

Therapy Development in Prostate Cancer

A medical oncologist's 'two cents'

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LEADING MEDICINE

Disclosures – Eleni Efstathiou MD PhD

Research Support/P.I.	Janssen, Sanofi-Genzyme, Astellas/Medivation, Tracon, Oric-Pharma, Astra Zeneca, Bayer, Eli-Lilly, Myovant, Pfizer
Scientific Advisory Board Honoraria	Janssen, Sanofi-Genzyme, Tolmar, Takeda, Astra Zeneca, Bayer, Oric Pharma, Pfizer, Merck

'Discovery is our Business'



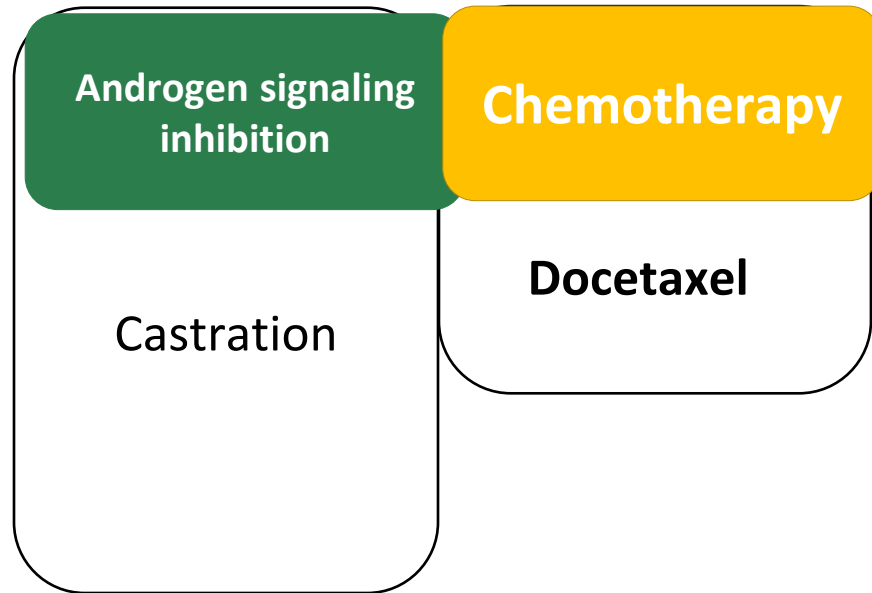
Charles Huggins (1902-1997)

Urologist

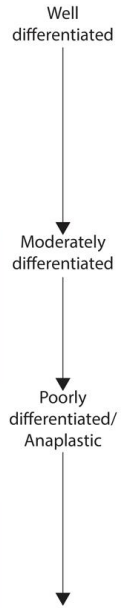
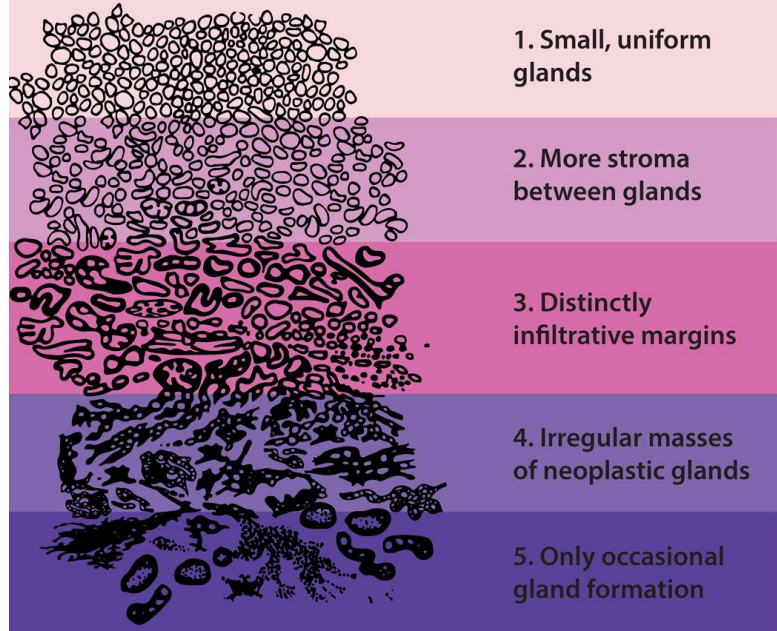
Nobel Prize in Medicine 1966

