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oncotype DX®
AR-V7 Nucleus Detect™
powered by EPIC SCIENCES

The Role of AR-V7 in the Management of Metastatic Castration-Resistant Prostate Cancer

Deborah Davison, DNP

Associate Director, US Medical Affairs

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oncotype IQ®
Genomic Intelligence Platform

Genomic Health®
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Important milestones in the treatment of prostate cancer

- 1941: Use of androgen deprivation therapy
- 1947: First radical prostatectomy for the treatment of prostate cancer
- 2004: Docetaxel approved for treatment of metastatic prostate cancer
- 2010: Provenge (immunotherapy) approved by FDA
- The targeted therapy era (ARSi):
  - 4/2011: Initial approval of abiraterone (ZYTIGA®)
  - 8/2012: Enzalutamide approved (XTANDI®)
  - 2/2018: Apalutamide approved (Erlead™)

How do these targeted therapies work? And what is AR-V7??

- Prostate cells (and most tumor cells) need androgen to grow and function.
- *Androgen Receptor Signaling Inhibitors* (ARSis) work either by targeting and inhibiting the androgen binding receptors in tumor cells or by preventing creation of androgen.
- **These drugs slow tumor growth.**

- AR-V7 is a variant of the normal androgen receptor and can allow prostate tumor cells to remain active and growing even *without* androgen.
    - It seems to develop as a resistance mechanism when men are exposed to ARSi therapy.

Why is it important to know AR-V7 status and who should be tested?

- The presence or AR-V7 in the nucleus of circulating tumor cells can tell us about prognosis and predict which treatment is better – ARSi or chemotherapy.
  - AR-V7 is measured in a blood sample.

- *Who should be tested?*

  1. Men with metastatic castration-resistant prostate cancer
  2. Men who have taken an ARSi in the past
  3. Men who are trying to determine their next treatment (chemotherapy or another ARSi)

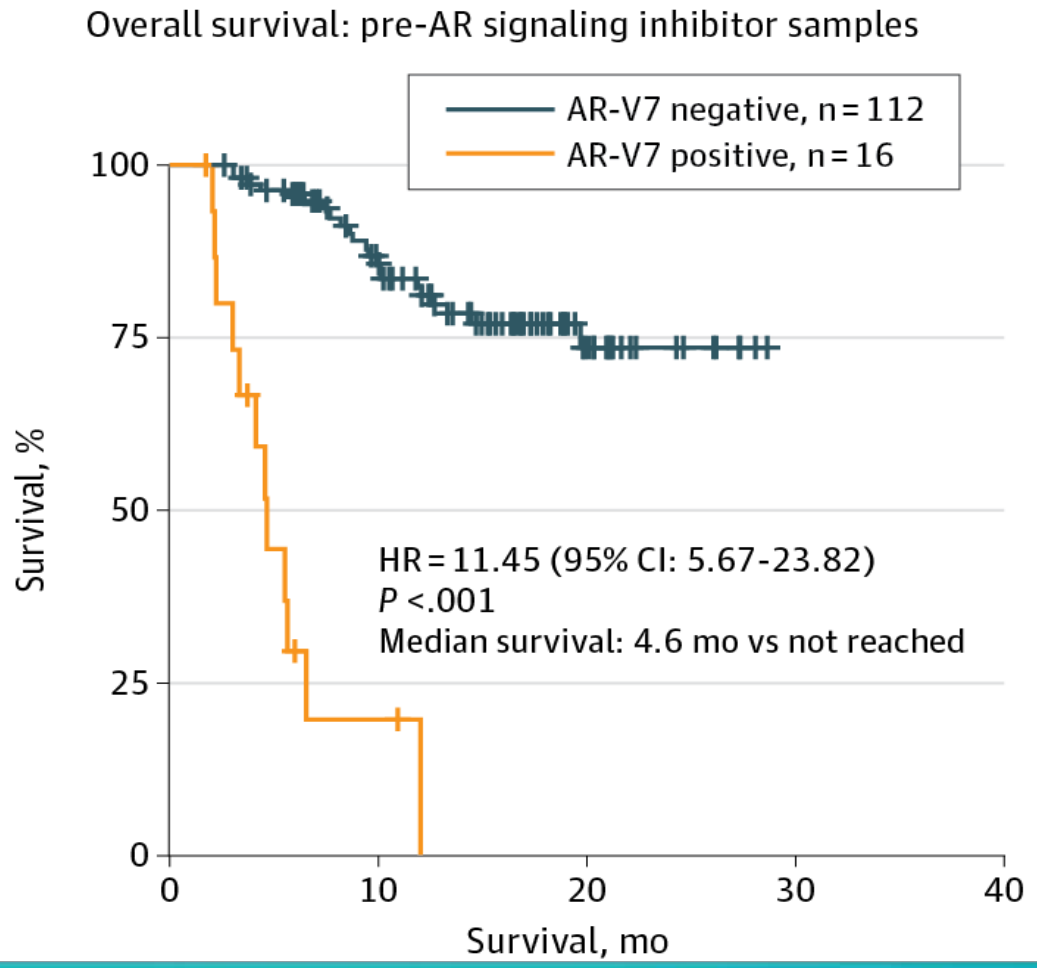
Why is it important to have taken an ARSi in the past?

Line of Treatment in mCRPC setting	First (n=67)	Second (n=50)	Third or greater (n=74)
Samples with AR-V7-positive CTCs n (%)	2 (3%)	9 (18%)	23 (31%)

AR-V7−androgen receptor splice variant 7; CTC−circulating tumor cells

Scher HI et al. JAMA Oncol. 2016;2(11):1441-1449.

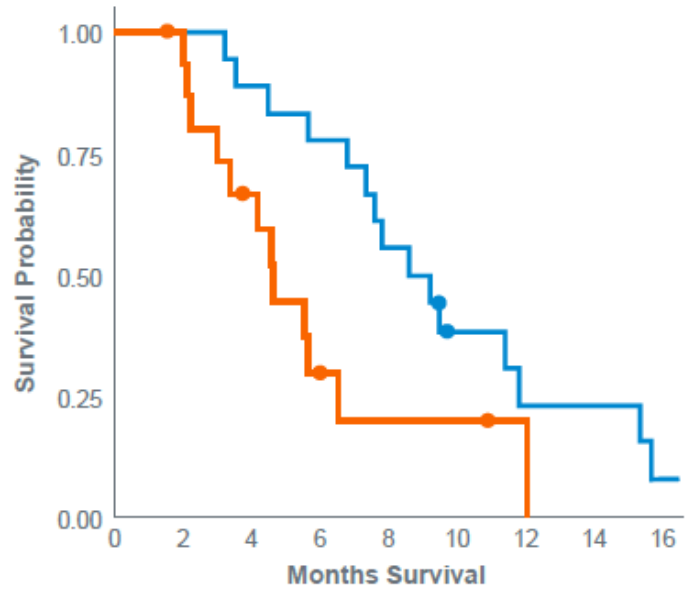
Men with AR-V7 nuclear-positive disease do worse on ARSi therapy…



