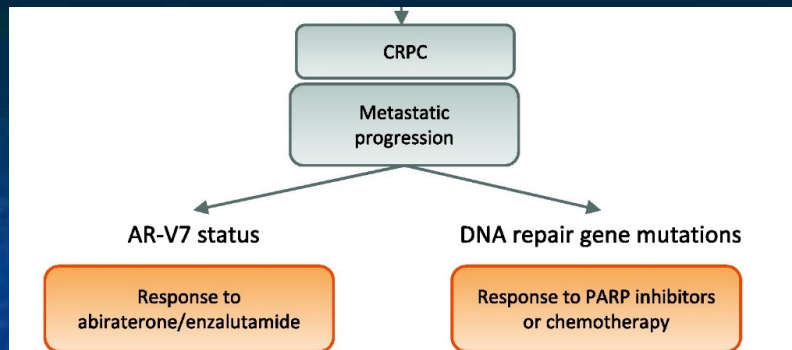
AR-V7 is the most clinically meaningful AR splice variant. The AR-V7 mRNA expression, detected in circulating tumor cells (CTCs) from CRPC patients receiving enzalutamide or abiraterone, has been associated with drug resistance.

DNA repair gene mutations: Recent advances in high-throughput genotyping and next- generation sequencing technologies contribute to better understand the potential application of genomic aberrations in the DNA damage repair pathways for PCa risk prediction and response to therapy.

Poly(ADP-ribose) polymerase (PARP) inhibitors have been considered an effective therapeutic option for tumors with impaired homologous recombination DNA repair. The recent phase-2 TOPARP trial investigated the antitumoral activity of olaparib, a PARP inhibitor. Of the 49 men enrolled, 33% responded to the therapy with an increased patient response (88%) in the subset that was identified to carry defects in DNA repair pathways.

Moreover, a retrospective sequencing analysis of mCRPC patients who benefited from platinum chemotherapy in the absence of neuroendocrine differentiation suggested the potential role of BRCA2 biallelic germline/somatic inactivation as a prognostic biomarker for platinum-based chemotherapy sensitivity

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Review – Prostate Cancer

Genomic Markers in Prostate Cancer Decision Making

Vito Cucchiara [a], Matthew R. Cooperberg [b], Marc Dall'Era [a], Daniel W. Lin [c], Francesco Montorsi [d], Jack A. Schalken [e], Christopher P. Evans [a,*]

Larger-scale, multi-institutional, and multinational studies will still be required to prospectively validate the utility of these markers, their cost effectiveness, and how they should truly be used in clinical practice. Nonetheless, we anticipate that the integration of genome information with transcriptomic, proteomic, and metabolomic data will help clinicians move the field toward personalized medicine, benefiting both patient quality of life and healthcare costs.

Review

Biomarkers in prostate cancer – Current clinical utility and future perspectives

Alexander Kretschmer[a,b], Derya Tilki[c,d,*]

The challenge for urologists as well as for scientists is to select patients that might actually profit from the use of a particular test out of a multitude of commercially available and marketed biomarker tests. Hereby, cost- benefit analyzes have to be considered. This becomes even more important regarding the current trends towards a more individual patient- driven precision oncology by innovative approaches such as liquid biopsy techniques

Molecular biomarkers, clinical and histopathological features and imaging diagnostics will have to be used in a complementary rather than a competitive fashion in order to provide the best possible patient selection.