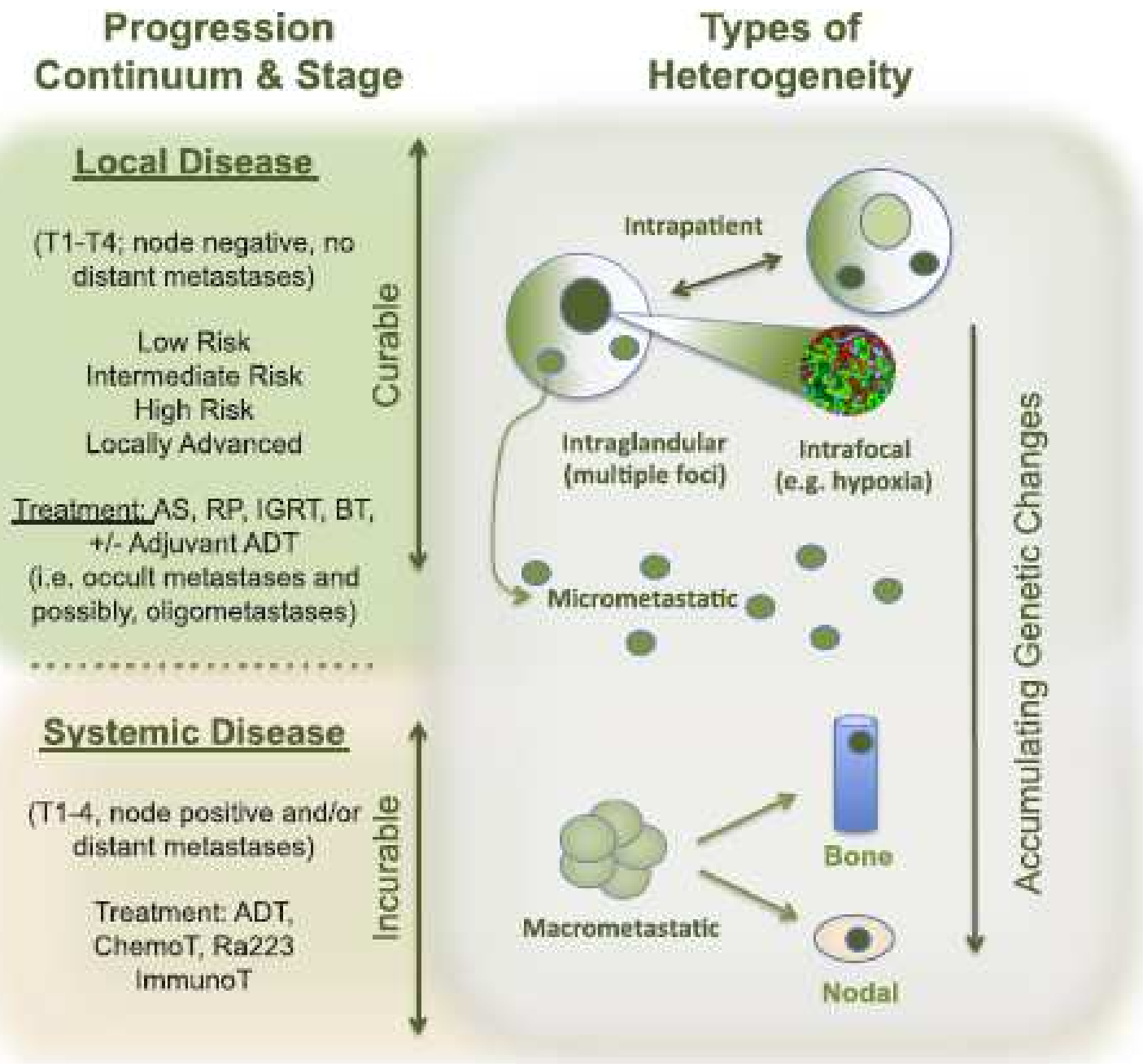
Role of genetic analysis in the management of PCa