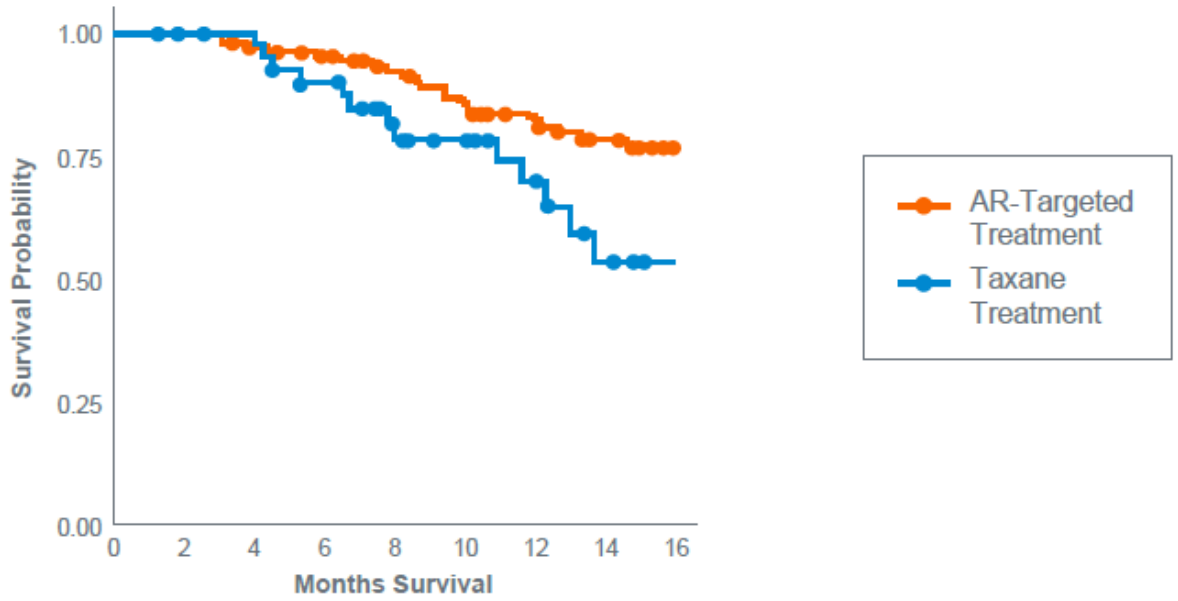
Scher et al, JAMA Oncology, November 2016

…but do better with chemotherapy

AR-V7 Positive Patients Do Better with Taxane Treatment



AR-V7 Negative Patients Do Better with AR-Targeted Treatment



EPIC SCIENCES™

JAMA Oncology

Memorial Sloan Kettering Cancer Center

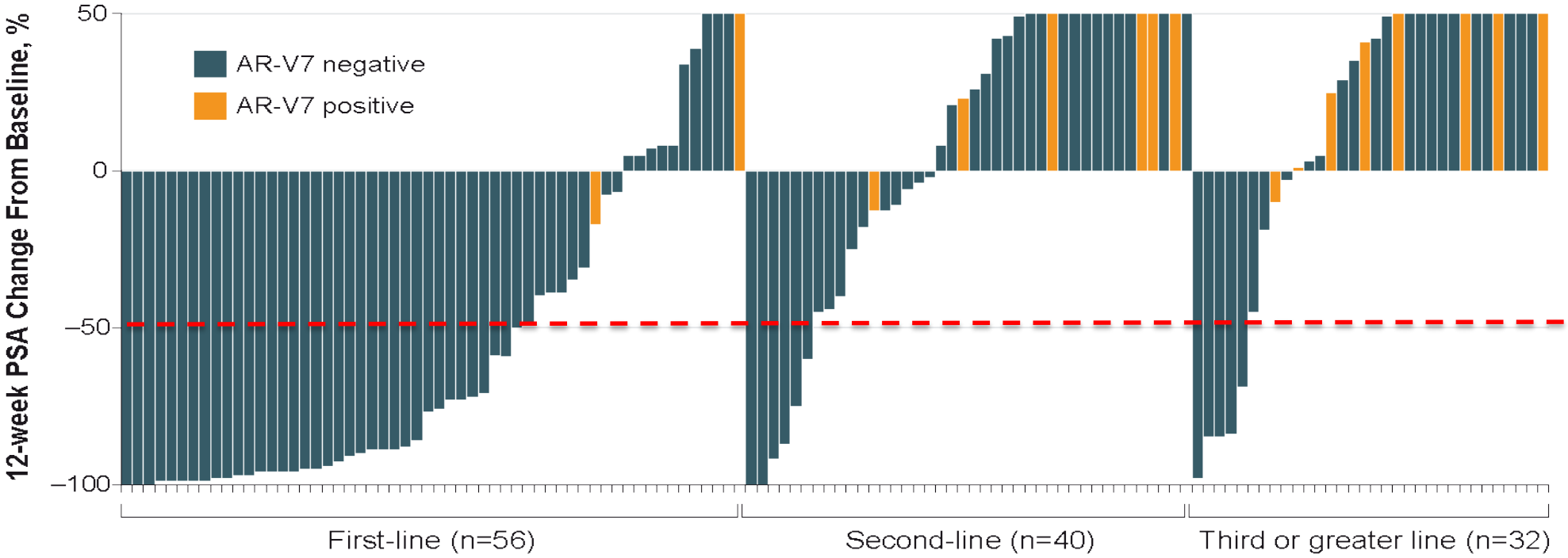
Scher et al, JAMA Oncology, November 2016

Genomic Intelligence Platform

LIFE, CHANGING.

Men with AR-V7 nuclear-positive disease do not respond to ARSi therapy

Patients Who Received AR-targeted Therapies



AR−androgen receptor; AR-V7−androgen receptor splice variant 7; PSA−prostate-specific antigen

Scher HI et al. JAMA Oncol. 2016;2(11):1441-1449.

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What should we remember?

- ARSi drugs have made a great impact on survival and quality of life for men with metastatic castration-resistant prostate cancer.
- If an ARSi seems to be losing its beneficial effect, another therapy may be required to maintain control of disease.
  - This could be another ARSi or chemotherapy.
- Knowing the nuclear AR-V7 status at this point is important to determine the best course of therapy and prolong survival.
- ZERO patients with nuclear AR-V7-positive disease respond to ARSi therapy but may get significant benefit from chemotherapy.

Patient Report

AR-V7 Nucleus Detect Report

oncotype DX® AR-V7 Nucleus Detect™ powered by EPIC SCIENCES

[LAST NAME], [FIRST NAME] [INITIAL]
Date Of Birth: **01-Jan-1950** Gender: **Male** Report Number: **OR000123456** Report Date: **23-Oct-2016**
Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

Medical Record/Patient #: **1234567-01**
Specimen Source/ID: **Blood/SP-16_0123456**
Date of Collection: **20-Jun-2016**
Additional Recipient: **Dr. Additional**
Client: **XXXX**
Study #: **XXXX**
Specimen Received: **23-Jun-2016**

Results

Nuclear AR-V7
Positive +

Positive: One or more nuclear localized AR-V7 positive CTCs identified

Additional Comments
None

Clinical Interpretation
In large clinical studies, patients with a positive test result were[1]:
- Not likely to respond to or benefit from abiraterone or enzalutamide
- Substantially more likely to live longer when treated with a taxane chemotherapy.

