

# *Patients, Passions and Pursuits*

AnCan

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University of California, San Francisco

March 2, 2022



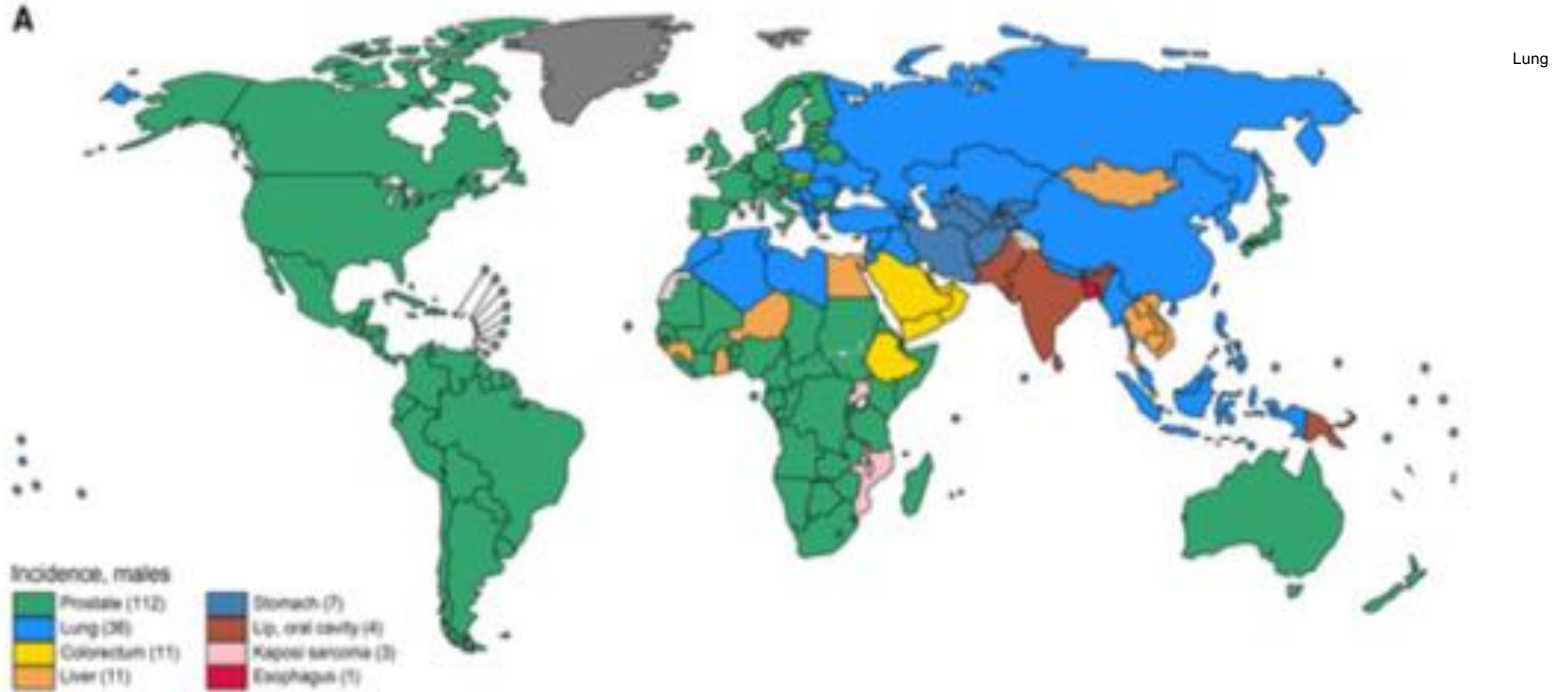
# Henry's story (the view from the oncologist)



- 59 yo male presents for consultation
  - Medical history:
    - Rising PSA, biopsy shows prostate cancer in 7/12 cores, Gleason score 3+4
  - Past medical history:
    - no other medical conditions
  - Family History:
    - Mother alive and well age 81, 3 sisters, no cancers
    - Father died of prostate cancer age 72
    - Brother age 57 with prostate cancer and younger sister with breast cancer age 46



# Frequency of Prostate Cancer.



# Current Approach to Cancer Screening



## **Breast cancer:**

Mammogram every 1 to 2 years starting age 50 up to age 70 (undefined 40-49 and older than 74)

## **Colon Cancer:**

Colonoscopy starting age 45, every 10 years, sooner as indicated

## **Prostate cancer:**

**PSA testing and digital rectal exam: > 50 years, younger if high risk or family history, BRCA mutations**

## **Lung cancer:**

consider computer tomography in smokers

## **Cervical Cancer:**

PAP smear, HPV testing, HPV vaccine

# Prostate Cancer: Major Risk Factors

Age

Race

Family history



Genetic mutations

Diet

Hormones

Table 1. Relative Risk (RR) Related to Family History of Prostate Cancer<sup>a</sup>

Risk Group	RR for Prostate Cancer (95% CI)
Brother(s) with prostate cancer diagnosed at any age	3.14 (2.37–4.15)
Father with prostate cancer diagnosed at any age	2.35 (2.02–2.72)
One affected FDR diagnosed at any age	2.48 (2.25–2.74)
Affected FDRs diagnosed <65 y	2.87 (2.21–3.74)
Affected FDRs diagnosed ≥65 y	1.92 (1.49–2.47)
<u>Second-degree relatives</u> diagnosed at any age	2.52 (0.99–6.46)
Two or more affected FDRs diagnosed at any age	4.39 (2.61–7.39)

CI = confidence interval; FDR = first-degree relative.

<sup>a</sup>Adapted from Kiciński et al.[24]

# Prostate Cancer: Major Risk Factors

Age

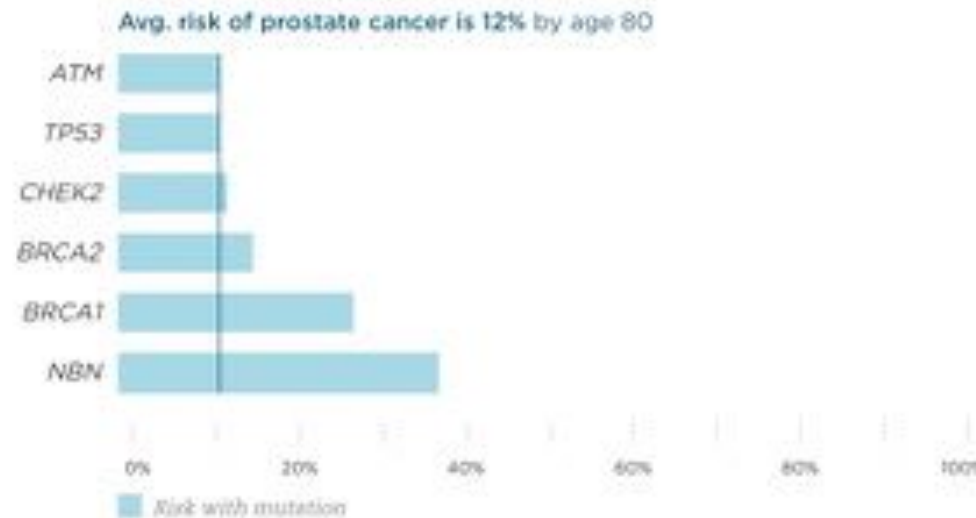
Race

Family history

/Genetic mutations 

Diet

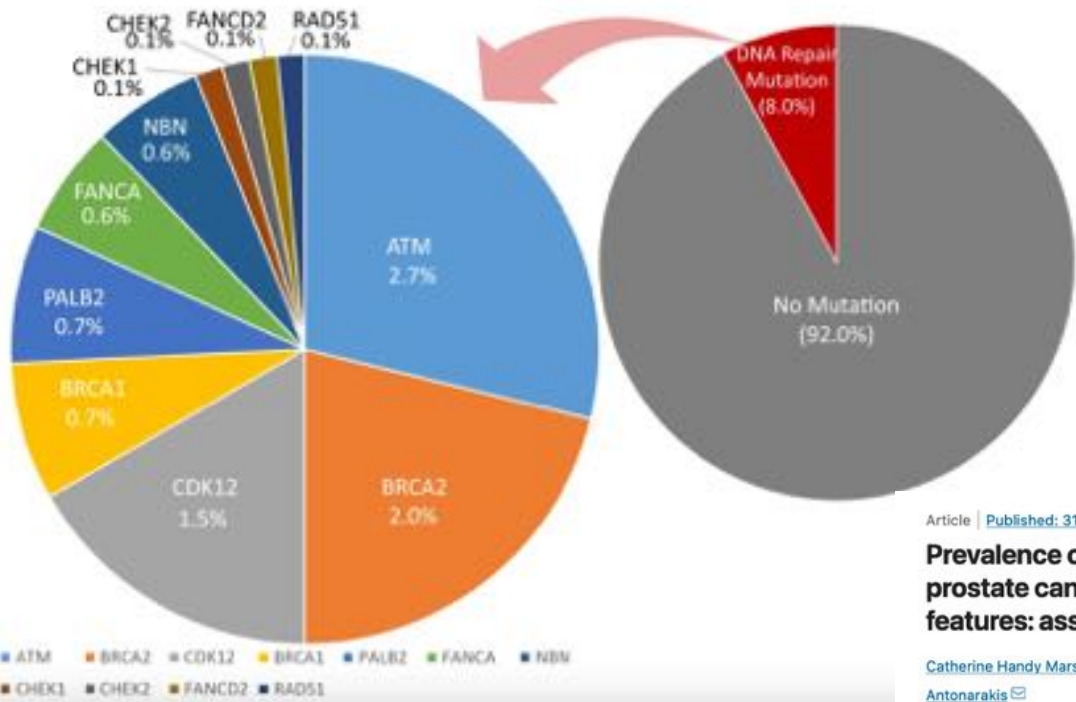
Hormones



# Major Mutations in localized prostate cancer

Fig. 1

From: Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage



Article | Published: 31 August 2018

## Prevalence of DNA repair gene mutations in localized prostate cancer according to clinical and pathologic features: association of Gleason score and tumor stage

Catherine Handy Marshall, Wei Fu, Hao Wang, Alexander S. Baras, Tamara L. Lotan & Emmanuel S. Antonarakis

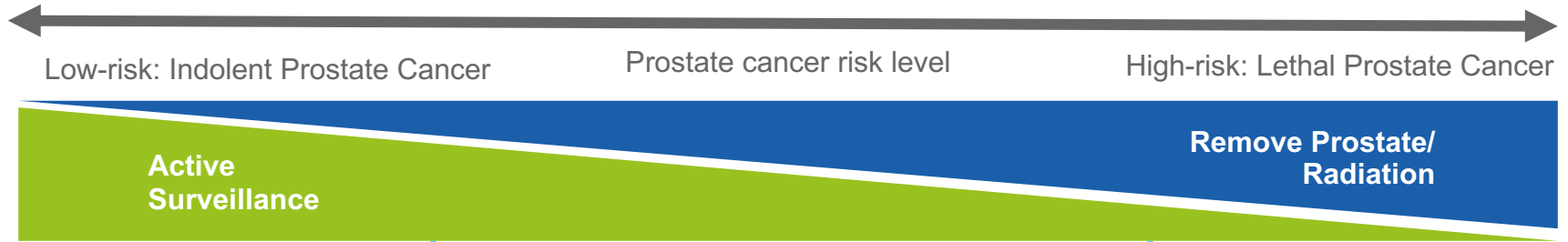




Families at risk

“Living with the Thought of  
Cancer.”