- Prostate cancer is a ***heterogeneous disease*** at the clinical, pathological, and ultimately at the genetic level
- Current diagnostic standards such as PSA levels, Gleason grade and stage have ***limitations in the stratification of individual risk***
- This causes significant ***overtreatment*** for low-risk patients and poor prognostic ability of intermediate or high risk patients expecially regarding the ***administration of adjuvant herapies***
- The development of ***novel genetic techniques*** has hugely improved our knowledge of the biology of Pca
- Genetic data have the ***potential to increase our ability of deciphering the complexity of Pca*** as compared to clinico-pathological approaches
- Biological knowledge can be used to develop more effective therapies



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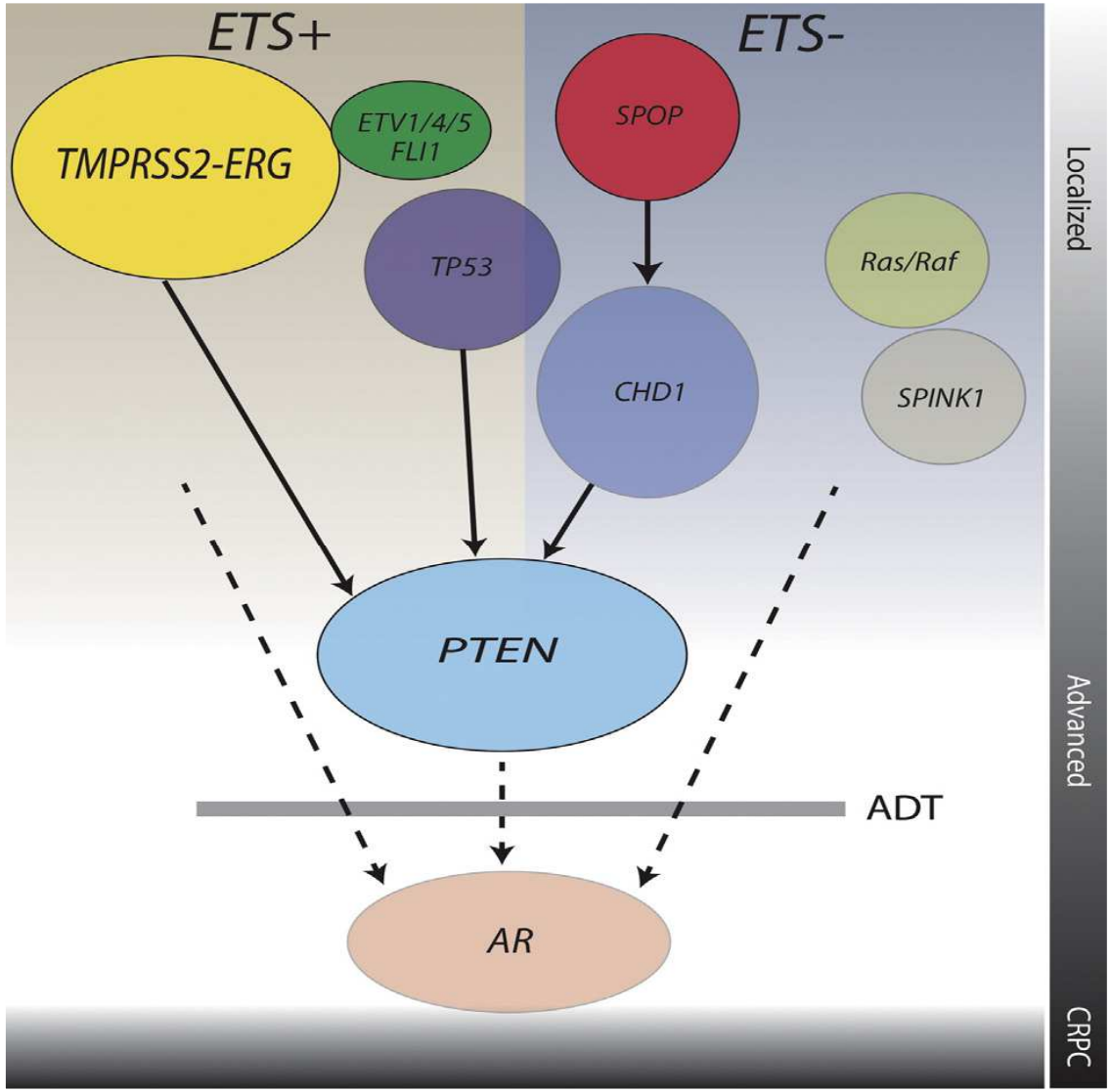
Genomic lesions in the timeline of prostate cancer