For fundamental discoveries
concerning Hormonal Dependence for
Prostate and Breast Cancer

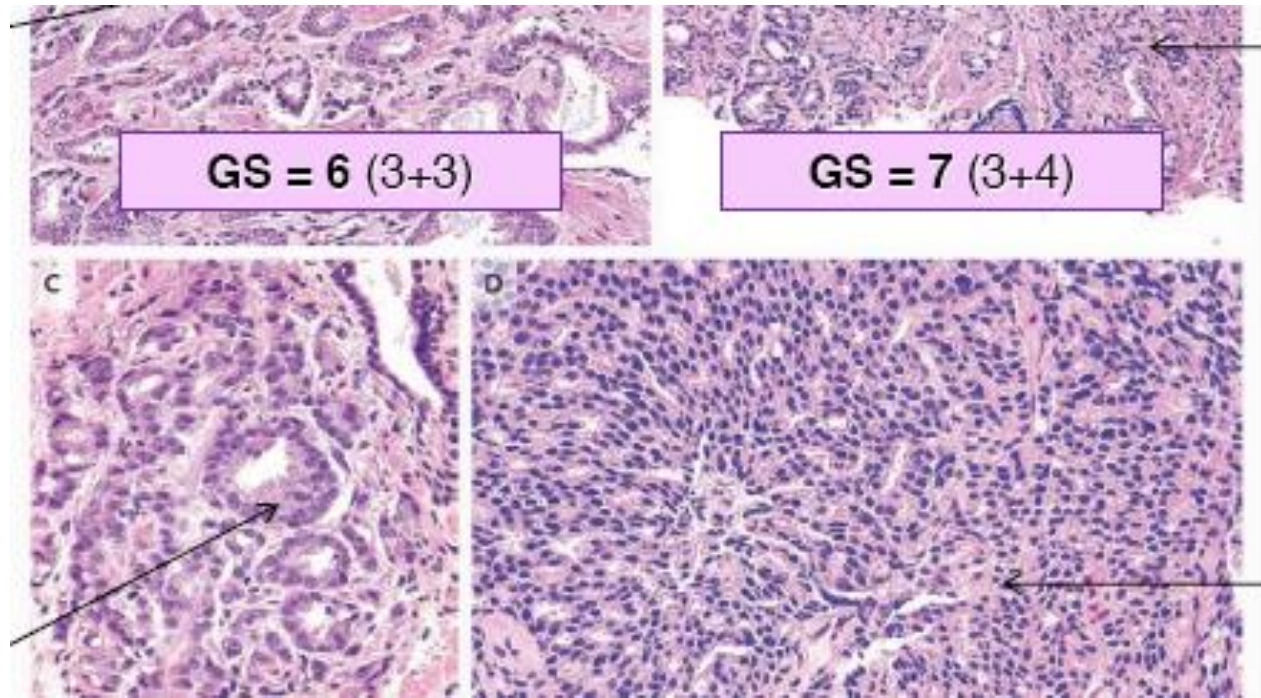
**Prostate Cancer lagged significantly in drug development ...
Drug Development in Prostate Cancer by biologic domain in 2010**