# Current options for localized prostate cancer therapy



## No treatment

- Includes Q 12 months PSA tests, DREs, biopsies, MRI
- Risk of cancer progression
- Psychological stress
- Increased chance of metastatic disease

## Localized strategies

Focal therapy  
US, Lase, Cryotherapy

## Complex treatment

- Procedural side effects
- Infection/inflammation
- Impotence
- Incontinence

# Swedish study

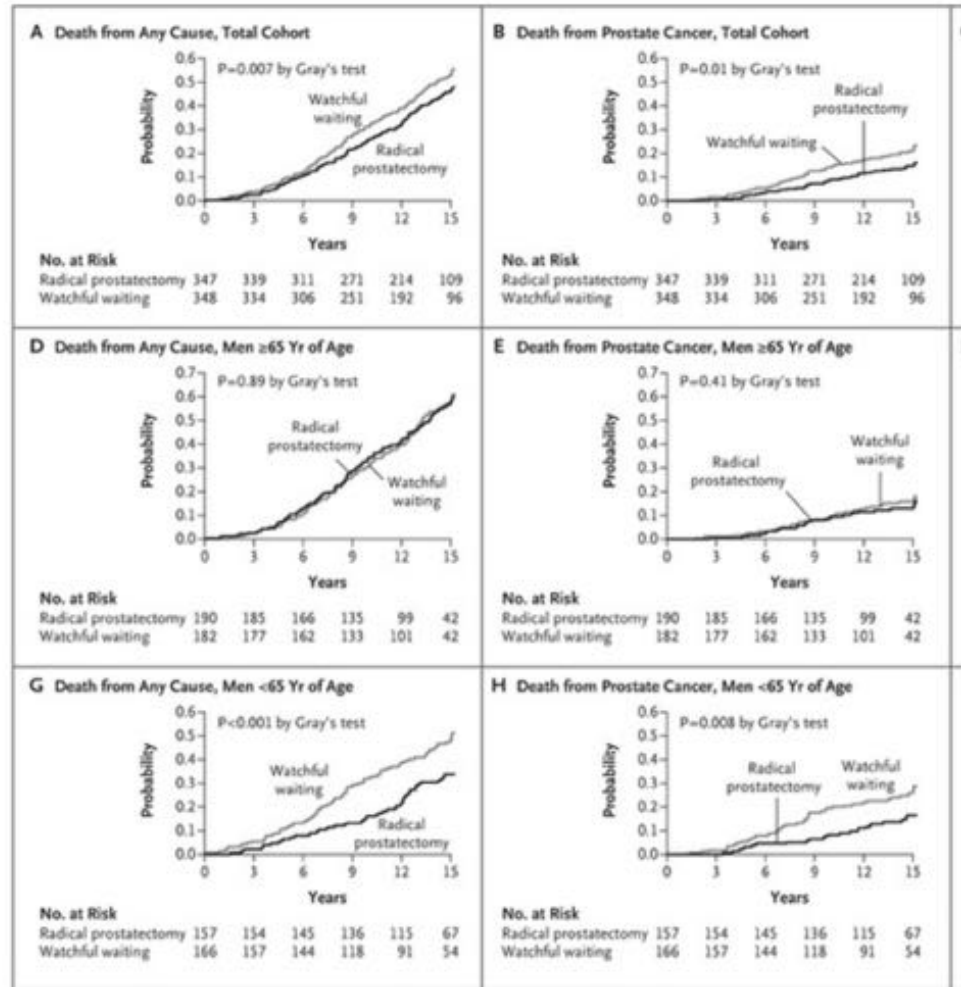
## Radical Prostatectomy or Watchful Waiting

in Prostate Cancer — 29-Year Follow-up  
 Anna Bill-Axelsson, NEJM 2018

Table 2. Cause of Death According to Treatment Group and Age at Diagnosis.

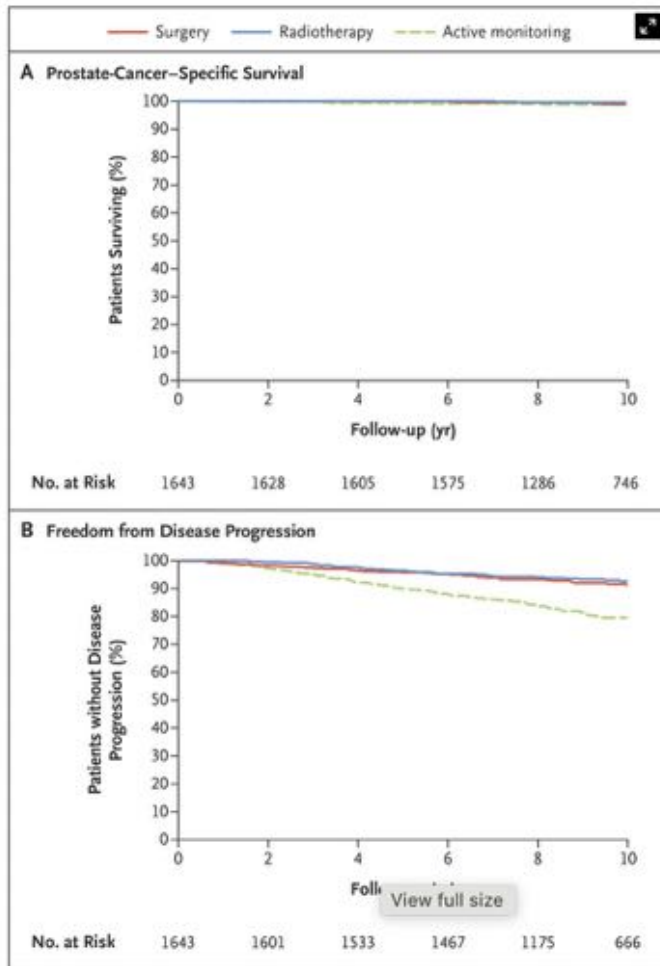
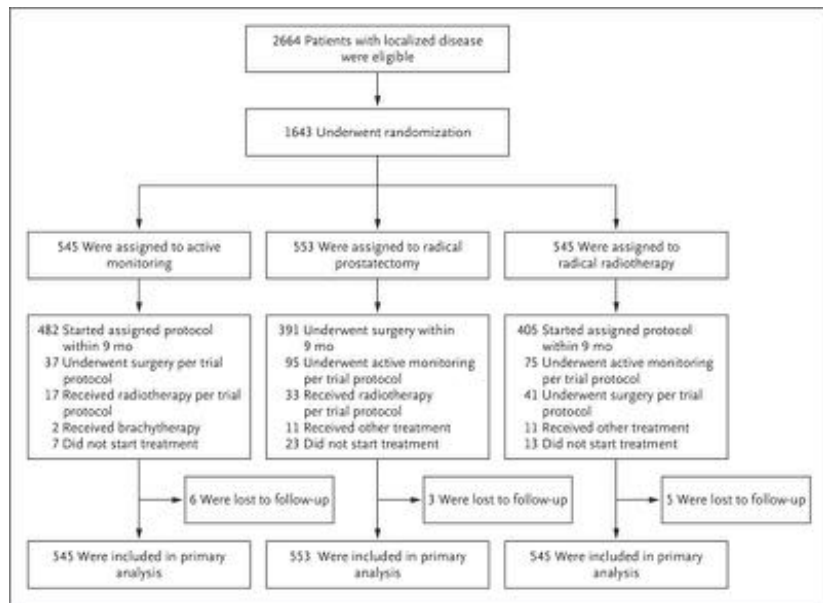
Cause of Death	Radical Prostatectomy (N=347)			Watchful Waiting (N=348)		
	All Men	<65 Yr of Age	≥65 Yr of Age	All Men	<65 Yr of Age	≥65 Yr of Age
	number					
Prostate cancer	55	28	27	81	49	32
Other cause	111	27	84	120	42	78
With metastases	6	2	4	16	5	11
Without metastases but with local progression or recurrence	12	2	10	26	8	18
With unknown status regarding metastases but with local progression	3	0	3	8	4	4
With no evidence of metastases or local progression or recurrence	89	23	66	69	24	45
Within first month after randomization	1	0	1	1	1	0
Any cause	166	55	111	201	91	110

\* All events were evaluated by the independent end-point c. [View full size](#)