Intended Use
The AR-V7 Nucleus Detect test is intended for use in patients with metastatic castration-resistant prostate cancer (mCRPC) who are considering androgen receptor signaling inhibitors (eg, abiraterone, enzalutamide). The test identifies the presence of AR-V7 protein in the nucleus of circulating tumor cells (CTCs) in blood samples from mCRPC patients to inform clinical decision-making.

AR-V7 Nucleus Detect Report

oncotype DX® AR-V7 Nucleus Detect™ powered by EPIC SCIENCES

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Additional Recipient: **Dr. Additional**
Client: **XXXX**
Study #: **XXXX**
Specimen Received: **23-Jun-2016**

Results

Nuclear AR-V7
Negative −

Negative: No nuclear localized AR-V7 positive CTCs identified

Additional Comments
None

Clinical Interpretation
In large clinical studies, patients with a negative test result[1]:
- May have clinical response to and benefit from abiraterone or enzalutamide regardless of prior line(s) of therapy.

Intended Use
The AR-V7 Nucleus Detect test is intended for use in patients with metastatic castration-resistant prostate cancer (mCRPC) who are considering androgen receptor signaling inhibitors (eg, abiraterone, enzalutamide). The test identifies the presence of AR-V7 protein in the nucleus of circulating tumor cells (CTCs) in blood samples from mCRPC patients to inform clinical decision-making.

Why Nuclear AR-V7

Ryan Dittamore

Chief of Medical Innovation

Epic Sciences, Inc.

Epic Sciences

Who is Epic Sciences? Where is my blood sample going?

Goal: To make *predictive*, *personalized* and *precise* tests designed around *clinical decisions* to improve patient survival.

- San Diego, CA
- 40,000 sq ft facility
- CAP accredited /CLIA registered lab

The Scripps Research Institute

2008 founded

75 employees

Partnerships

- Academic: 35
- Biopharma: 48
- Commercial: Genomic Health LIFE. CHANGING.
- Consortium: BloodPAC BLOOD PROFILING ATLAS IN CANCER

Clinical Research

- 175+ clinical trials
- 35,000+ patient blood samples

It started with the question?

In 2012, I visited Dr. Howard Scher at MSKCC in NY.

Dr. Scher posed a question to me:

Can we develop a blood test that can help guide therapy decisions between AR signaling therapies (Abiraterone & Enzalutamide) vs. taxane chemotherapy?

Why is this question important?

Prior therapy history, therapy response didn't predict which drug would work best. In short, there was no way for him to predict which drug to give a patient

Our Goal:

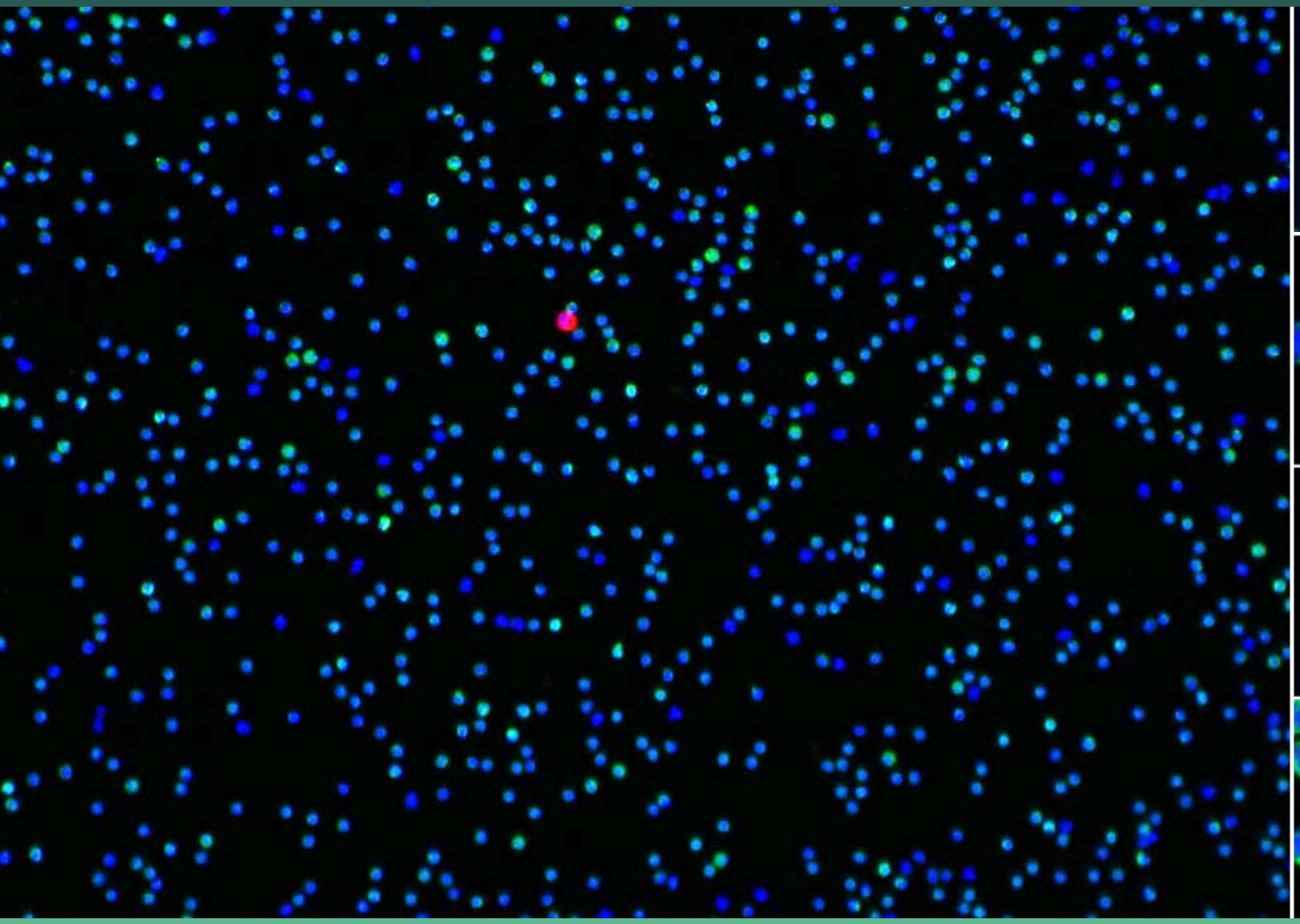
Could a single, simple tube of blood **and Epic's technology**