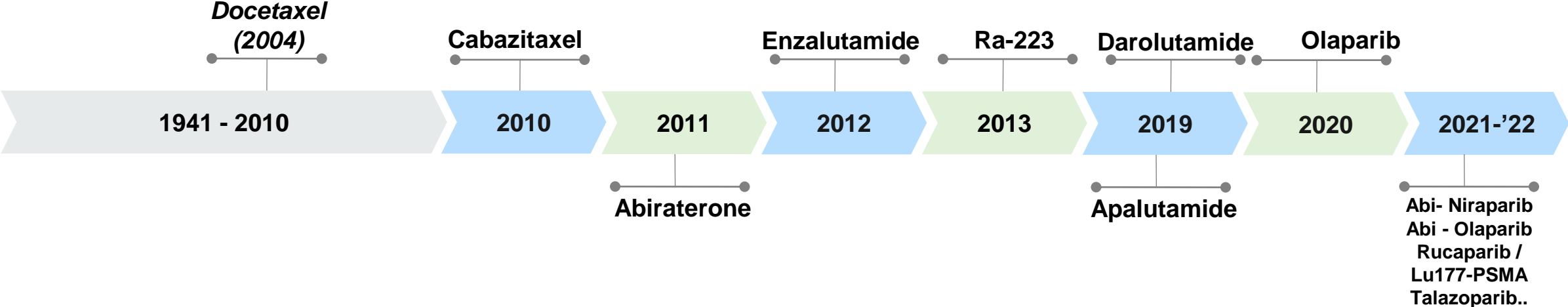
Gleason's Pattern



***And Lagged in Molecular Tumor Characterization
Pathology dictated by Morphology
Gleason Grade and
Score
to this Day !!***



Drug development Prostate Cancer :