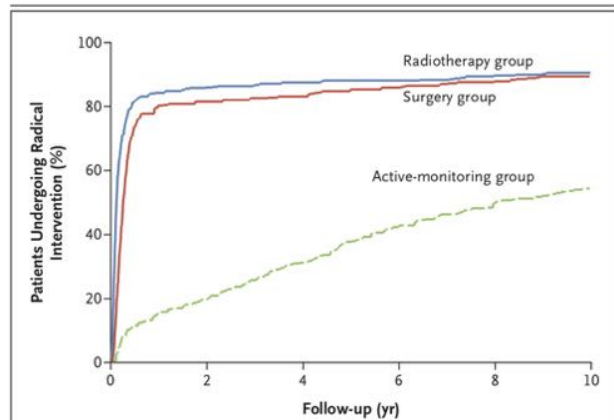
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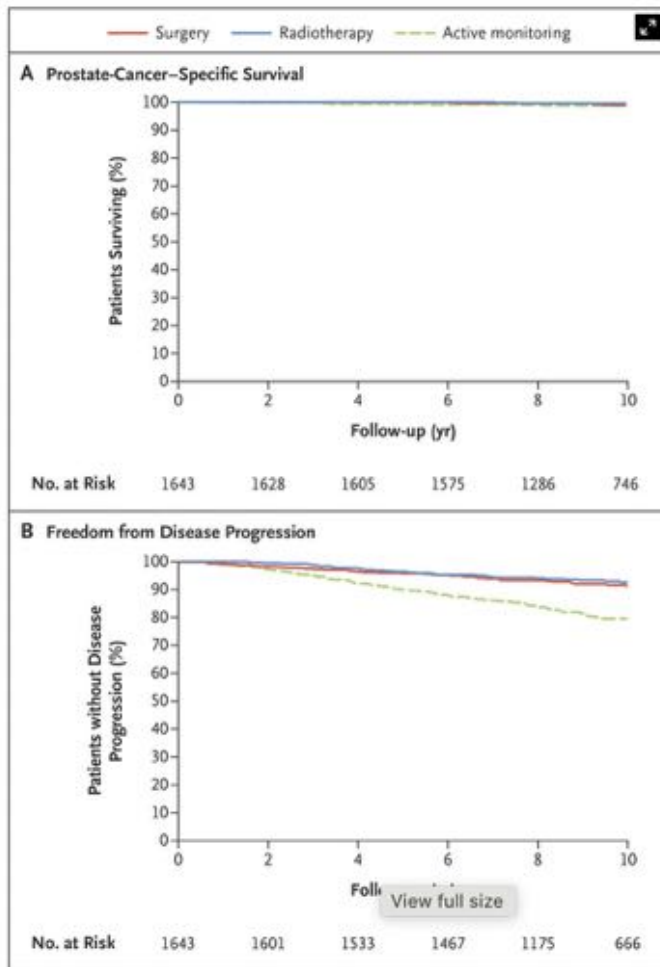
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**Figure 2.** Kaplan–Meier Estimates of the Cumulative Probability of Undergoing Radical Intervention during the Follow-up Period, According to Treatment Group.

Radical intervention was defined as radical prostatectomy, per-protocol radiotherapy, nonprotocol radiotherapy (including brachytherapy), or high-intensity focused ultrasound therapy.

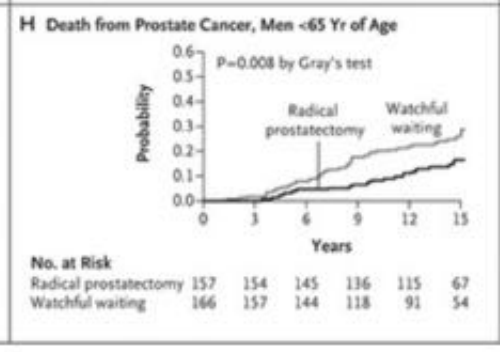
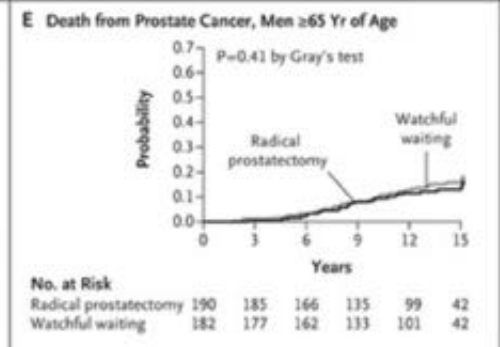
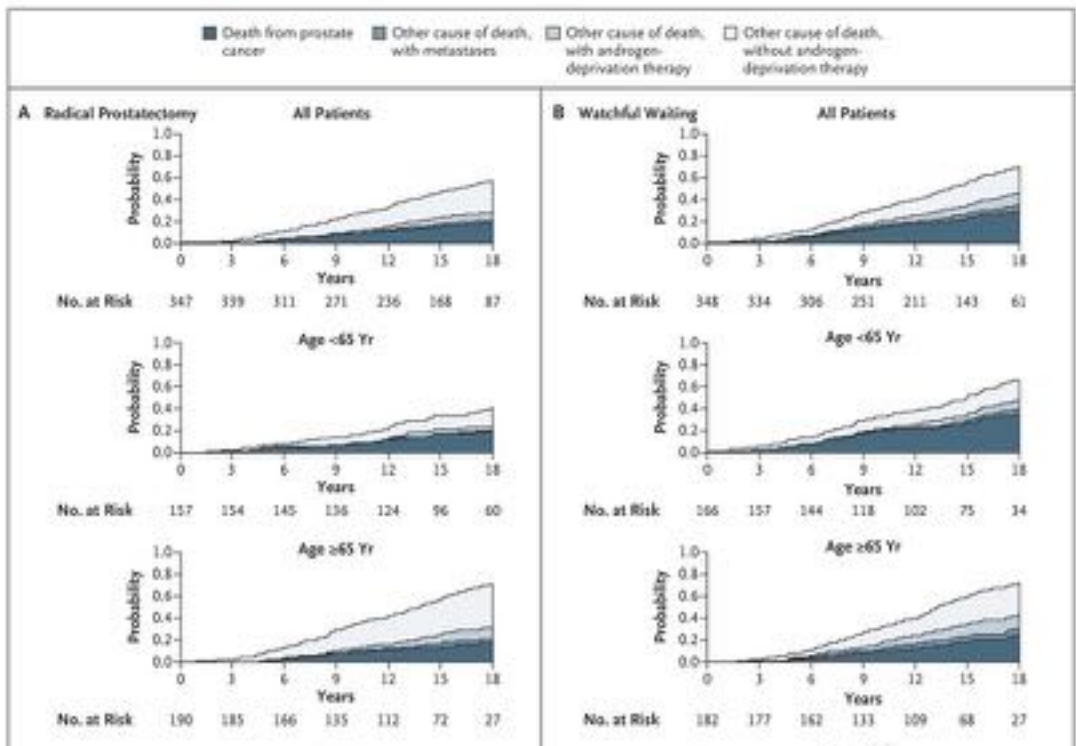
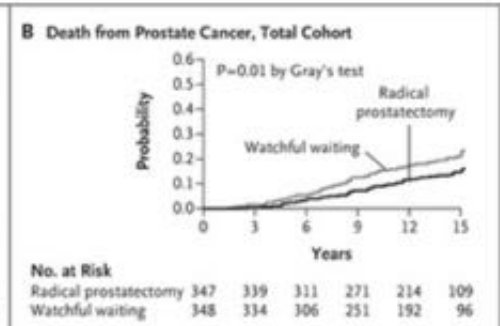
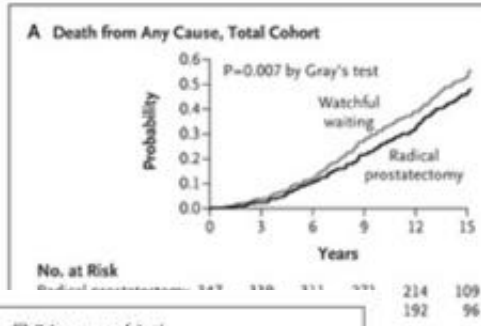


# Swedish study

ORIGINAL ARTICLE

## Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

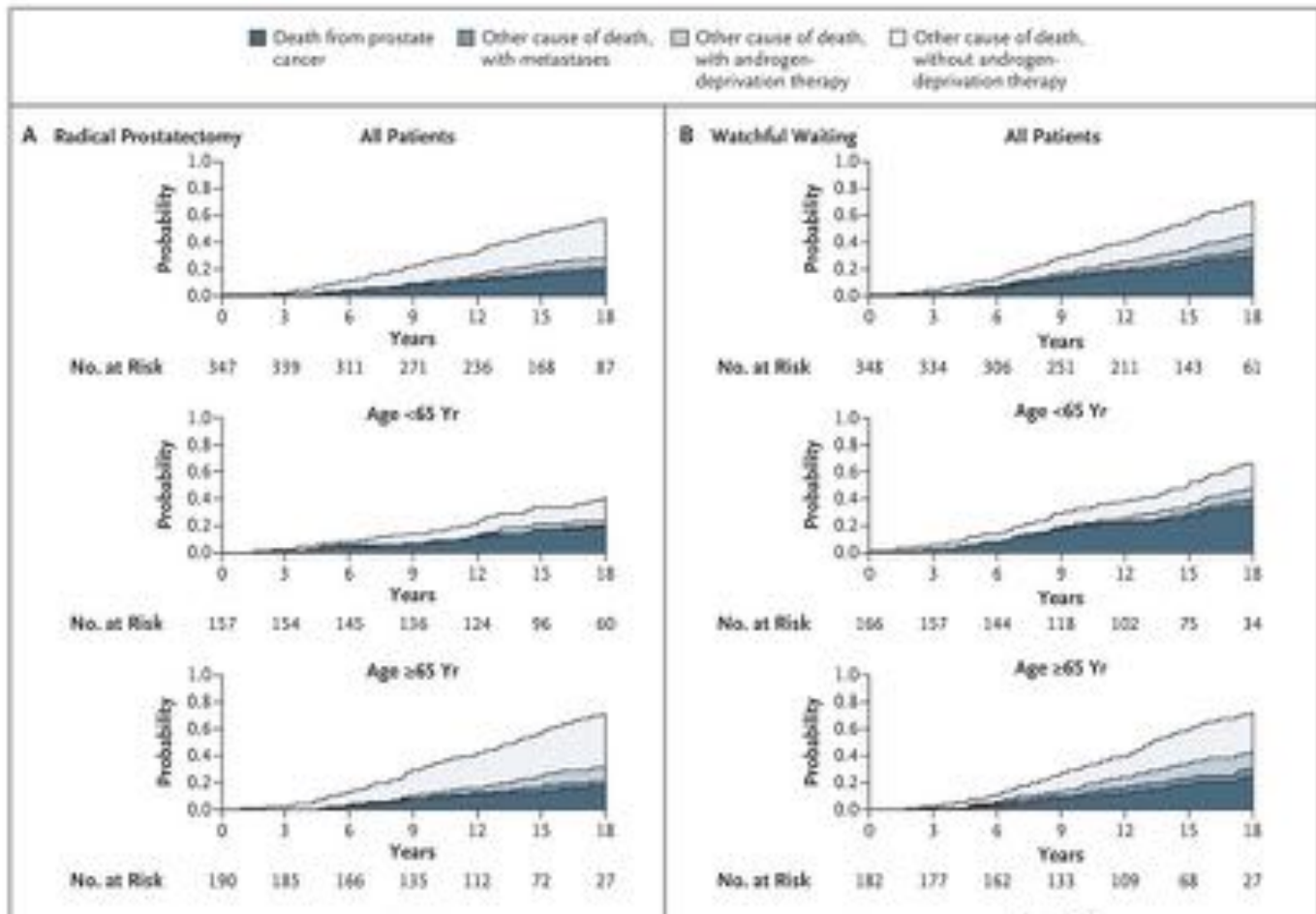
Anna Bill-Axelsson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Carro, Ph.D., Jennifer R. Rider, Sc.D., Kimmo Taari, M.D., Ph.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Ove Andrén, M.D., Ph.D., Juni Palmgren, Ph.D., et al.