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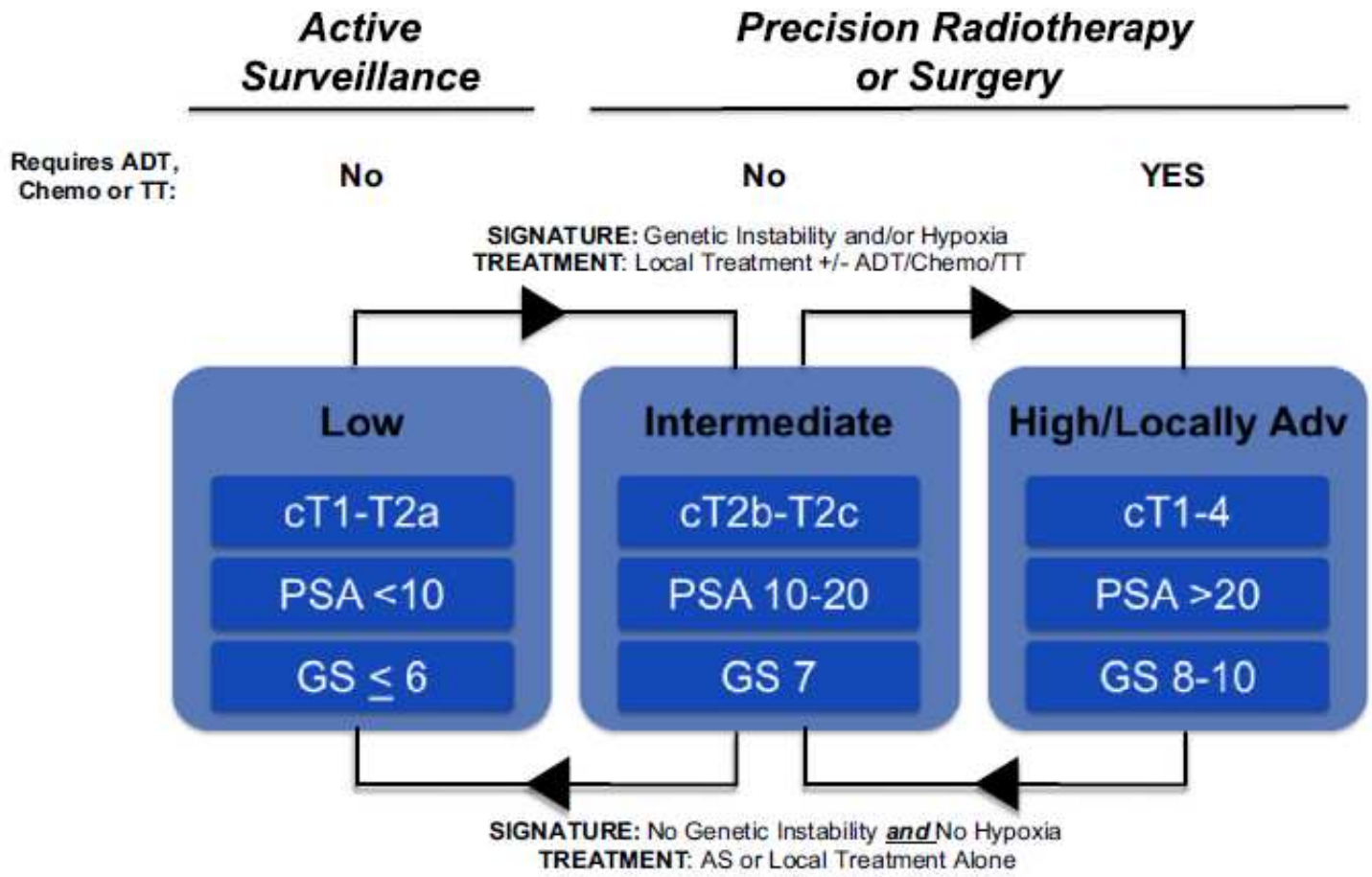
'Precision' or personalized management of PCa