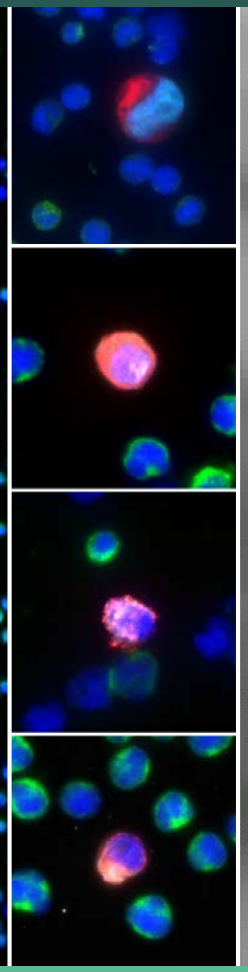
inform treatment decisions and

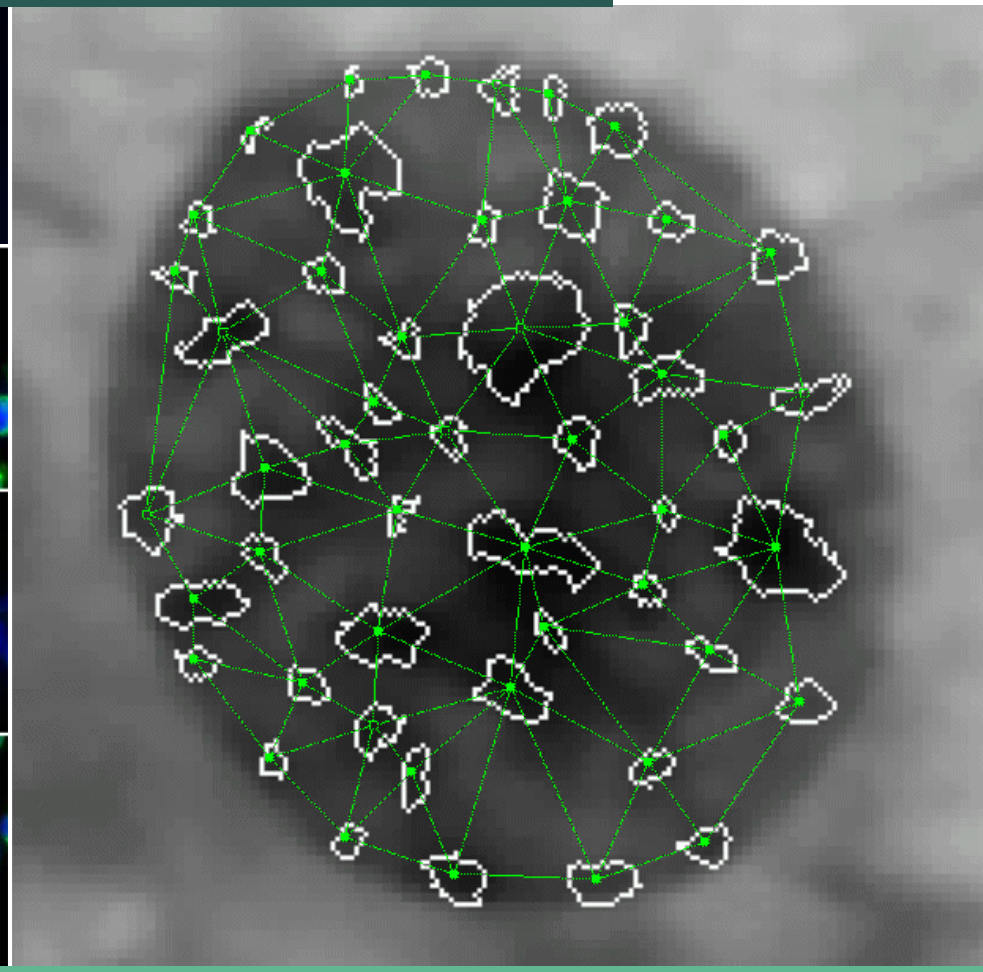
extend **lives**

As good as Abiraterone or Enzalutamide?

Query the cell – find 1 in 50 million with deep, advanced analysis



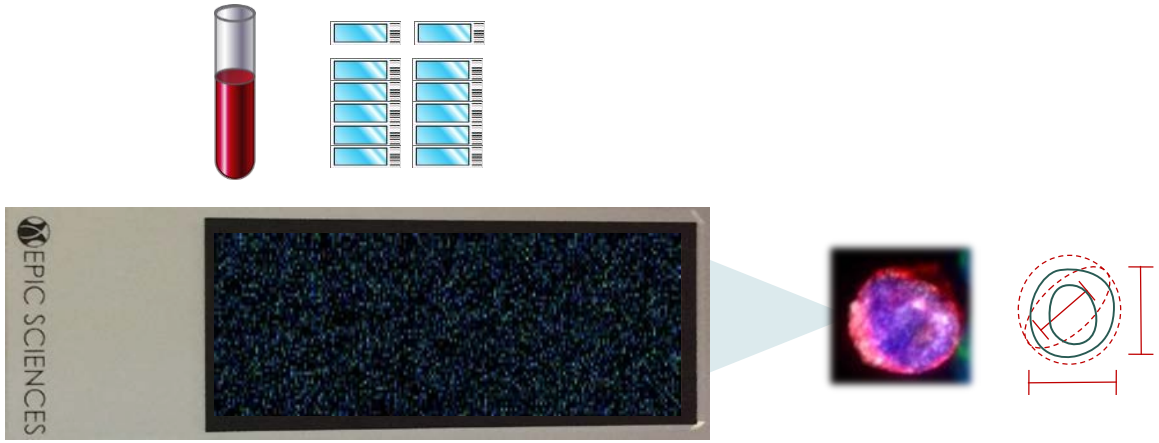




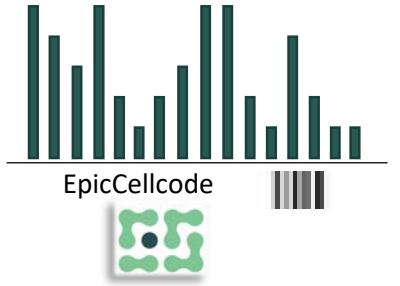
Epic's *no cell left behind*™ technology was founded with computer vision and machine learning.
We look at ***6 million cells*** per patient to find rare circulating tumor cells

Disruptive platform for finding patterns of cells that matter

Tagging proteins in cells with fluorescence to analyze morphology and functional status