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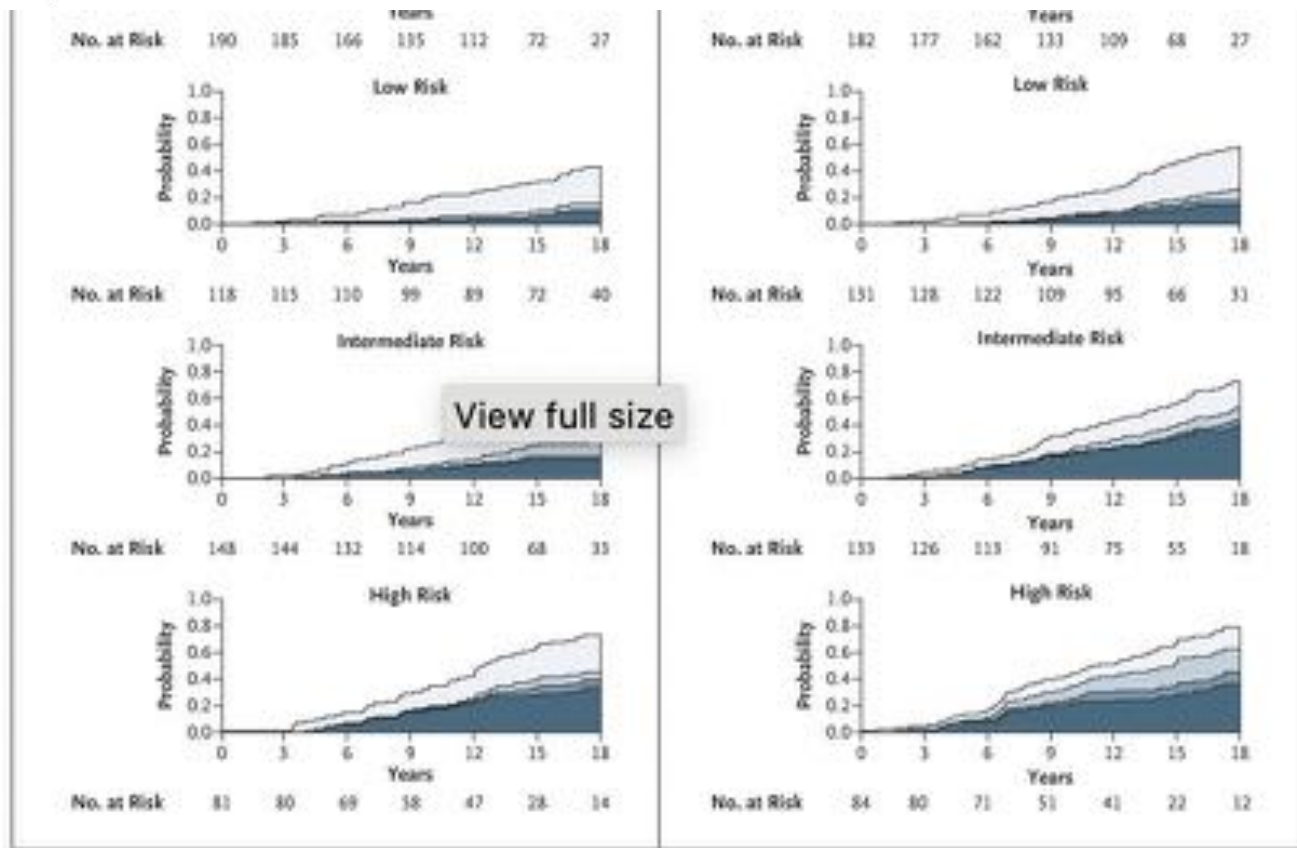
## Risk by age



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## Risk by grade

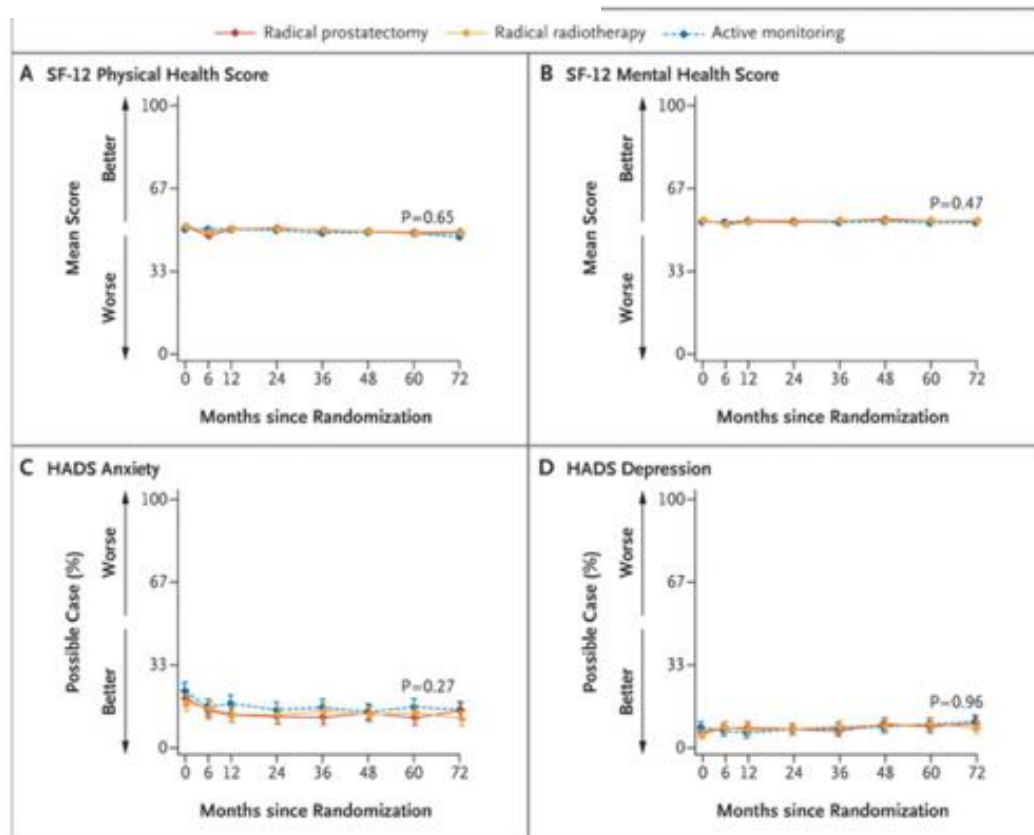


Death from prostate cancer
  Other cause of death, with metastases
  Other cause of death, with androgen-deprivation therapy
  Other cause of death, without androgen-deprivation therapy



# Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

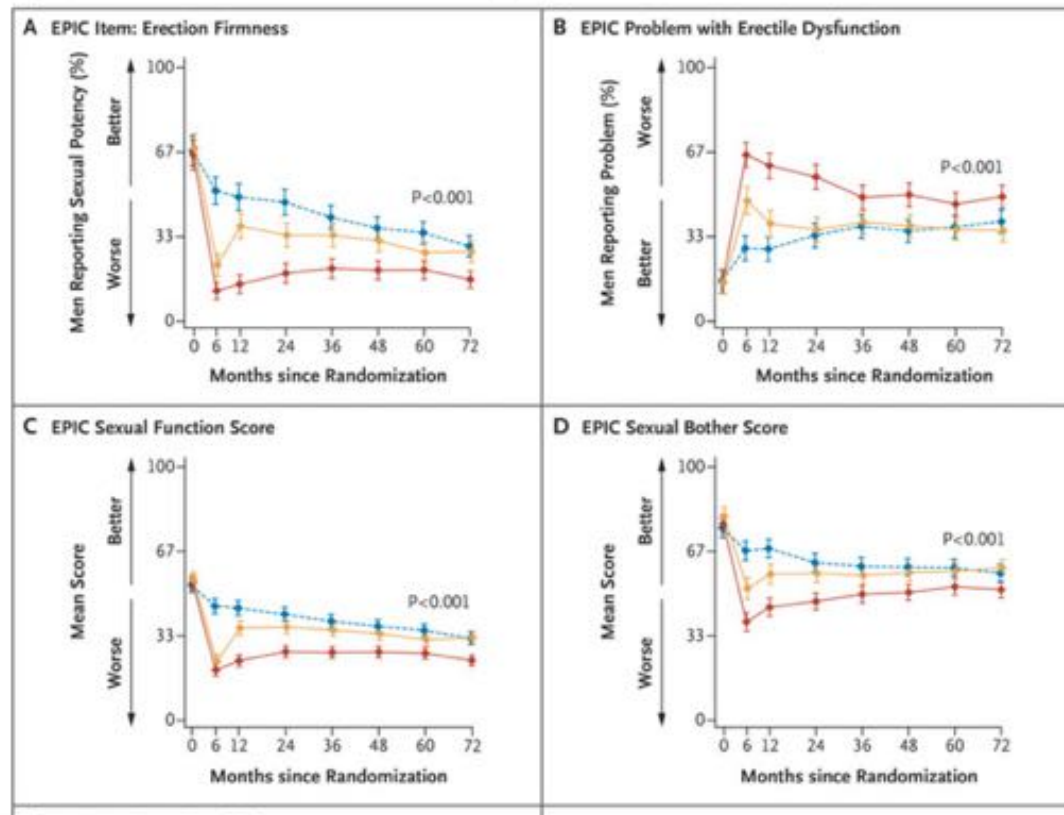
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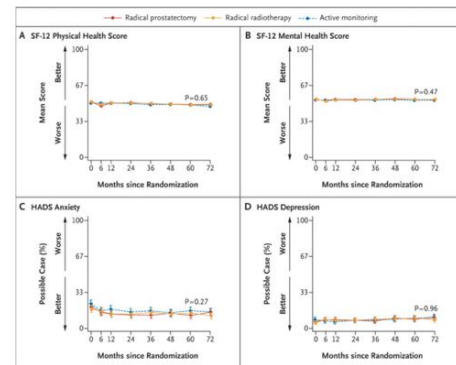
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**Figure 2.** Outcomes for Sexual Function and Effect on Quality of Life.



