

Chemoprevention of Prostate Cancer

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Methods to Reduce Cancer Morbidity and Mortality

- **Screening**
- **Improved Therapy**
- **Prevention**

Chemoprevention

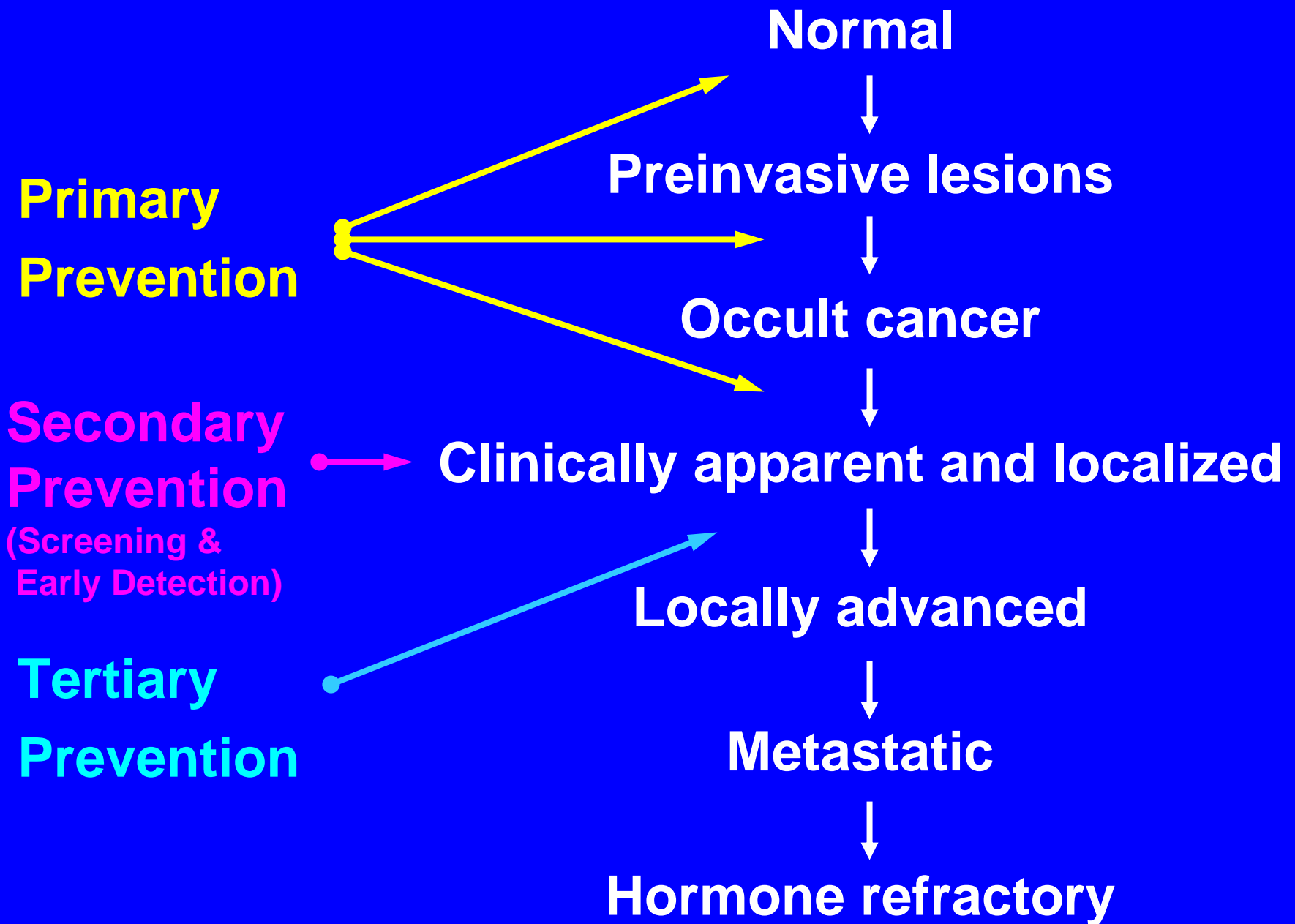
- Pharmacologic approach to arrest or reverse carcinogenesis