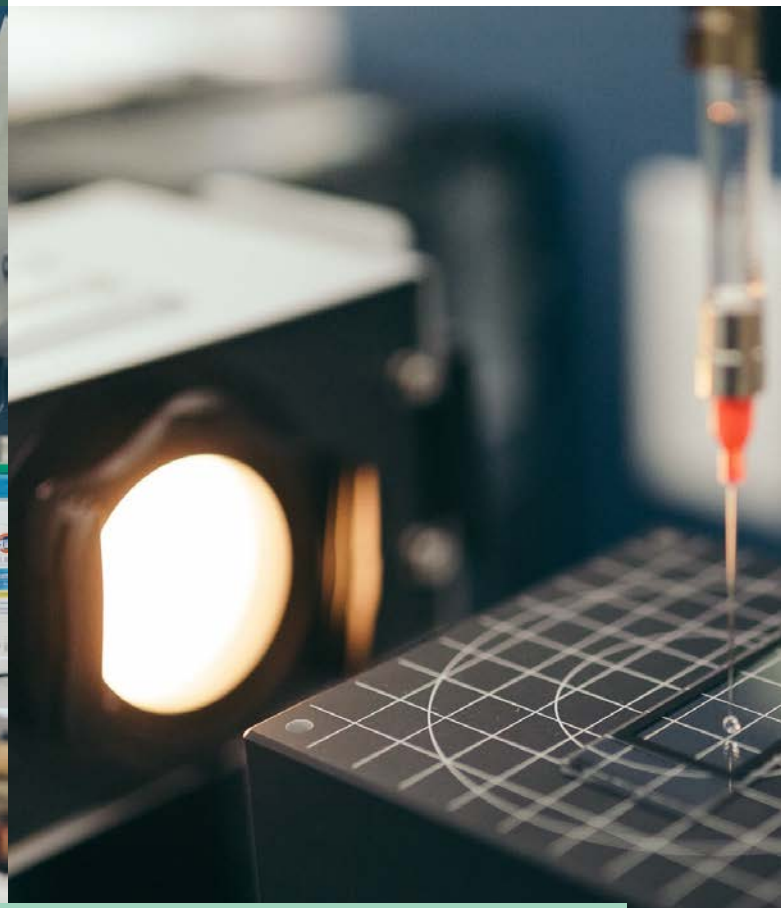


Nuclear size
Nuclear convex area
Nuclear major axis length
Nuclear minor axis length
Nuclear Circularity
Nuclear entropy
Nuclear speckling
CK expression
Cytoplasm area
Cytoplasm convex area
Cytoplasm circularity
⋮
Nuclear/cytoplasm ratio



>12,000 prostate cancer patients samples

Billions of cells analyzed with clinical context

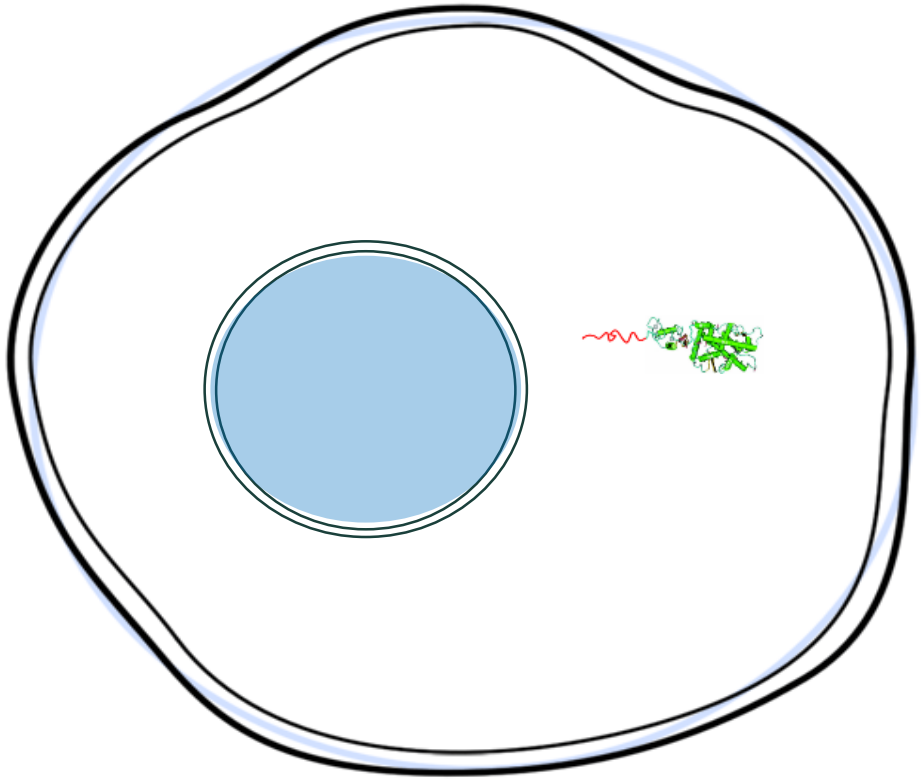


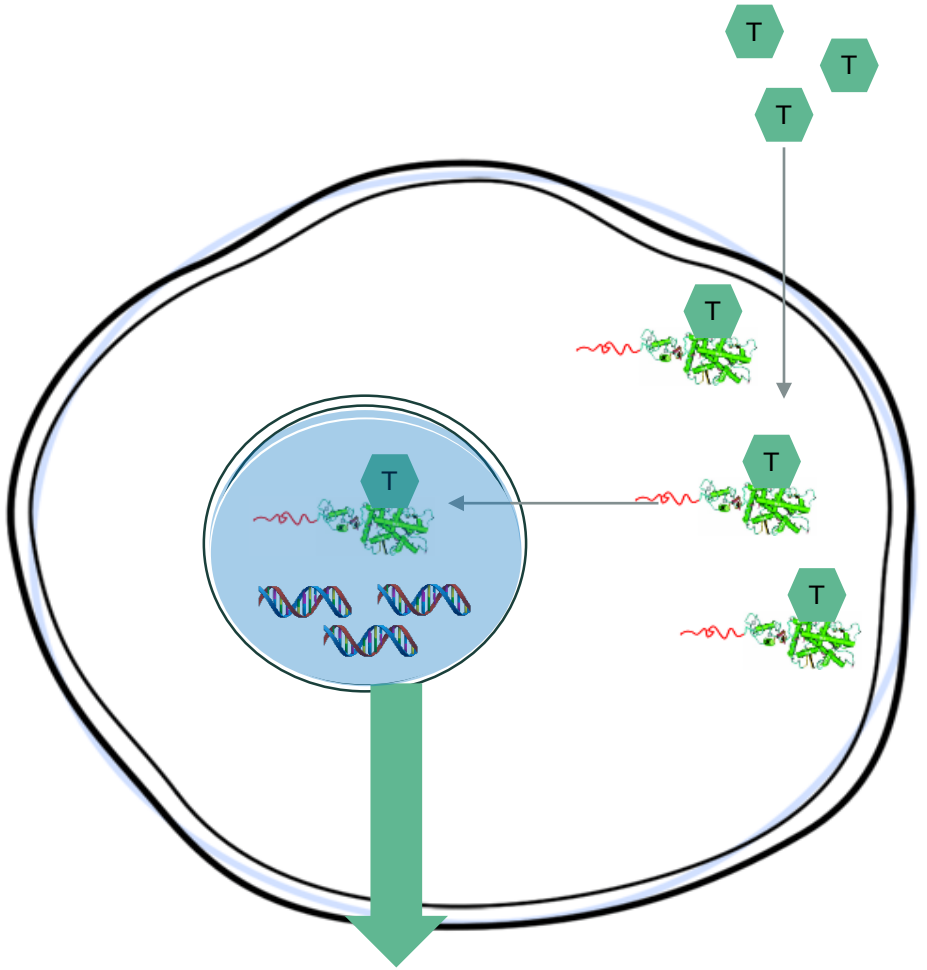
Over the last 6 years we have accumulated the largest biobank of mCRPC patient blood samples. Specifically to ensure we can answer the question