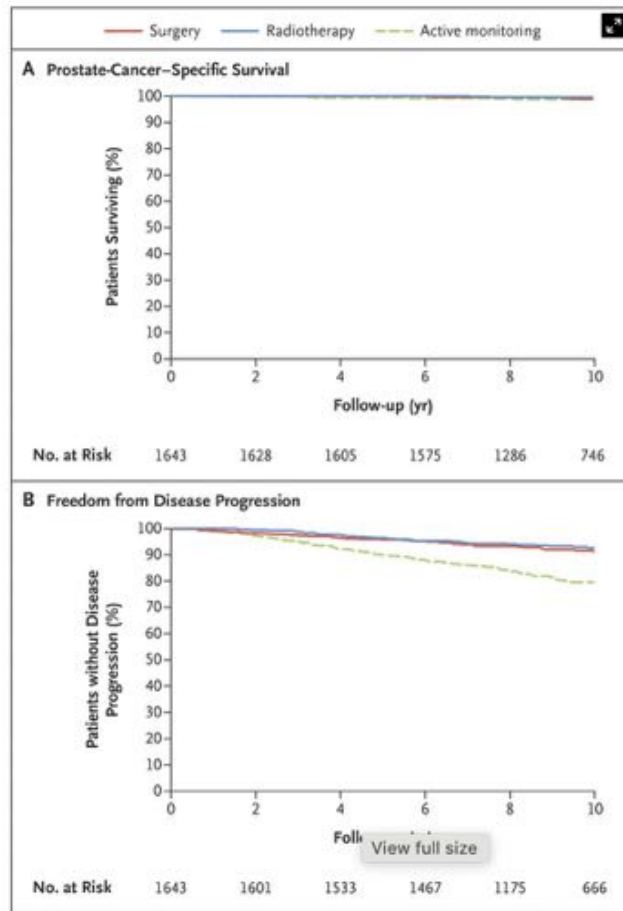
**Figure 4.** Outcomes for Health-Related Quality of Life.



ORIGINAL ARTICLE

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# Alternatives to risk reducing surgeries

## Localized anti cancer drug delivery



### Targets and opportunities

#### **Organ with identified cancer**

- 1) risk for progression
- 2) benefits must come from treating the organ only
- 3) no covert metastatic disease

#### **Organ at high risk for cancer**

- 1) precursor lesions
- 2) measurable/monitor
- 3) surgical removal of indicator lesion difficult/debilitating

#### **Organ with space-occupying process**

- 1) growth amenable to reduction by drug intervention
- 2) measurable/monitor

# Localized drug delivery

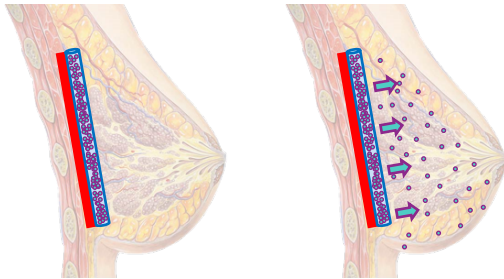
## Principles and Preclinical data



Early Interception

Organ Preservation and Avoidance of Systemic Side Effect

# Drug Delivery implant for Breast Cancer:

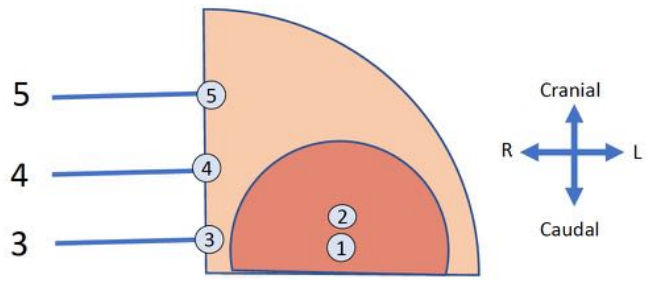
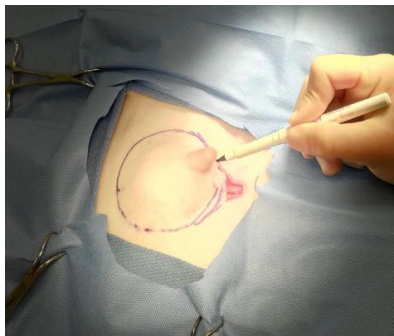
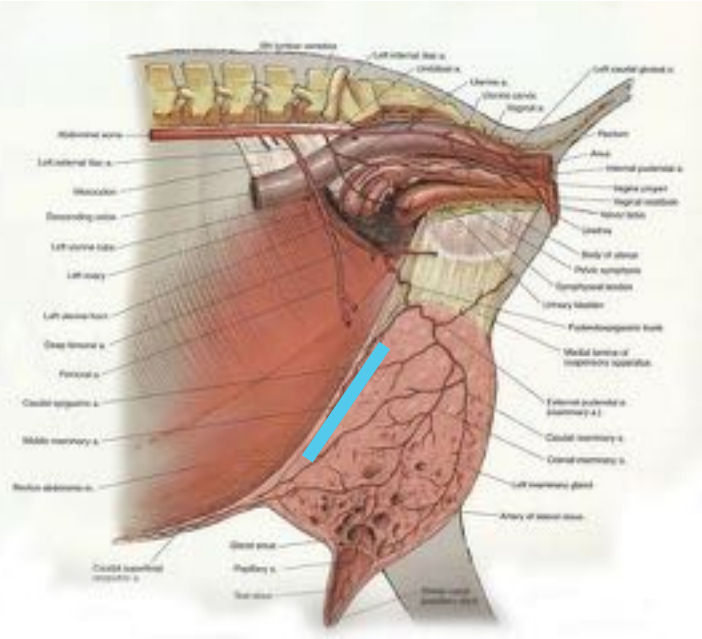
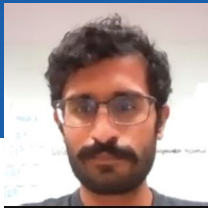


- Passive diffusion of approved anti-estrogen drugs through silastic-silicone implant
- Directed diffusion - impermeable backing prevents diffusion into the chest wall
- Sustained drug release at therapeutic levels for up to 5 years

## Outcomes

Drastically reduce the risk of breast cancer  
Avoid early-menopause effects  
Eliminate the need for mastectomies

# Sheep: Fulvestrant implant (n=2)



Sample#	Sample conc (ng/g)	Tissue Type	Sample Type
1	107	Capsule	Biopsy
2	341	Capsule	Biopsy
3	35.7	Gland	Biopsy
4	24.4	Gland	Biopsy
5	24.3	Gland	Biopsy

# 2014-2017: UCSF development

## Milestones:

sustainable drug delivery for treatment and prevention  
of breast cancer *in vitro and in vivo* with a silicon-based implant

Large Animal models:

PK and toxicity studies: Goat and sheep

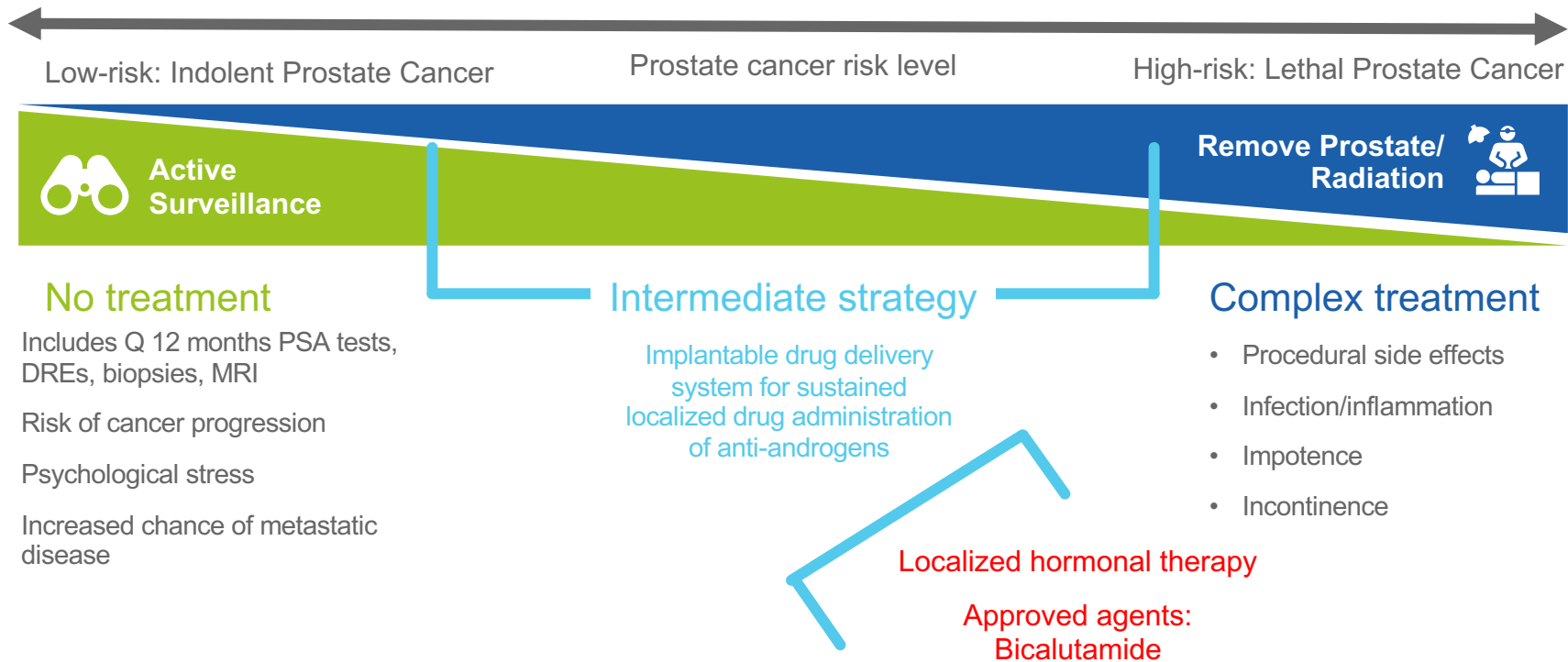
Human Breast Cancer Device Design:  
second generation models