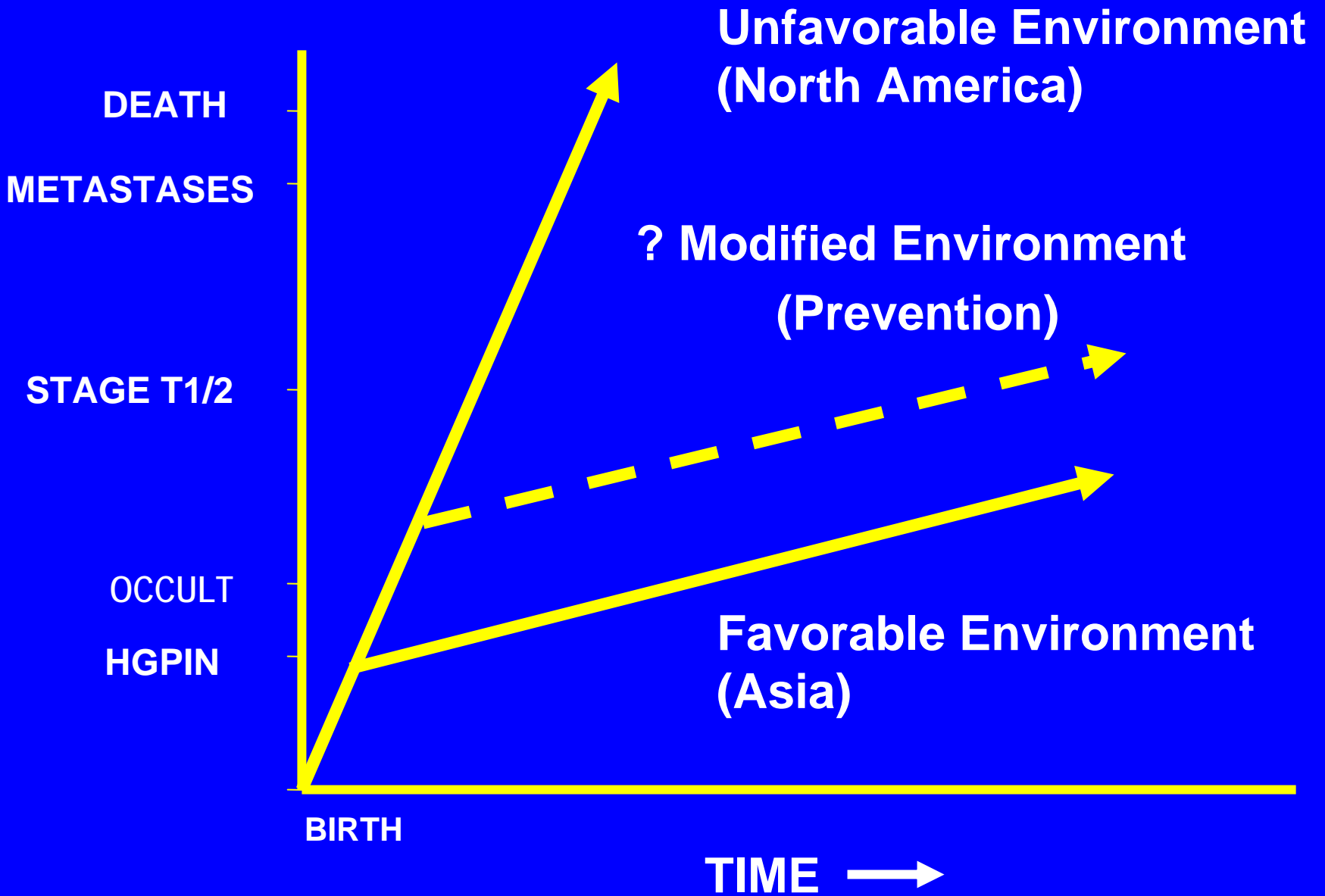
Sporn

- Does not specify whether prevention is
 - normal → cancer
 - premalignant → cancer
 - occult → clinically apparent cancer

Goals of Chemoprevention

- **Decrease number of cases**
 - **Reduce rx-related morbidity**
- **Decrease mortality**





Large Scale 1° Prevention Trials

Trial	Risk Group	Molecular Target	Expected Results
PCPT	Low	Type II 5AR	Reported
REDUCE	Intermediate	Types I and II 5AR	2008
Toremifene	High	Estrogen Receptor	2008
SWOG/Se	High	Se-mediated effects	2009
SELECT	Low	Oxidative Stress	2012

Statins and Prostate Cancer Risk

Risk Group	Risk Ratio
Any Px Cancer	1.09
Advanced Px Cancer	
Any use	0.51
Use < 5 yrs	0.60
Use > 5 yrs	0.26

Health Professionals Follow-up Study, N = 34,989

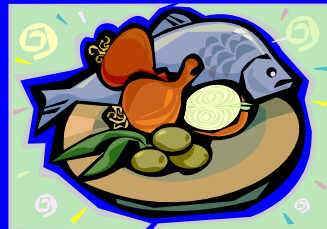
Platz et al, JNCI 98:1819-25, 2006

Prostate Cancer

Diet & Exercise Risk Factors

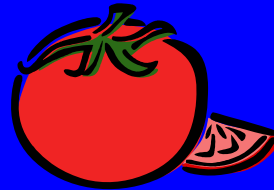
- May Increase Risk

- Fat / Red Meat
 - Cooking methods
- Dairy/Calcium
- Smoking
- Total Calories, Body size