ADT

Rise of precision medicine: PARPi and beyond

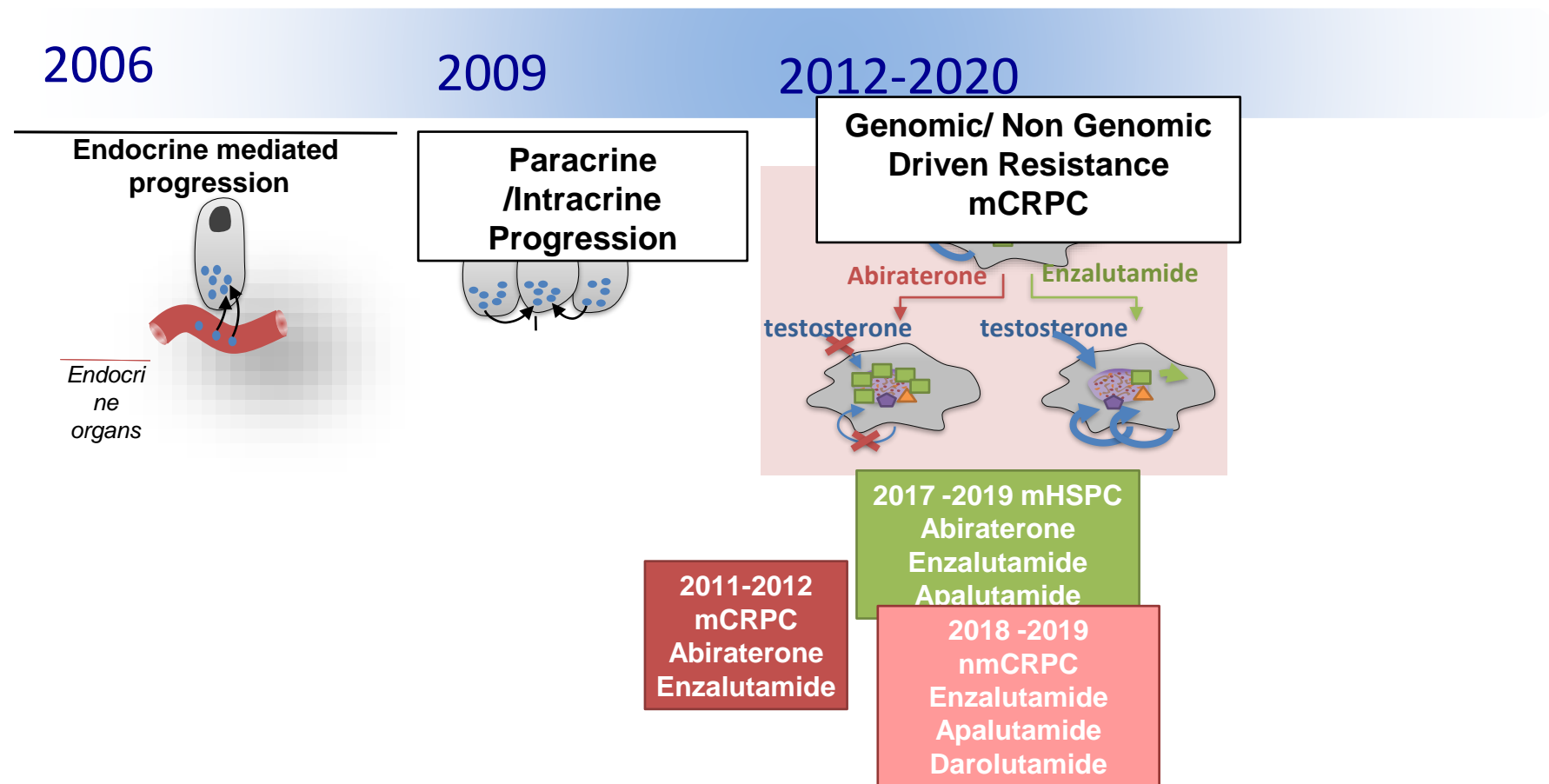
1st generation anti-androgens

2nd generation anti-androgens

1st and 2nd generation chemotherapy

Contagious Enthusiasm Era...

Androgen Signaling Inhibition Therapy Development



How Long Does it take ? Targeting DDR mutations in Prostate Cancer

1997
First evidence of genetic predisposition to prostate cancer.

2015
Feasibility of multi-institutional molecular characterization in mCRPC

2016
Germline pathogenic DDR mutations in metastatic prostate cancer 11.8%

2017