*Major Pivot to prostate cancer*

Formation of company



# Why??



# Drugs to choose from

## Hormone Sensitive

## Castrate resistant

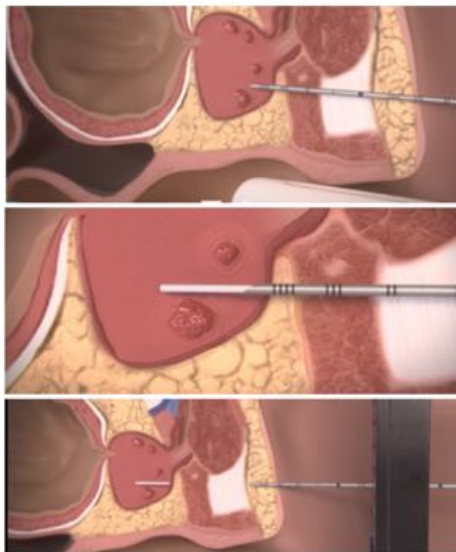
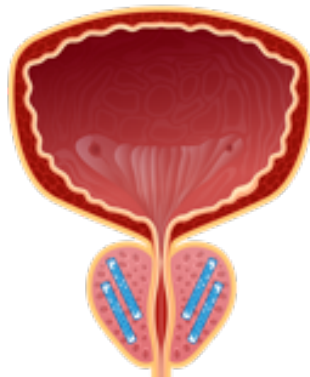
Loco-Regional Disease	Biochemical Recurrence (BCR)	Metastatic HSPC	Non-Metastatic CRPC	Metastatic CRPC	Metastatic CRPC Post-Docetaxel
Active Surveillance	ADT	<b>Docetaxel 2015</b> CHAARTED (OS) STAMPEDE (OS)	<b>Apalutamide 2018</b> SPARTAN (MFS)	<b>Docetaxel</b> TAX327 - 2004	<b>Cabazitaxel</b> TROPIC - 2010
Surgery					
Radiation +/- ADT		<b>Abiraterone 2017</b> LATITUDE (OS) STAMPEDE (OS)	<b>Enzalutamide 2018</b> PROSPER (MFS)	<b>Sipuleucel-T</b> IMPACT - 2010	<b>Abiraterone</b> COU-301 - 2011
*STAMPEDE (Abiraterone x 2 yrs)					
		<b>Enzalutamide 2019</b> ARCHES (rPFS) ENZAMET (OS)	<b>Darolutamide 2019</b> ARAMIS (MFS)	<b>Abiraterone</b> COU-302 - 2012	<b>Enzalutamide</b> AFFIRM - 2012
		<b>Apalutamide 2019</b> TITAN (rPFS,OS)		<b>Enzalutamide</b> PREVAIL - 2014	<b>Alpharadin</b> ALSYMPCA - 2013
				<b>Pembrolizumab (MSI-high)</b> 2017	
				<b>Olaparib (rPFS-BRCA/ATM)</b> PROFOUND	

ADT=  
LHRH  $\pm$  bicalutamide

# Options of therapy for prostate cancer

# Prostate Cancer Localized Hormonal Therapy

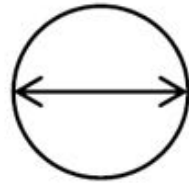
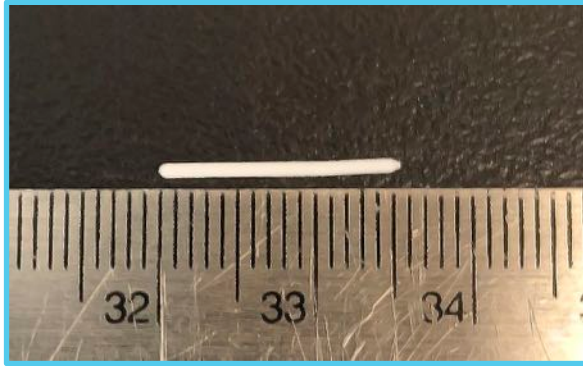
Polymer-based implant  
delivering anti-androgen  
drugs to the prostate



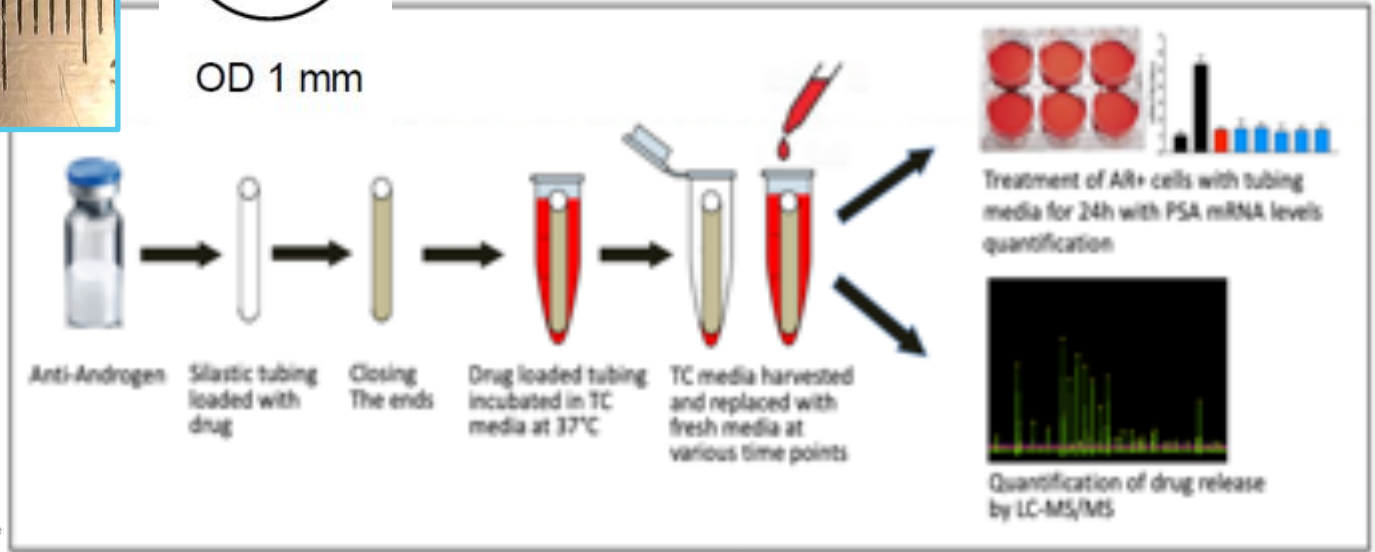
## Features:

- 1 Localized delivery to the prostate
- 2 Sustained delivery for a minimum of 2 years
- 3 Minimally-invasive procedure similar to prostate biopsy
- 4 Implant material and anti-androgens with previous FDA approval

# Prostate models Bench Study, G1 device



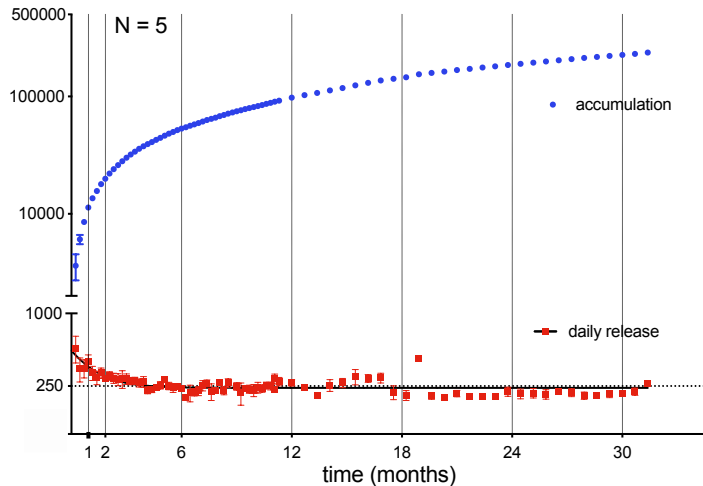
OD 1 mm



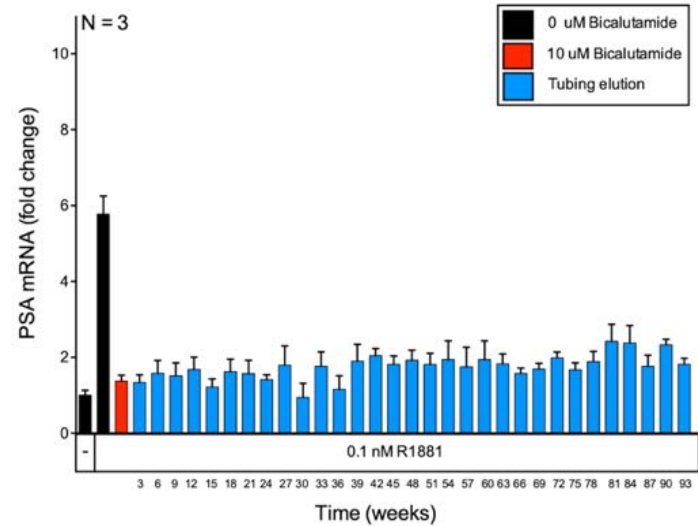
# Pre Clinical Studies: Duration of drug elution from implant and stability of drug



## first generation device Bicalutamide through Silicone Reservoir:



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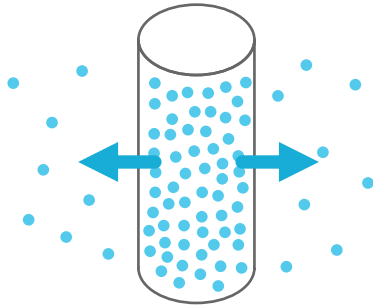


2 y

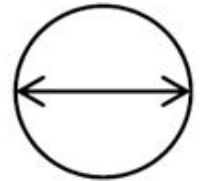
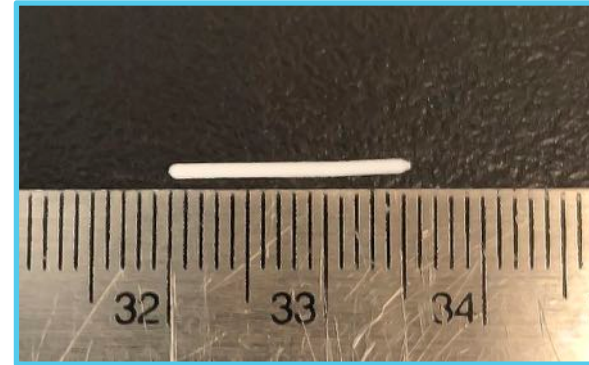
# Alessa Therapeutics: Gen 2 Mode of Action: Drug uniformly distributed through Polymer Matrix