The biology of metastatic prostate cancer drugs – I

Androgen receptor (AR), full length protein

T Testosterone hormone



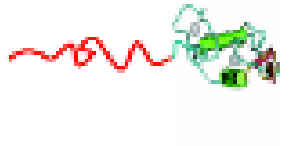


Cancer cell growth

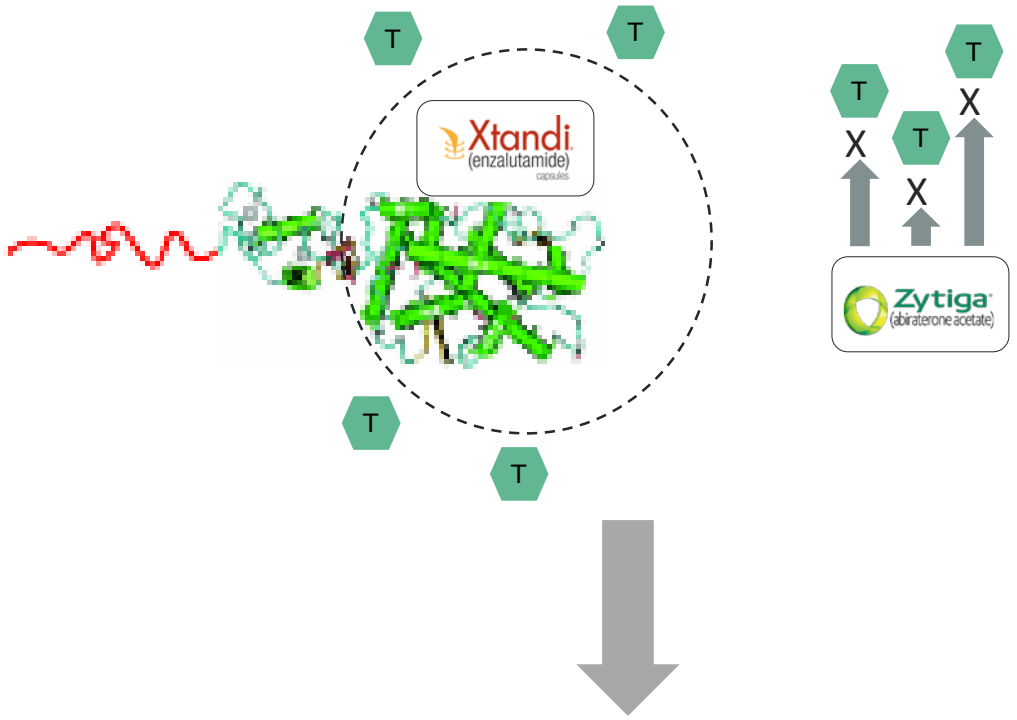
The biology of metastatic prostate cancer drugs – II

Androgen receptor (AR), full length protein

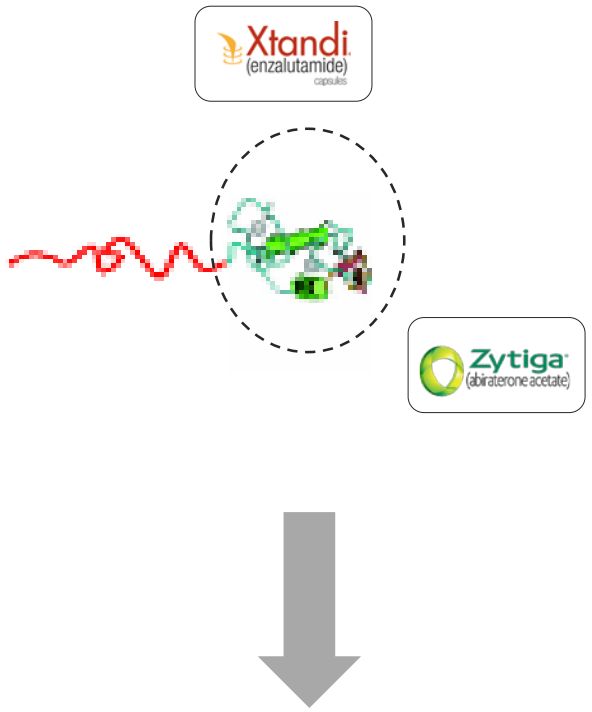
T Testosterone hormone



Truncated androgen receptor protein (AR-V7)