NCCN 2017 first guidelines: DDR testing for m Pca and expanded 2018 to men with high risk localized, metastatic or strong family history

2019
PROFOUND

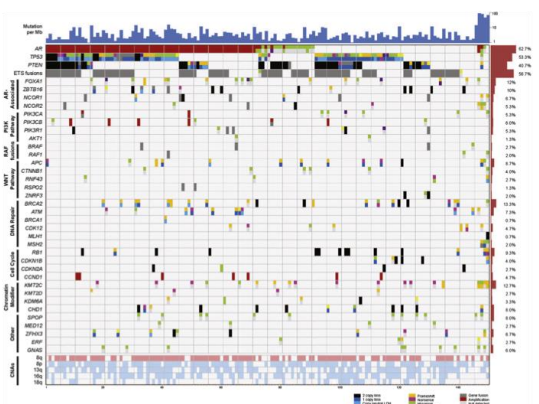
2019
-FDA Approvals
Olaparib for DDR mutated mCRPC post enhanced androgen signaling inhibition

Table 3 Relative risks for prostate cancer in relatives of prostate cancer cases by degree of relationship (from [15])

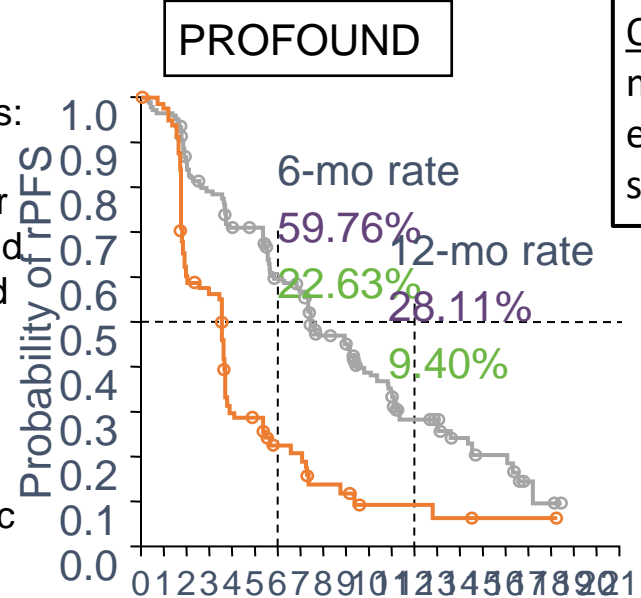
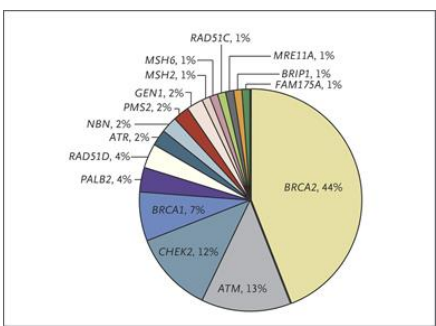
Affected relatives	Relative risk (95% CI)
First-degree	2.0 (1.2-3.3)
Second-degree	1.7 (1.0-2.9)
Both first and second	8.8 (2.8-28.1)