## Concentration Gradient Driven Molecular Diffusion



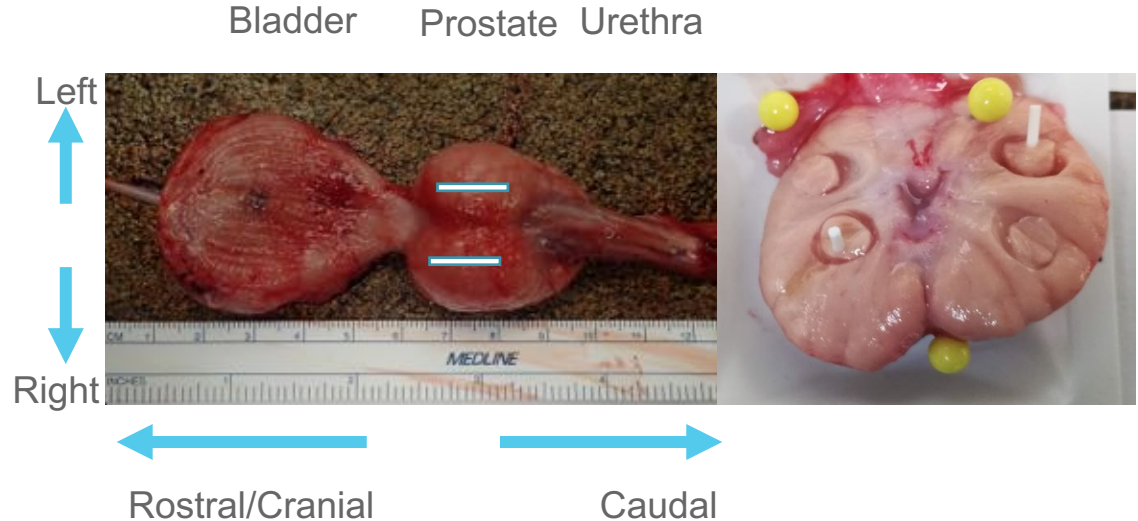
## 2<sup>nd</sup> Generation Prototype



OD 1 mm

# Study Design: Canine model

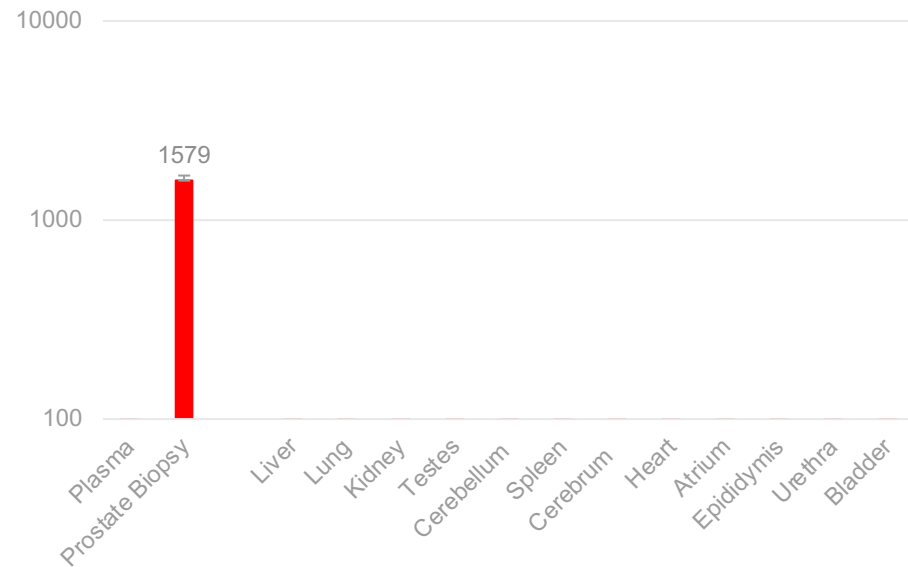
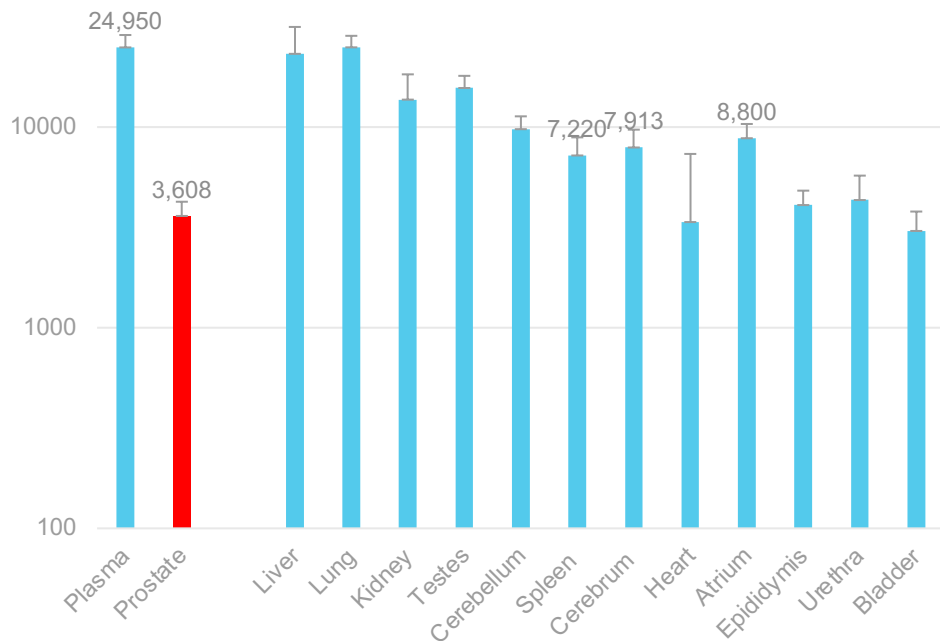
- 3 sexually mature canines (~11-18 months)
- 2 implants per prostate
- Prostate size (3cm)
- 55-day study
- 60% bicalutamide w/w silicone





# Gen 2 device: In vivo canine study oral vs implant

Expected human plasma level:  
8800 ng/ml

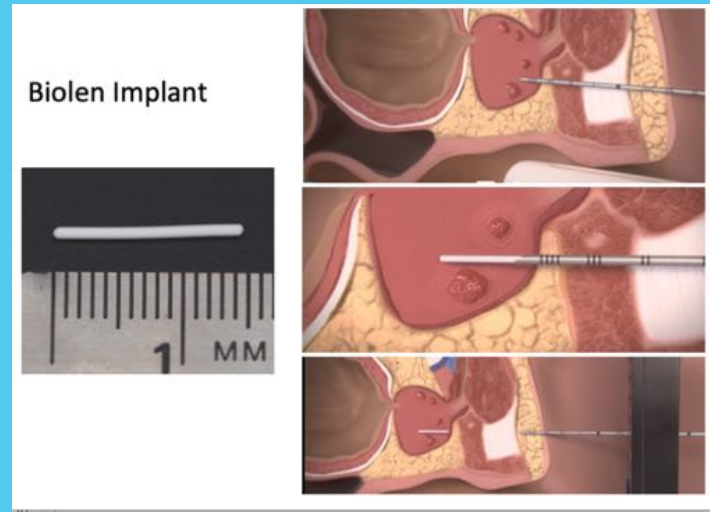




# The Biolen-PC Phase I Study

Window trial in men scheduled for prostatectomy  
(Australia and New Zealand)

ClinicalTrials.gov Identifier: NCT04284761



# Biolen-PC: First-in-Man

- > Safety and feasibility of localized delivery in men planning radical prostatectomy
- > 2° Objectives – effect on PSA, prostate and tumor size and local histopathology
  - Exploratory objectives – effect on LUTS, androgen gene expression
- > 6 to 12-week implant period followed by surgery
- > N=20 @ 4 sites in Australia and New Zealand
- > First Patient enrolled in New Zealand – October 2020...Data in December.

MRI followed by 8  
Biolens into prostate

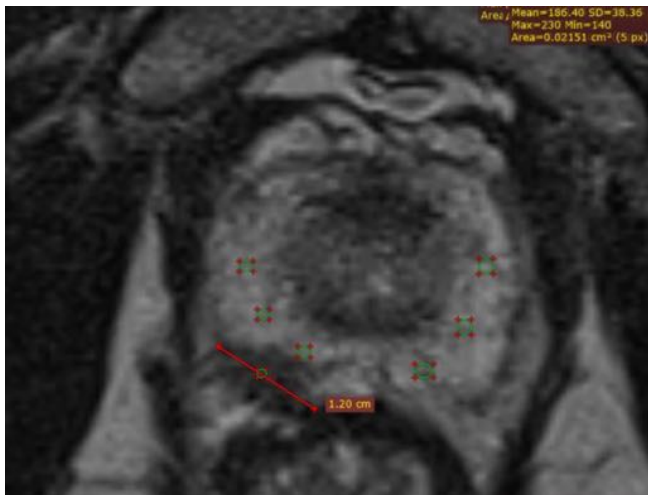
6 to 12 weeks PSA, pk and  
LUTS serially measured

MRI pre-RP for prostate and  
tumor size assessment

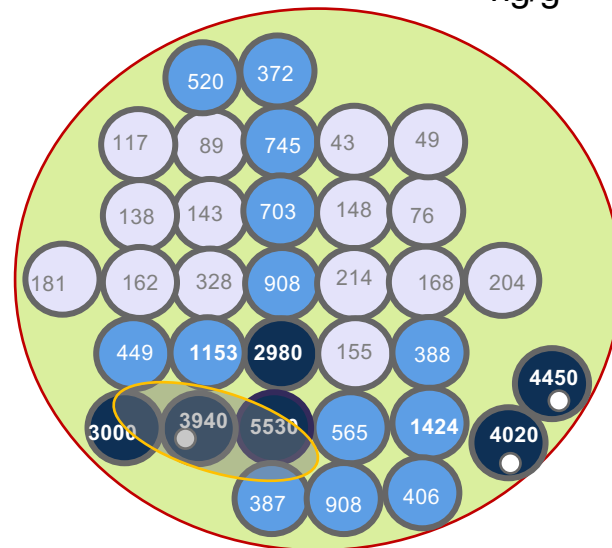
## Radical Prostatectomy (RP):

- Local tissue effects
- Drug deposition levels and location
- Androgen gene expression changes