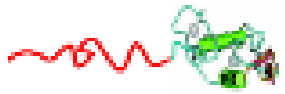


No T binding
AR can't get to the nucleus

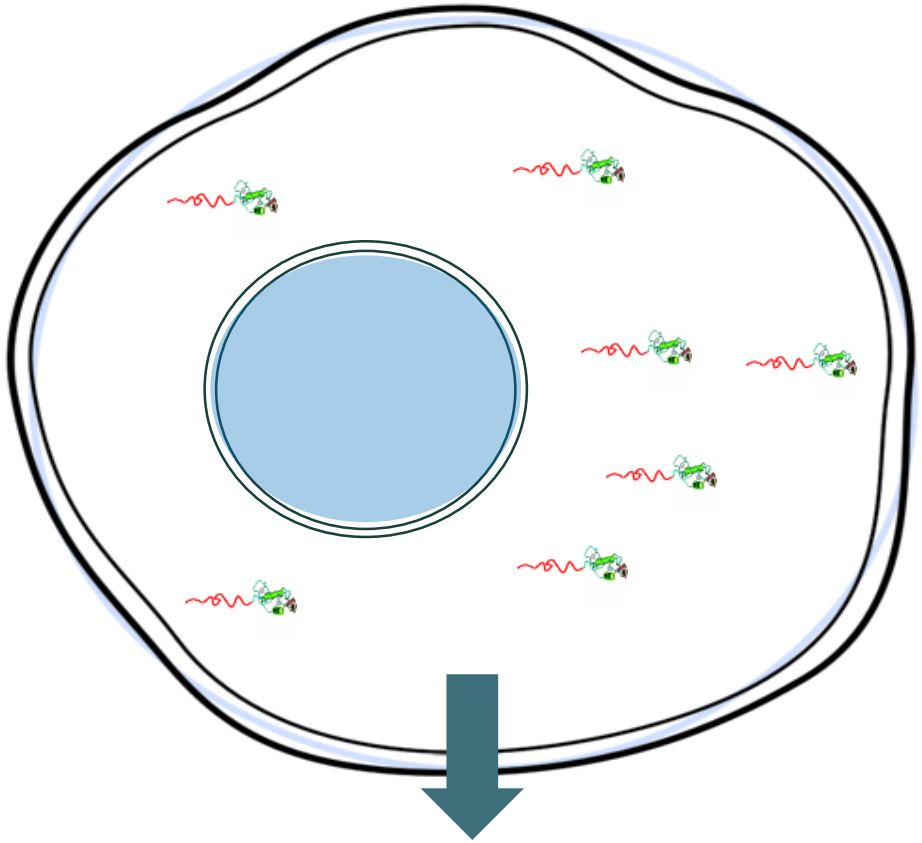


Don't need T binding, drugs can't bind
AR-V7 can go to the nucleus and be active

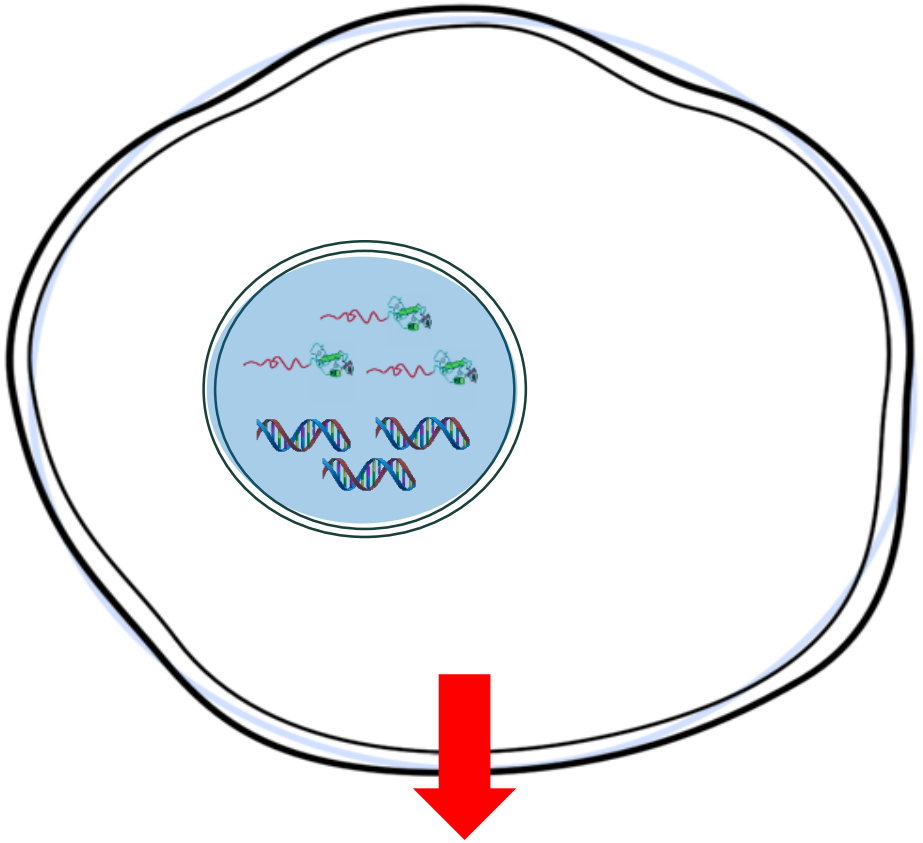
The biology of metastatic prostate cancer drugs – III



Truncated androgen receptor protein (AR-V7)

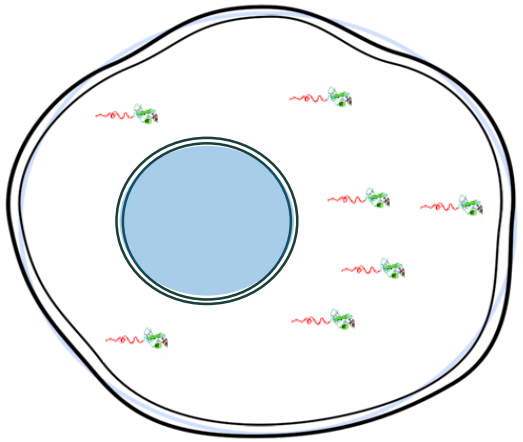


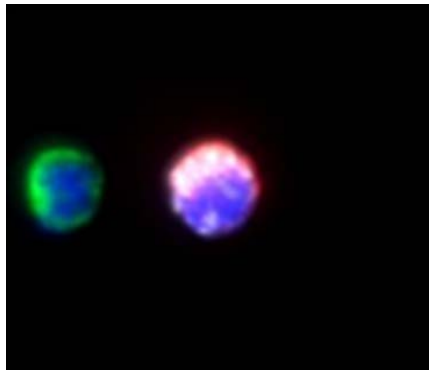
- AR-V7 is in the cytoplasm.
- Functionally ***INACTIVE***.
- No resistance to Enzalutamide (Xtandi) or Abiraterone (Zytiga).



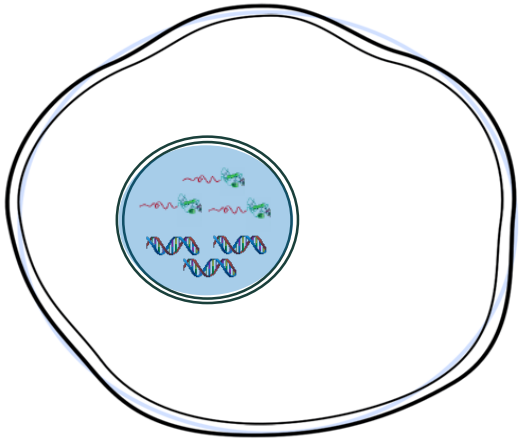
- AR-V7 is in the nucleus.
- Functionally ***ACTIVE***.
- ***RESISTANT*** to Enzalutamide (Xtandi) or Abiraterone (Zytiga).

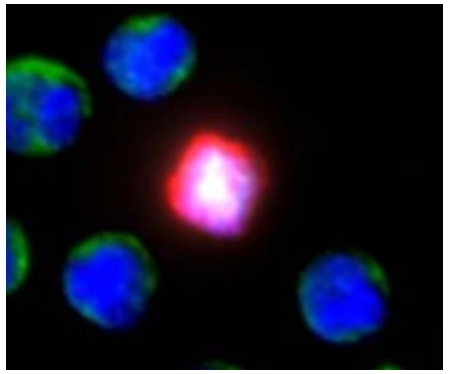
AR-V7 – Nuclear Localization Matters!





= AR-V7 negative; may benefit from another ARSi





= AR-V7 positive; chemotherapy may be the better option

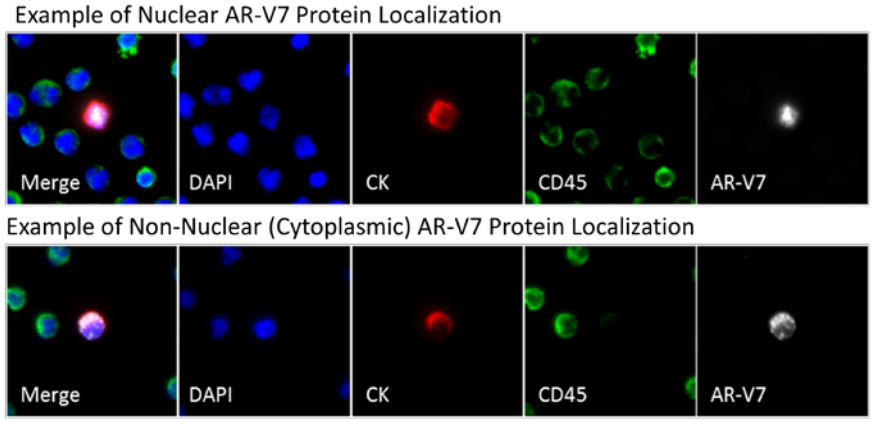
AR-V7 Nucleus Detect Test is superior to AR-V7 mRNA tests