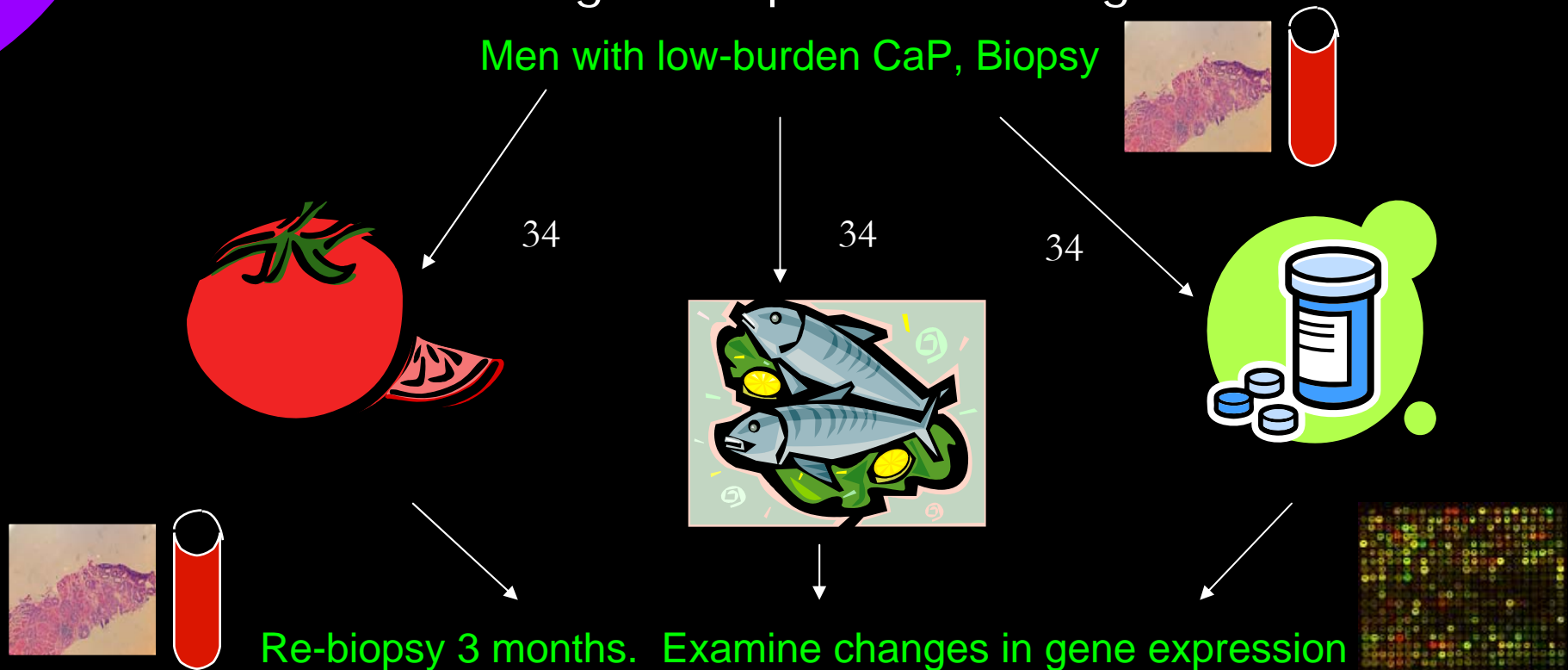
- May Decrease Risk

- Plant-based Foods/ Vegetables
 - Tomatoes
 - Cruciferous
 - Soy/Legumes
- Specific Nutrients
 - Selenium
 - Vitamin E
 - Carotenoids/Lycopene
 - Total Antioxidants
- *Fish / Marine Omega 3 Fatty acids*
- *Moderate to Vigorous Exercise*

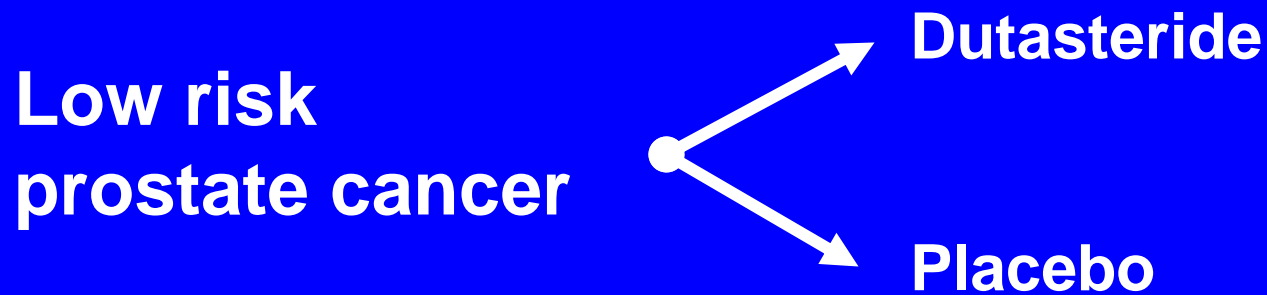


The Molecular Effects of Nutrition Supplements Study (MENS)

- Carroll PR, Haqq C, Chan JM et al (*Funding: NCI/NIH*)
- n=114 watchful waiters, low risk CaP
- Intervention=tomato, fish oil supplement, or placebo
- Outcome = gene expression changes in bx @ 3 mths