- There has been an ***explosion of genetic biomarkers*** for prognosis and prediction of PCa
- Several test have been ***cleared by FDA and CLIA*** for diagnostic use
- They have been recently included in the ***NCCN guidelines***
- Whether and how they will be incorporated in current diagnostic algorithms is presently unclear
- Issues of ***reproducibility*** among cohorts, ***clinical use*** compared to current parameters, ***cost-efficacy***, and comparisons among tests must be solved before a widespread use can be recommended

Integration of genomic markers in current strategies of risk stratification



M. Fraseretal./UrologicOncology:SeminarsandOriginalInvestigations 33(2015)85–94

The spectrum of tumor biomarkers in PCa

- ***Germline*** biomarkers (SNPs, CNV, mutations)
- ***Tissue*** biomarkers (biopsy, RP)
- ***Circulating*** biomarkers (free NA, CTC)

- ***Single gene*** approach
- ***Gene panel*** approach
  - NGS
  - Gene expression or epigenetic profiling
  - CNVs
  - miRNAs

- ***Potential applications*** in almost every aspect of Pca care
  - Individual genetic risk
  - Repeat biopsy
  - Intervention vs. active surveillance
  - Administration of adjuvant therapies

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Biomarkers based on single gene analysis

TMPRSS2:ERG fusion	PTEN
SPOP	SPINK1
CDH1	Androgen signaling

PROs

- sound ***biological premises***
- ***easy and economic*** to implement in diagnostic practice
- can be easily trasferred to IHC
- predictive value for ***target therapy*** (PARP inhibitors ETS+ PCa)

CONs

- ***poor individual prediction ability***, insufficient to intepret the biological complexity of PCa
- ***non-company driven***
- ***non consistent results*** among studies

Gene panel tests cleared or validated for clinical application

- Based on the concept that single gene analysis is not informative enough for clinical decisions

- ***Prolaris CCPS (cell cycle progression score)*** (Myriad Genetics, Salt Lake City, UT, USA), 31 cell-cycle progression genes and 15 housekeeping genes
- ***Oncotype DX Genomic Prostate Score*** (Genomic Health Inc, Redwood City, CA, USA), 17 gene panel
- ***Decipher genetic test*** (GenomeDX Biosciences, Vancouver, BC, Canada), 22 gene panel
- ***Massachussets General Hospital,*** 32-gene RNA expression signature
- ***Confirm MDx*** (MDxHealth, Inc. Irvine, California), methylation test of GSTP1, APC, and RASSF1 genes

Repeat biopsy

- ***75% of men with increased PSA do not have cancer at biopsy***
- Prostate biopsy has a ***false-negative rate of 30%*** due to sampling error
- In patients with histologically negative biopsies, ***epigenetic field defect*** can be used to detect prostate cancer

- The ***ConfirmMDx epigenetic assay*** showed a ***88-90% negative predictive value (NPV) for a negative repeat*** at 24-30 m. of the initial biopsy after correction for patient age, PSA, DGR and first biopsy histology, compared to 70% NPV of histology alone
- ***The number of unnecessary repeat biopsies was decreased to 64%***
- Based on data from 5 US urology practices, 138 men with a negative ConfirmMDx assay had a ***<5% rate of repeat prostate biopsies***, indicating a potential 10-fold reduction from previous rates

Stewart GD, et al. J Urol 2013;189:1110–6
Partin AW, et al. J Urol 2014;192:1081–7
Wojno KJ, et al. Am Health Drug Benefits 2014;7:129–34
Ruong M, et al. J Urol 2013; 189, 2335-41