# Bicalutamide Levels in Human Tissue & IC50 Efficacious Levels Near Implant



Representative Plot for Subject  
ng/g



Represents a 5mm punch biopsy on tissue slice

Represents an implant in the biopsy

# NCI Feasibility Study



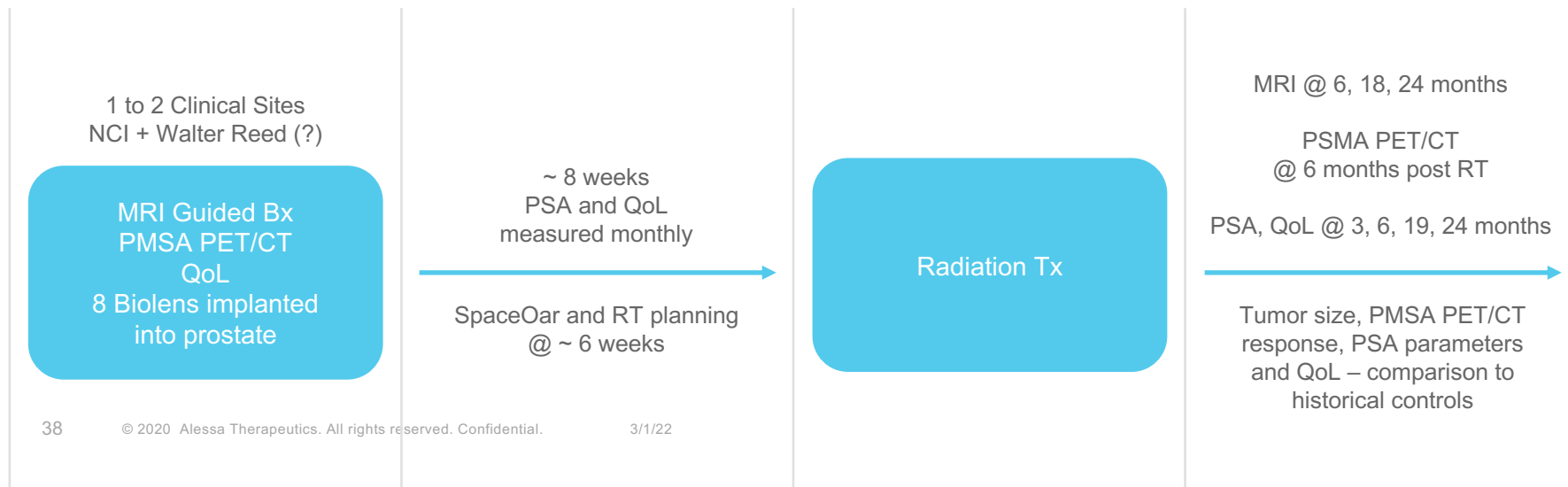
# Proposed NCI Feasibility Study

## Patient Population

Men with biopsy proven localized prostate cancer in whom prostate radiation and Androgen Deprivation Therapy (ADT) is appropriate

At least 1 prostate lesion measurable by mpMRI  $\geq 0.5$  cm

ECOG status  $\leq 2$  and estimated life expectancy  $> 5$  years



# Biolen + RT Study, CP-002

## Collaboration with Radiation Oncology Branch of NCI

- To evaluate the feasibility of replacing systemic androgen deprivation therapy (ADT) with targeted local delivery of an anti-androgen agent alone in patients indicated for hormonal + radiation therapy for the treatment of localized prostate cancer.
- Bioanalytic (bicalutamide level) testing – plasma, seminal fluid, tissue
- 8 to 16 Biolens to be implanted dependent on TUMOR VOLUME
  - MRI / AI modeling planned pre-procedure
  - Goal to implant in ‘center’ of tumor(s) with 5mm spacing to cover tumor(s)

# Summary clinical trials to date: CP-001 and CP-002

## CP-001

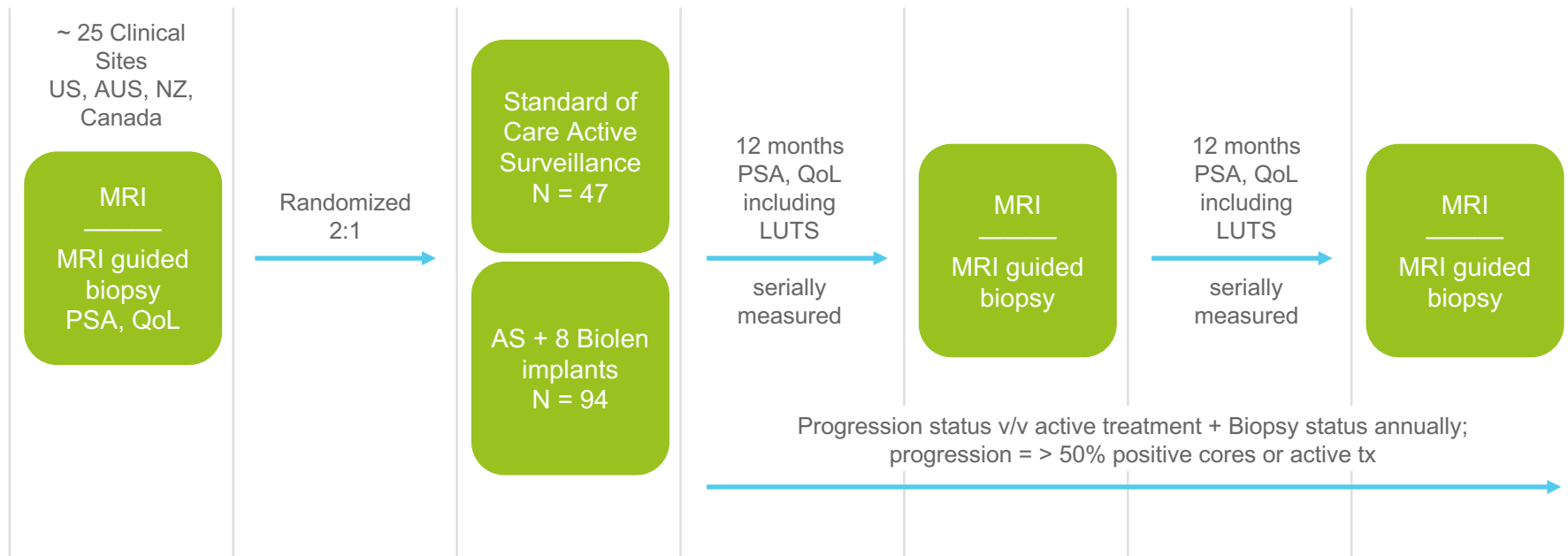
- March 2020: pre-prostatectomy feasibility study initiated with 8 implants:
  - no safety concerns
- Jan 2022: Approved for up to 16 (CP-001 (AUS+NZ))
- In progress consider lactose formulation
- **Goal:** complete feasibility with 20 patients

## CP-002

- Oct 2021: Biolen implant pre radiation therapy (US IND))
- Up to 16 implants
- First 2 patients started in Jan 2022,
- **Goal:** complete feasibility with 20 patients



# Pilot Phase 2 The BASIC Trial: Biolen + AS vs AS alone



# What is on the horizon?

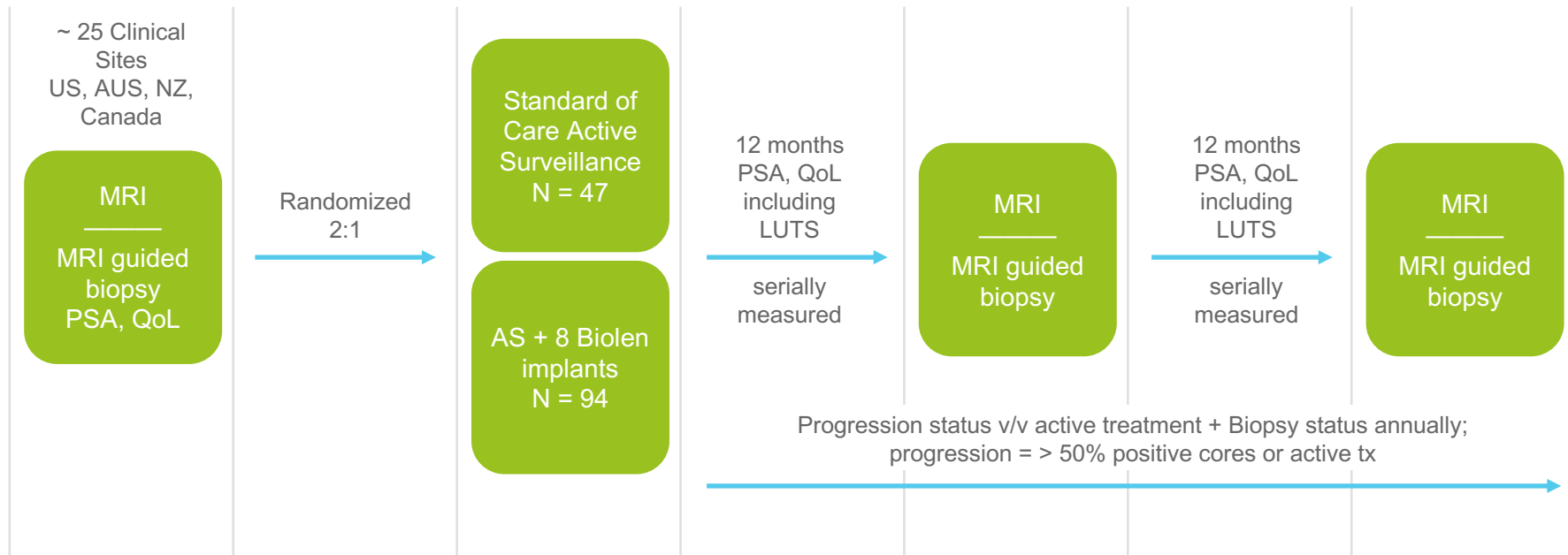
Other anti-androgens (apalutamide, enzalutamide, darolutamide others\_

Implants with PARP inhibitors for BRCA or ATM mutation carriers

Breast implants

Benign Prostate Hyperplasia

# Pilot Phase 2 The BASIC Trial: Biolen + AS vs AS alone



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Patricia Oto  
Jonathan Feuchtwang



# BRCA: the family curse

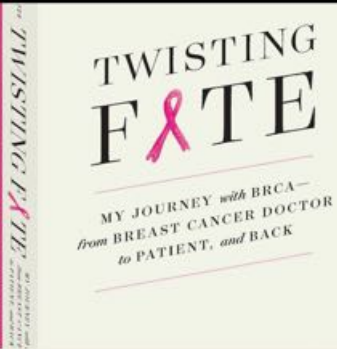


## the story behind

*Twisting Fate* describes my journey from a breast cancer specialist to a breast cancer patient and back. The story brings you to the cancer clinic, the operating room and into the heart and minds of patients and families going through cancer. Along the way you will also learn about the inherited risk of cancer and how it may affect your children.

I will take you through some of the most challenging and difficult questions in medicine and let you hear the voices of those who have won and lost the battle with cancer.

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THE SATURDAY ESSAY

## My Father's Fight Against the Breast-Cancer Gene

My grandmother and I both survived the disease, and knowing our genetic legacy turned out to be crucial in saving him

WSJ.com