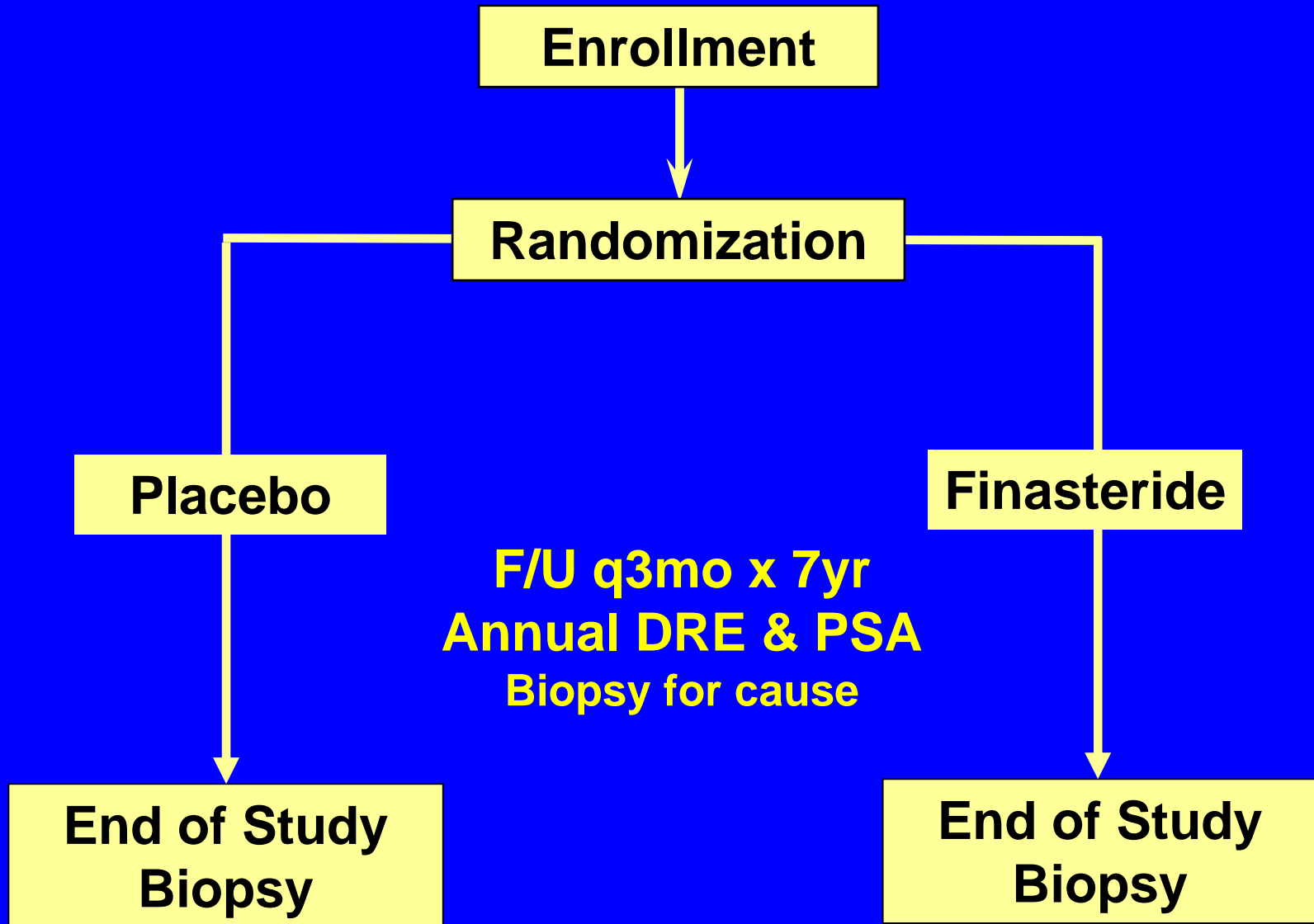


REDEEM Trial



Endpoint: 50% reduction in definitive therapy

The Prostate Cancer Prevention Trial



PCPT Results

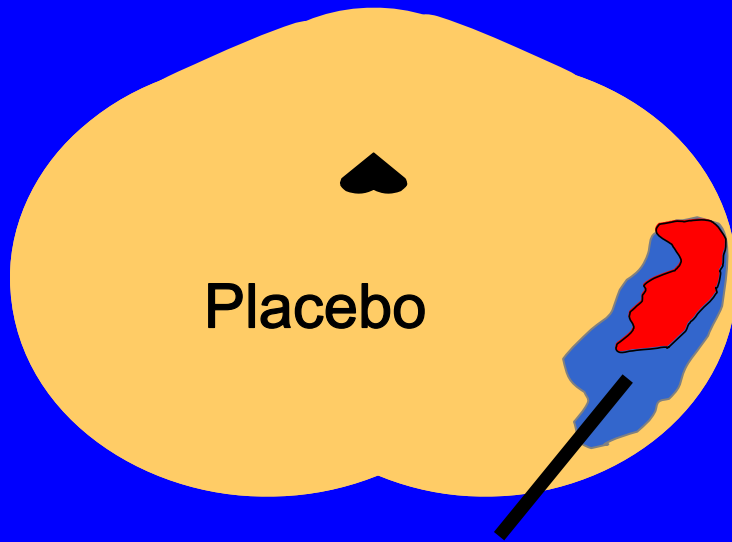
- 6.4% reduction (RR = 0.75) in prevalence of prostate cancer
- 1.3% increase (RR = 1.27) in high grade disease