Intervention vs. active surveillance

- ***AS is not entirely safe*** and there is ***resistance to its widespread adoption*** in current practice
- Serial prostate biopsies are uncomfortable, are associated with risks of bleeding, serious infection and other ***adverse effects***
- There are also concerns of ***understaging*** and ***biopsy undersampling***. 30% of patients eventually will progress to intermediate grade and RP over a 7-10 yrs period and there is a 30% rate of pathologic upgrading and/or upstaging between biopsy and RP
- ***Gene expression profiles can provide independent prognostic information*** compared to current risk nomograms
- They can contribute to ***reduce the uncertainty*** in identifying subgroups of patients with a low risk of death that can be managed conservatively

Klein EA, et al. Eur Urol 2014;66:550–60.
Cuzick J, et al. Lancet Oncol 2011;12:245–55

Intervention vs. active surveillance

- The 17-gene signature used in the ***Oncotype DX Genomic Prostate Score*** was shown to be an ***independent predictor of adverse pathology*** (p = 0.002) in a two prospectively cohorts of men with low- to low-intermediate-risk PCa candidates for AS
- The test was significantly associated with adverse pathologic features and also ***independently predicted time to BCR and metastases***
- The ***Prolaris CCPS (cell cycle progression score)*** assessed on biopsy or TURP was the ***strongest independent predictor of cancer death for conservatively managed patients*** with clinically localised PCa
- The CCP score increased the ***ability to identify men with a less than 10% risk of dying*** from Pca within 10 years and wider ranges of prediction in patients with Gleason score 6 where considerable uncertainty exist as to the most appropriate treatments

Klein EA, et al. Eur Urol 2014;66:550–60
Cullen J, et al.. Eur Urol. In press
Cuzick J, et al. Lancet Oncol 2011;12:245–55
Cuzick J, et al. Br J Cancer 2012;106:1095–9

Adjuvant therapy

- ***30-40% of men with curable intermediate-risk disease will recur*** despite radical local therapy

- Four studies have reported the use of the ***Decipher genetic test*** to predict biochemical recurrence, metastatic progression, or death after RP
- The test also improved ***prediction of biochemical and metastatic progression*** risk in a cohort of 139 men undergoing EBRT after RP
- The prognostic accuracy was highest when the ***genomic classifier and clinical nomograms were combined*** with favorable net benefit compared with current prediction models
- The test had a potentially ***significant impact on treatment decisions after RP*** changing the recommendation for adjuvant and salvage therapy in 43% and 53%, respectively

Erho N, et al. PLoS One 2013;8:e66855.
Cooperberg MR, et al. Eur Urol 2015;67:326–33.
Ross AE, et al. Prostate Cancer Prostatic Dis 2014;17:64–9
Karnes RJ, et al. J Urol 2013;190:2047–53
Den RB, et al. Int J Radiat Oncol Biol Phys 2014;89:1038–46
Badani K, et al. Oncotarget 2013;4:600–9

Adjuvant therapy

- The ***Prolaris CCPS*** was externally validated in two RP studies of >1300 patients, both on biopsy and RP specimens, as an ***independent prognostic factor for BCR and metastasis***
- In an EBRT cohort, the same panel was an independent prognostic factor after adjusting for clinical variables
- When added to a risk nomogram (CAPRA-S score), the ***gene classifier provided incremental prognostic value beyond standard clinical models***
- In one study where physicians were surveyed about treatment recommendations, ***the genetic test changed indications in 65% of the cases***, and in 40% there was descalation in treatment
- The ***Oncotype DX GPS*** has also been investigated as a predictor for the risk of recurrence and PCa death

Cooperberg MR, et al. J Clin Oncol 2013;31:1428–34.
Bishoff JT, et al. J Urol 2014;192:409–14
Freedland SJ, et alInt J Radiat Oncol Biol Phys 2013;86: 848–53
Crawford ED, et al. Curr Med Res Opin 2014;30:1025–31
Cullen J, et al. Eur Urol. In press

Biomarkers based on gene panels

PROs

- ***quantitative assays*** *(pyrosequencing, Q-PCR)*
- work on ***standard pathological material***
- ***large, multicenter company-driven studies***
- adherence ***to strict design criteria*** (ei. Reporting Recommendations for Tumor Marker Prognostic Studies, REMARK)
- ***externally validated***