EUROPEAN UROLOGY

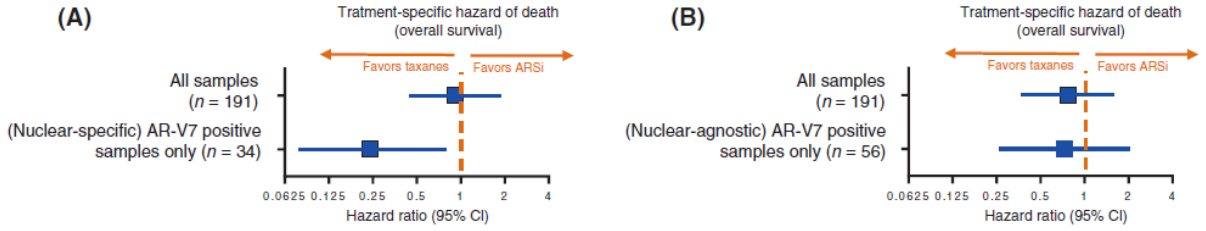
Nuclear-specific AR-V7 Protein Localization is Necessary to Guide Treatment Selection in Metastatic Castration-resistant Prostate Cancer

Howard I. Scher[a,b,], Ryon P. Graf[c], Nicole A. Schreiber[a], Brigit McLaughlin[a], David Lu[c], Jessica Louw[c], Daniel C. Danila[a,b], Lyndsey Dugan[c], Ann Johnson[c], Glenn Heller[d], Martin Fleisher[e], Ryan Dittamore[c]*

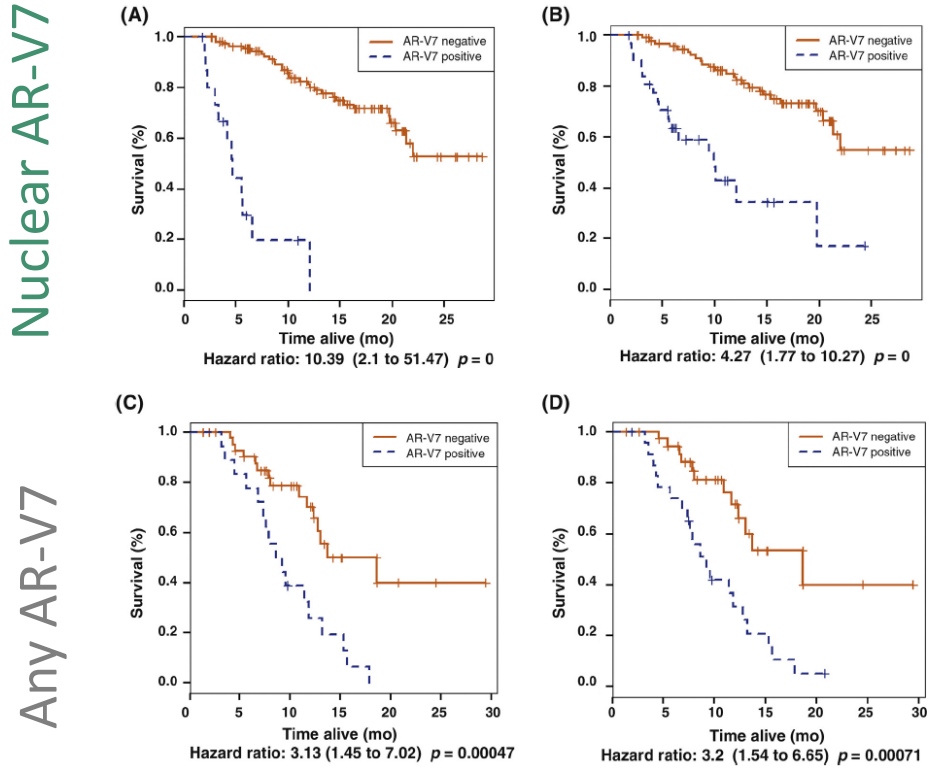
AR-V7 can be nuclear or cytoplasmic



Nuclear AR-V7 is only PREDICTIVE Test



Outcome difference between: Nuclear and Any AR-V7



What about other studies?

2nd Blinded Clinical Utility Validation

- Patients who had already received a systemic therapy (Abiraterone, Enzalutamide, Docetaxel) were received from:
  - MSKCC (New York)
  - ICR (Sutton, UK)
  - LHS (London, Canada)
- Physicians were blinded of nuclear AR-V7 status; Epic Sciences was blinded of patient outcomes
- 84 patients had received Abiraterone or Enzalutamide
- 84 patients had received taxane chemotherapy

Patient Overall Survival was the endpoint!!!

Scher et al. ASCO GU 2018

Nuclear AR-V7 Overall Survival Results

Patient Median Overall Survival:

ARSi= 8.6 months

Taxane= 14.3 months

Patient Median Overall Survival:

ARSi= 22.3 months

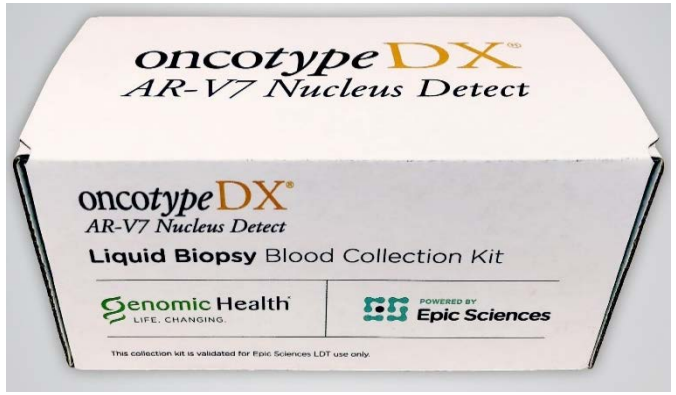
Taxane= 12.9 months

Either results has the ability to add ~
1.7X life expectancy

Scher et al. ASCO GU 2018

Medicare Reimbursement is expected very soon!

Launched February 2018



~4-5 months

Expected Medicare Reimbursement
~ July 2018

Acknowledgements

MSKCC

Howard Scher

Nicole Schreiber

Glenn Heller

Brigit McLaughlin

Richard Bambury

Daniel Danila

Dana Rathkopf

Karen Autio

Herbert Vargas

Lauryn Slavin

Ethan Barnett

Martin Fleischer

Ryan Brennan

ICR

Gerhardt Attard

Anuradha Jayaram

LHS

Alison Allan

Eric Winquist

Lori Lowes

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Acknowledgements

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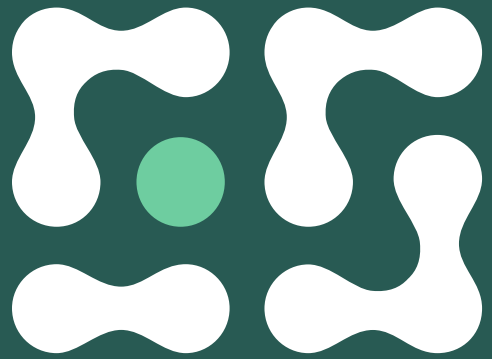

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