Gleason Sum	Observed Prevalence
≤ 6	Decreased
7	Unchanged
≥ 8	Increased*

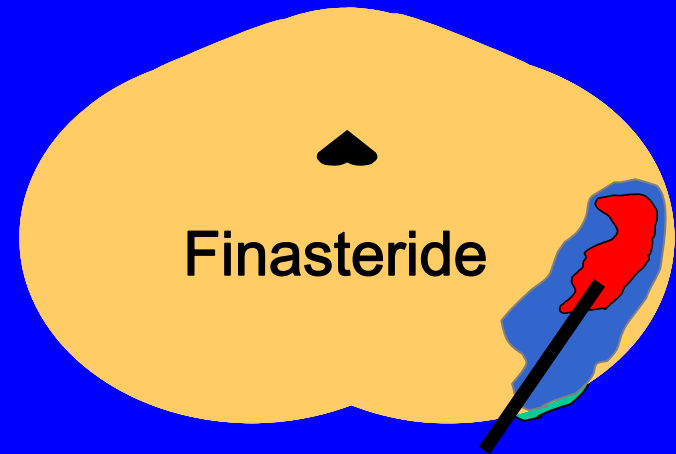
* For cause biopsies only

Detection bias: The effect of prostate volume

Simulated Needle Biopsy

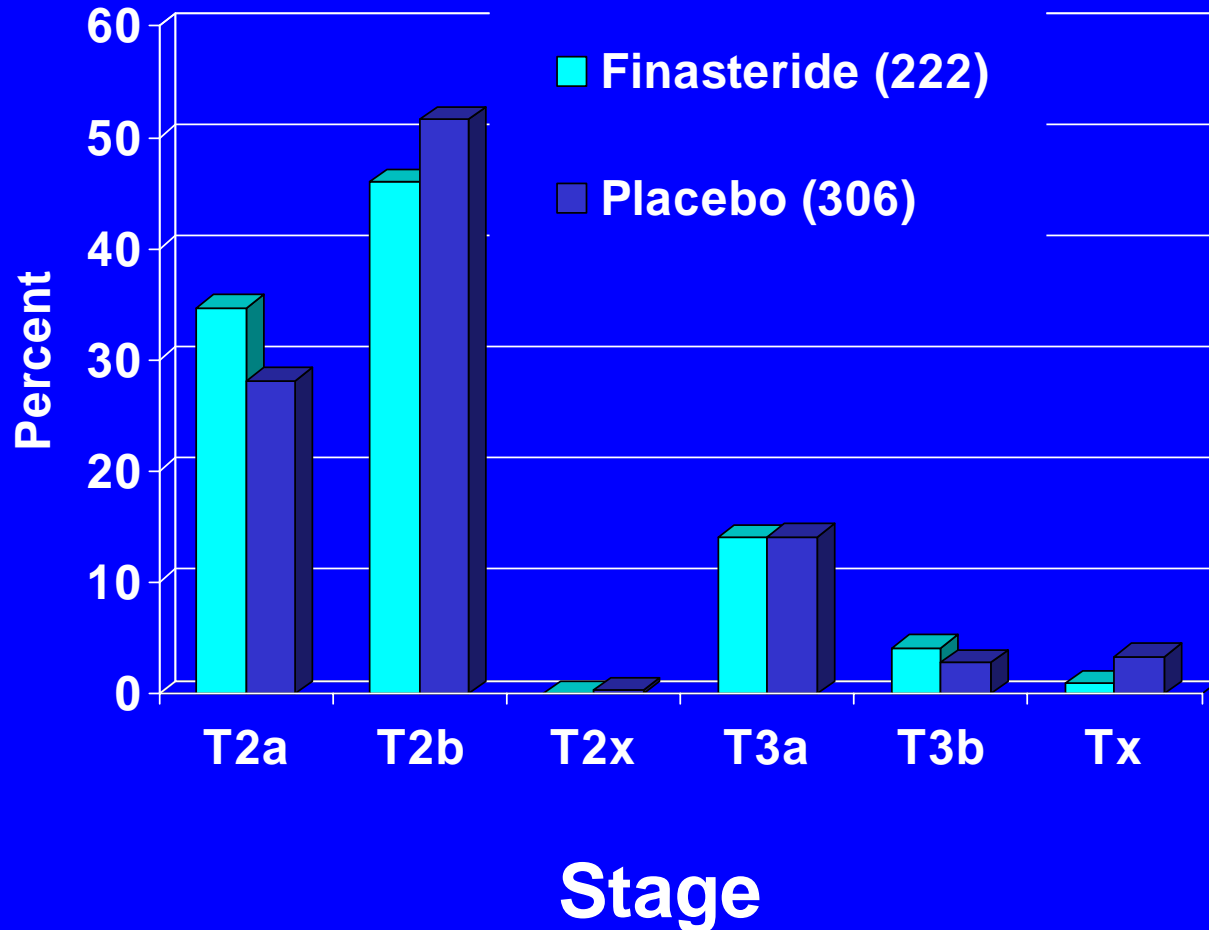


Needle misses high grade cancer (**red**) due to increased ratio of benign tissue/cancer