Biomarkers based on gene panels

CONs

- ***company-driven***
- ***poor biological premises***
- ***no gene overlap*** among tests
- risk of ***chance association***
- need for ***external validation*** due to differential expression between groups of patients
- unclear ***added value compared to established standards***
- ***no prospective RCTs***; ***no follow-up data*** were not reported to determine the long-term impact
- ***no comparative data*** among tests
- ***high cost*** (Prolaris approximately $3400)
- ***no cost-efficacy analysis***

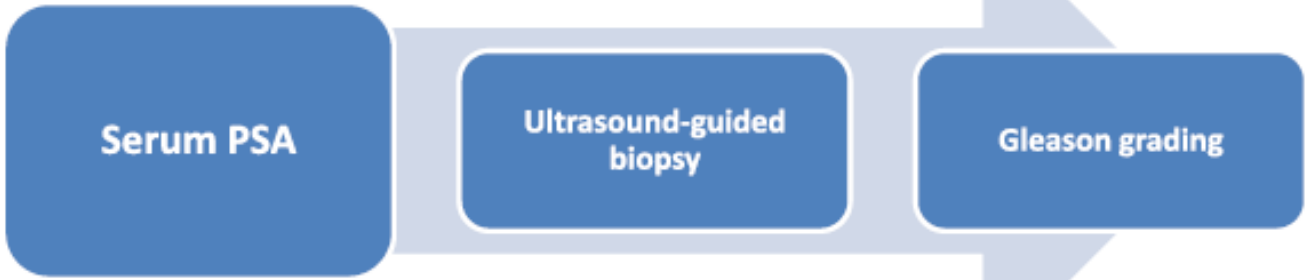
'A Bad Tumor Marker Is as Bad as a Bad Drug '

- ***'Technology'*** should be distinguished from ***'biomarkers'*** or ***'diagnostic tests'***
- A cancer "biomarker test" should provide :
    1. ***analytical validity*** (technically accurate and reproducible)
    2. ***clinical validity*** (stratify patients in clinically meaningful groups)
    3. ***clinical utility*** (improve outcomes compared with known tests)
- The fact that a test is marketed as a "cancer assay" does not mean that the test is clinically useful
- Many commercial cancer risk panels were developed based on the knowledge of cancer biology and analytic technology, but not on the ***ability to affect clinical outcomes***

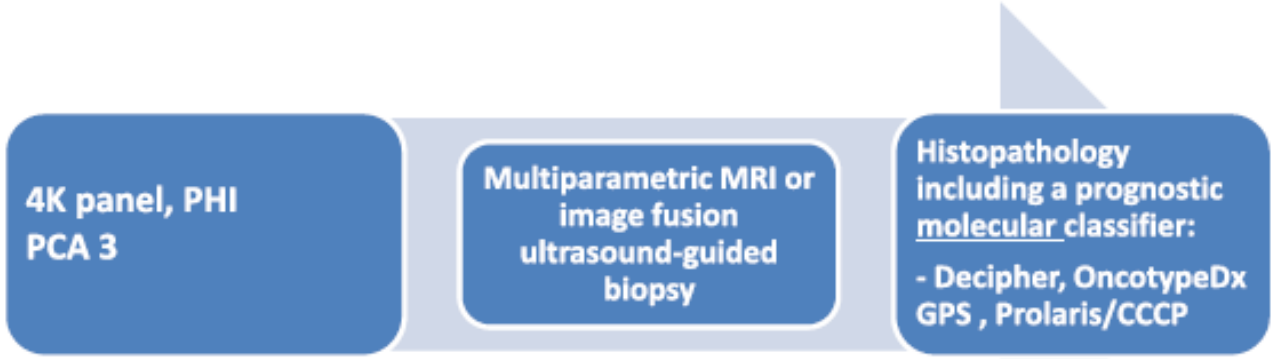
Hayes Df. BMC Medicine 2013, 11:221
Yu PP, et al. Arch Pathol Lab Med, 2015; 139:451-6
Schott AF, et al. Cancer Res; 75(10) May 15, 2015

Prostate cancer;
Early diagnosis and prognosis

- ‘Classic’ tools



- Molecular classifiers 2015



Sedelaar and Schalken BMC Medicine (2015) 13:109