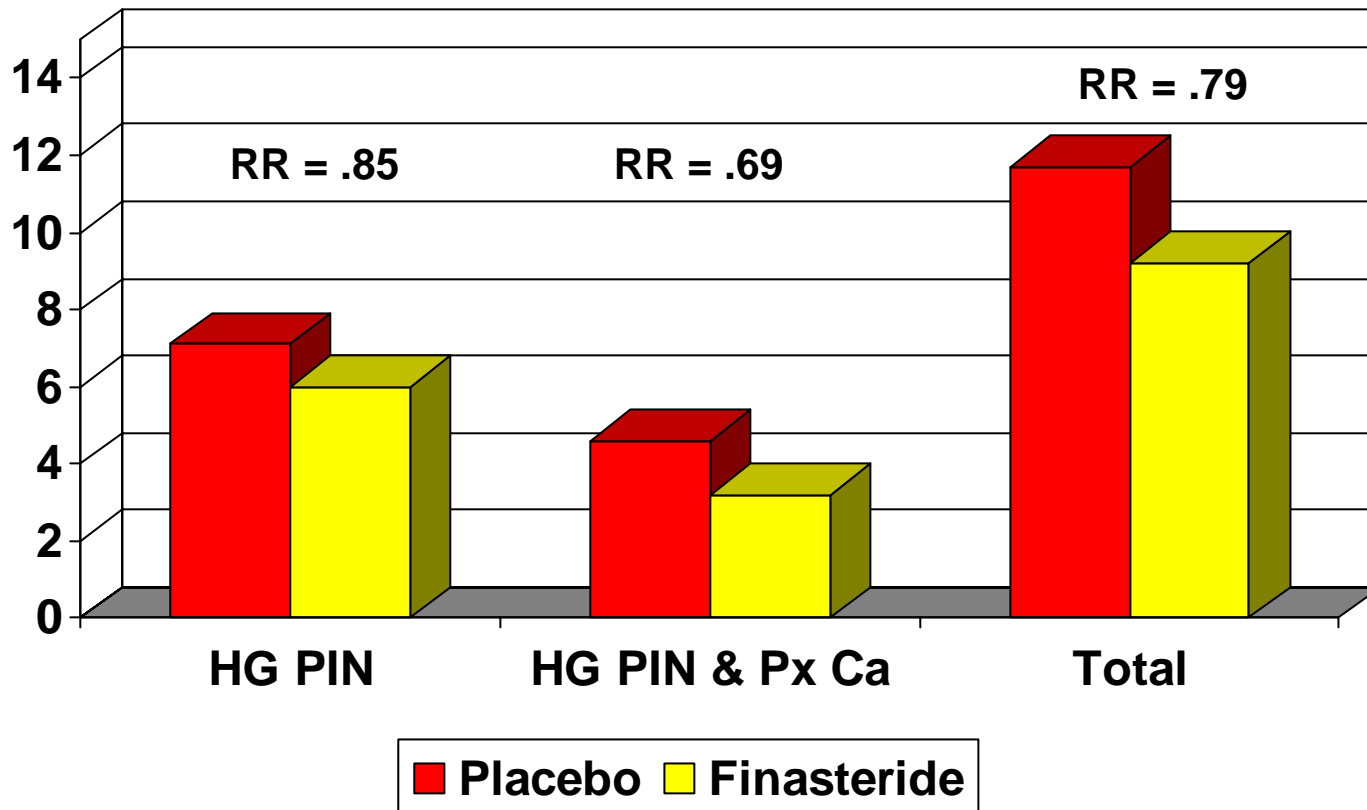


With shrinkage of benign prostate tissue relative to high grade cancer, there is an increased likelihood of sampling high grade cancer

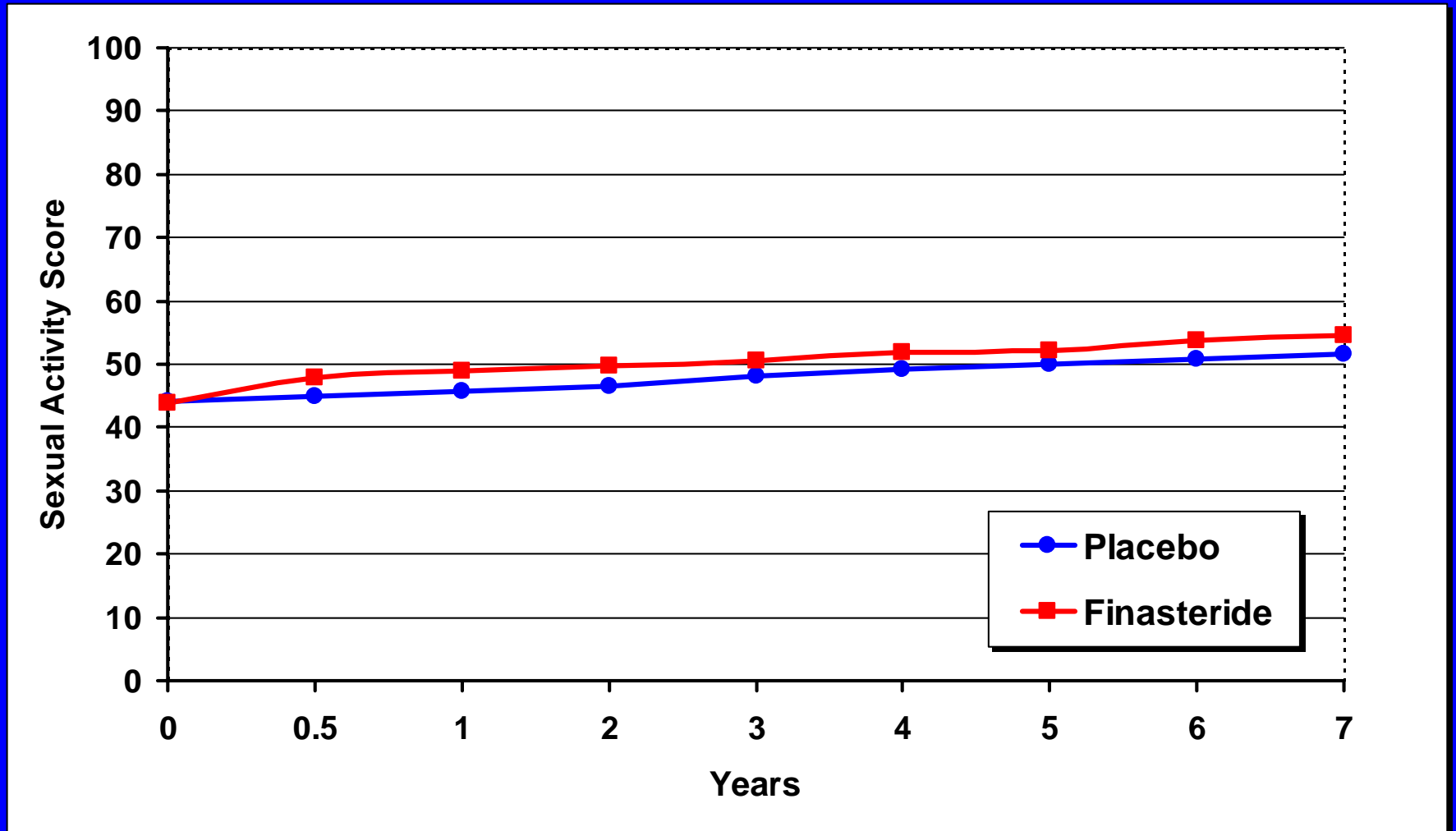
Pathological Features at RP



Finasteride Reduces the Incidence of HG PIN



Effect of Finasteride on Sexual Function



Finasteride as a Preventative

- **Benefits**

- 25% reduction in cancer detection
- 21% reduction in high grade PIN
- Fewer urinary symptoms & lower risk of AUR/TURP
- Improves diagnostic accuracy of PSA
- Avoids “burden of cure”

- **Costs**

- Increased risk of high grade disease
 - More aggressive rx
 - ? Excess mortality
- Sexual side effects
- Cost of finasteride

Population Impact

- **17% lifetime risk of being diagnosed with prostate cancer (US men)**
- **With finasteride, the risk is reduced to 13%**
- **250,000-360,000 person-years saved over 10 years in the U.S. (Unger)**

Infections and Cancer

- **17.8% of all cancers world-wide**
 - 1.9 million cases

Agent	Cancer
H. Pylori	Gastric (63%)
HPV	Cervical, anal, genital (100%)
HBV, HCV	Hepatic (86%)
HHV-8	Kaposi's sarcoma (100%)
EBV	Burkitt's lymphoma, Nasopharyngeal
HIV	KS, lymphoma, cervical
HTLV-1	T cell leukemia/lymphoma
Schistosomes	Bladder
Liver flukes	Bile duct

U.S. Approves Cervical Cancer Vaccine

By [GARDINER HARRIS](#)

Published: June 8, 2006

WASHINGTON, June 8 — Federal drug officials announced today that they had approved a vaccine against cervical [cancer](#) that could eventually save thousands of lives in the United States each year and hundreds of thousands in the rest of the world.

Called Gardasil, the vaccine is the culmination of a 15-year scientific effort that began at the [National Cancer Institute](#) and a research center in Australia, and it may one day be seen as one of the major health advances of the early 21st century.

Is Prostate Cancer an Infectious Disease?

Epidemiologic Data

- Increased Risk of Prostate Cancer with
 - STI OR 1.44 *Dennis et al, Epidemiology 2002; 13:72*
 - Prostatitis OR 1.60 *Dennis et al, Urology 2002; 60:78*
 - T. Vaginalis OR 1.43 *Sutcliffe et al, CEBP 2006; 15:939*
 - HHV8 OR 4.67 *Hoffman et al, JID 2004; 189:15*

Is Prostate Cancer an Infectious Disease?

Genetic Data

–Variants in *RNaseL*, *MSR1*, & *TLR4* associated with increased risk for

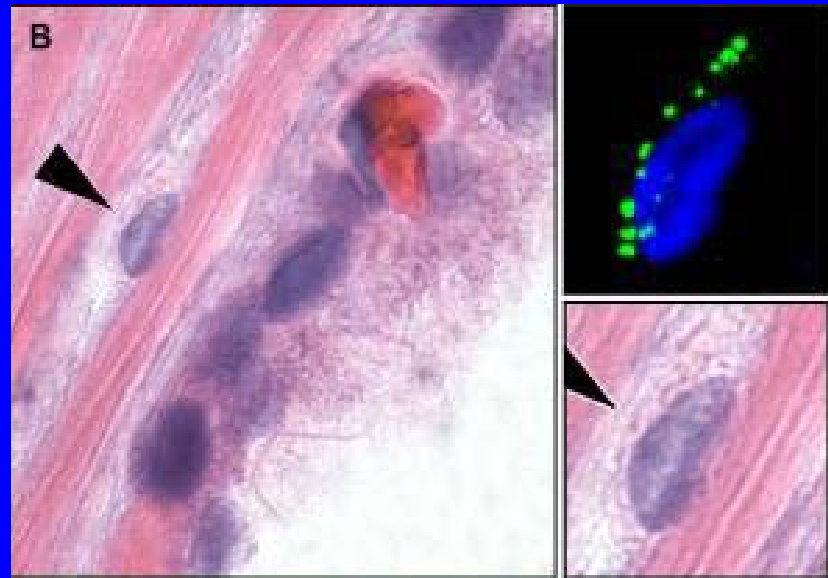
- Infections in animals
- Prostate cancer in humans

Identification of a Novel Gammaretrovirus in Prostate Tumors of Patients Homozygous for R462Q *RNASEL* Variant

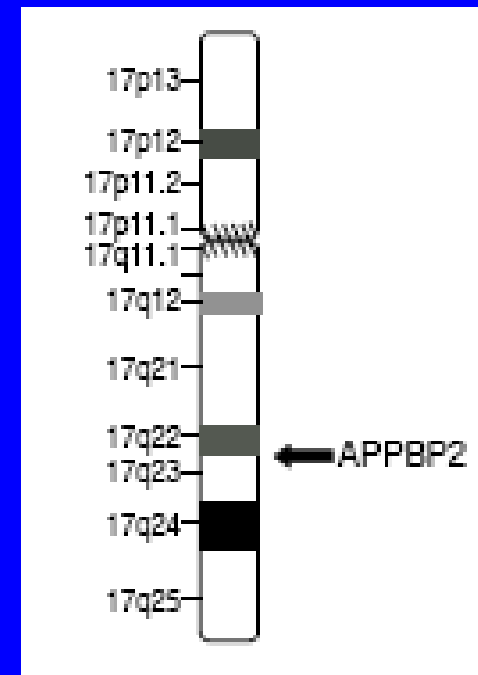
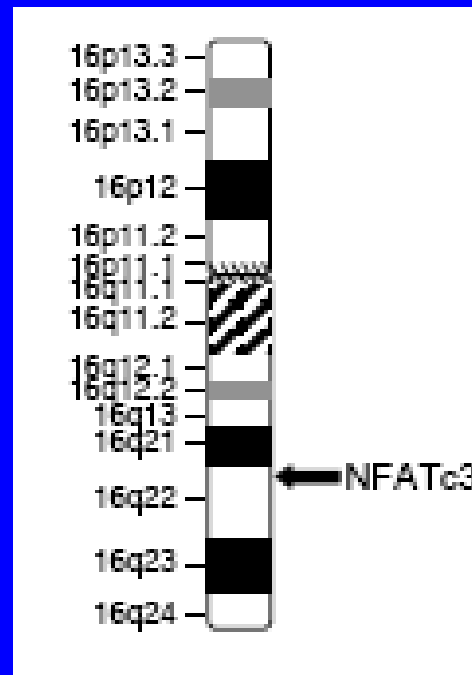
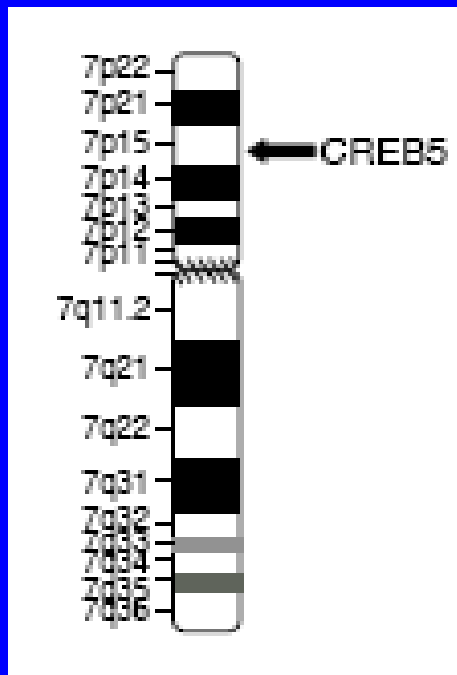
Anatoly Urisman¹, Ross J. Molinaro^{2,3}, Nicole Fischer⁴, Sarah J. Plummer², Graham Casey², Eric A. Klein⁵, Krishnamurthy Malathi², Cristina Magi-Galluzzi⁶, Raymond R. Tubbs⁶, Don Ganem^{4,7,8}, Robert H. Silverman^{2*}, Joseph L. DeRisi^{1,8*}

PLoS Pathogens, 2:211, 2006

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XMRV Integration Sites



“Prevention is so much better than cure because it saves the labor of being sick.”

Thomas Adams, 1618