Table 4 Age-adjusted relative risk estimates for prostate cancer by number of additional affected family members (from [15])

Affected relatives (besides proband)	Odds ratio (95% CI)
1	2.2 (1.4-3.5)
2	4.9 (2.0-12.3)
3	10.9 (2.7-43.1)

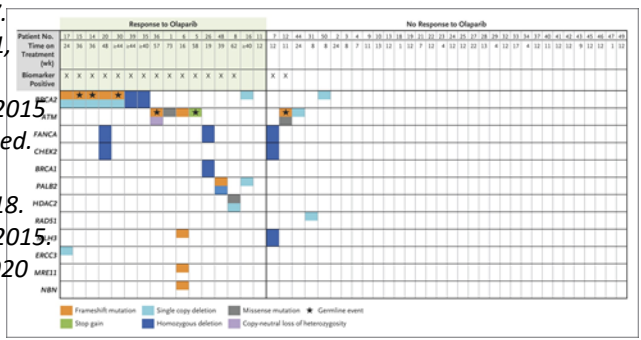


TOPAARP-A Study

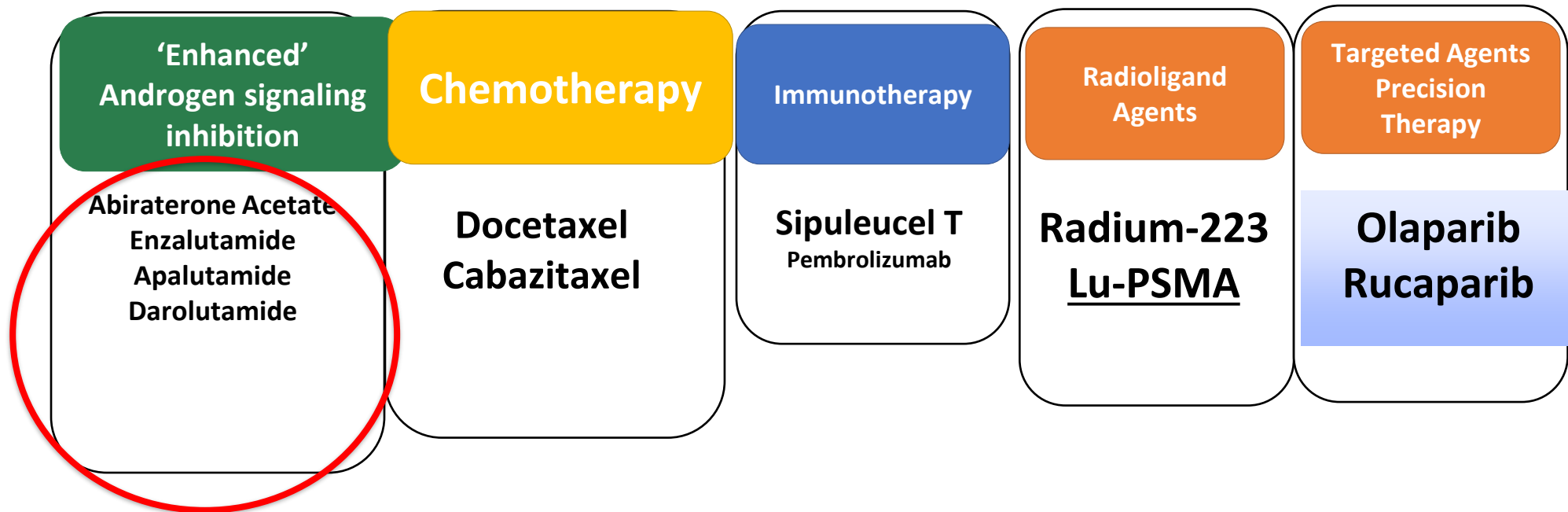


2020
FDA approval of companion diagnostics: FoundationOne CDx and BRACAnalysis

Eeles RA, et al. *Br J Urol*. 1997.
 Robinson et al., 2015, *Cell* 161, 1215-1228
 Mateo J, et al. *N Engl J Med*. 2015
 Pritchard CC, et al. *N Engl J Med*. 2016.
 Giri VN, et al. *J Clin Oncol*. 2018.
 Mateo J, et al. *N Engl J Med*. 2015
 Abida W et al. *J Clin Oncol*. 2020



Drug Development in Prostate Cancer by biologic domain in 2022



**Treatment of Primary
A systemic (equivalent) therapy ?**

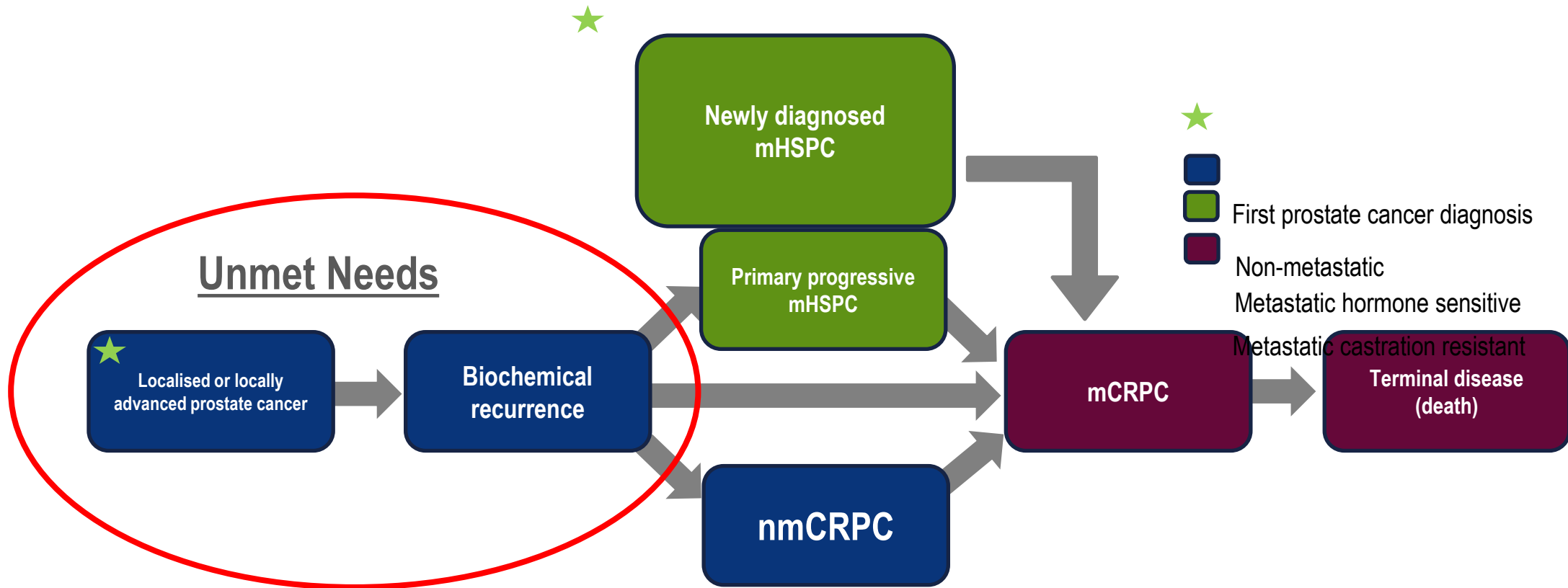
Source: Personal File

Grey Listings: phase III data but no indication

Therapy Development across Prostate Cancer Spectrum

Unmet Needs:

Increasing The Curative Fraction



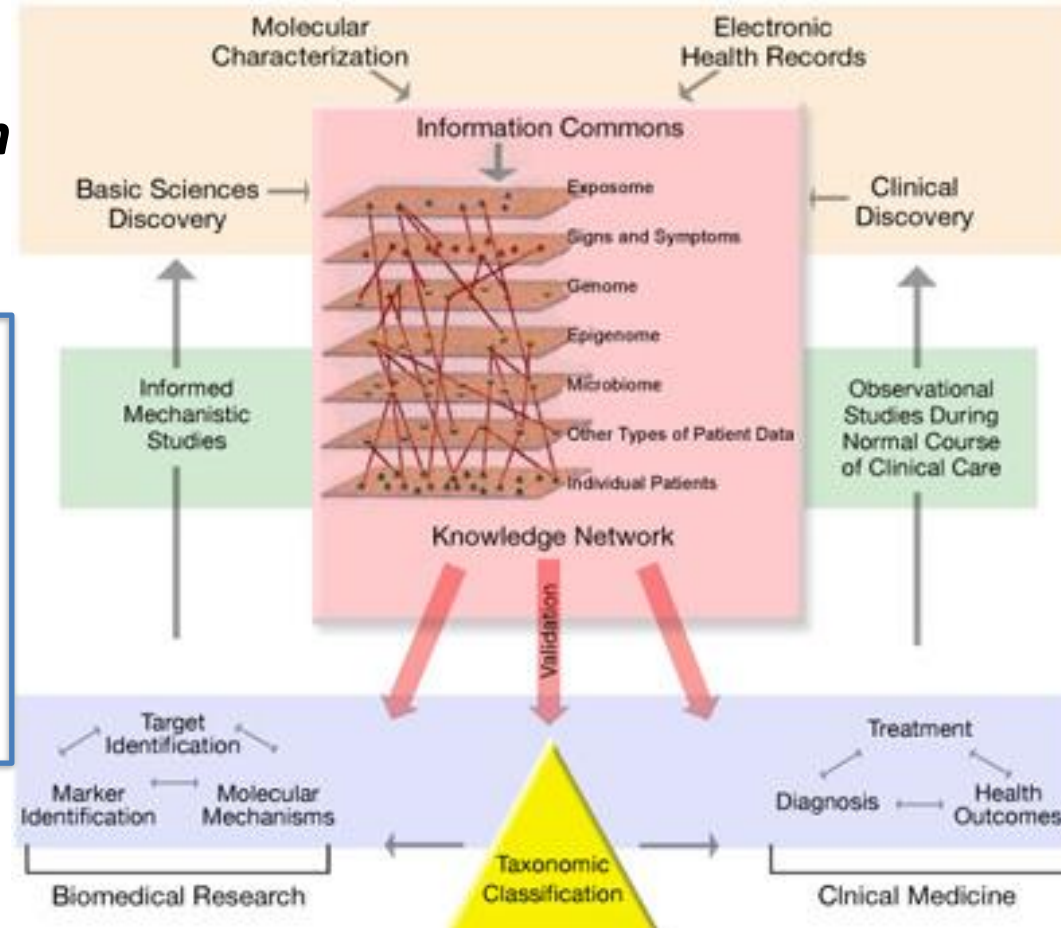
Precision Medicine Development

Aim : A clinically meaningful Prostate Cancer Reclassification to Guide Therapeutic Strategies that maximize Therapeutic Index

**Integrating
Molecular Characterization
& Clinical Data**

**Tissue and Liquid Biopsy
Driven
Clinical Research
Co-Clinical Research**

**Discovery
Testing
Validation**



Ουκ ενι ιατρικην ειδεναι οστις μη οιδεν ο τι εστιν ανθρωπος

Hippocrates
460-370 B.C.

‘It is impossible to master medicine if one does not fully comprehend the man’



Asclepeion of Epidauros
The inception of holistic healing

Revisit The Principle of Medicine
Treat the man not just a disease

Precision Medicine: Precise towards both the host (man) and the tumor

Technology to Provide Access to Resources

Deliverables: Therapeutic Index improvement
Healthcare : Care of health rather than disease

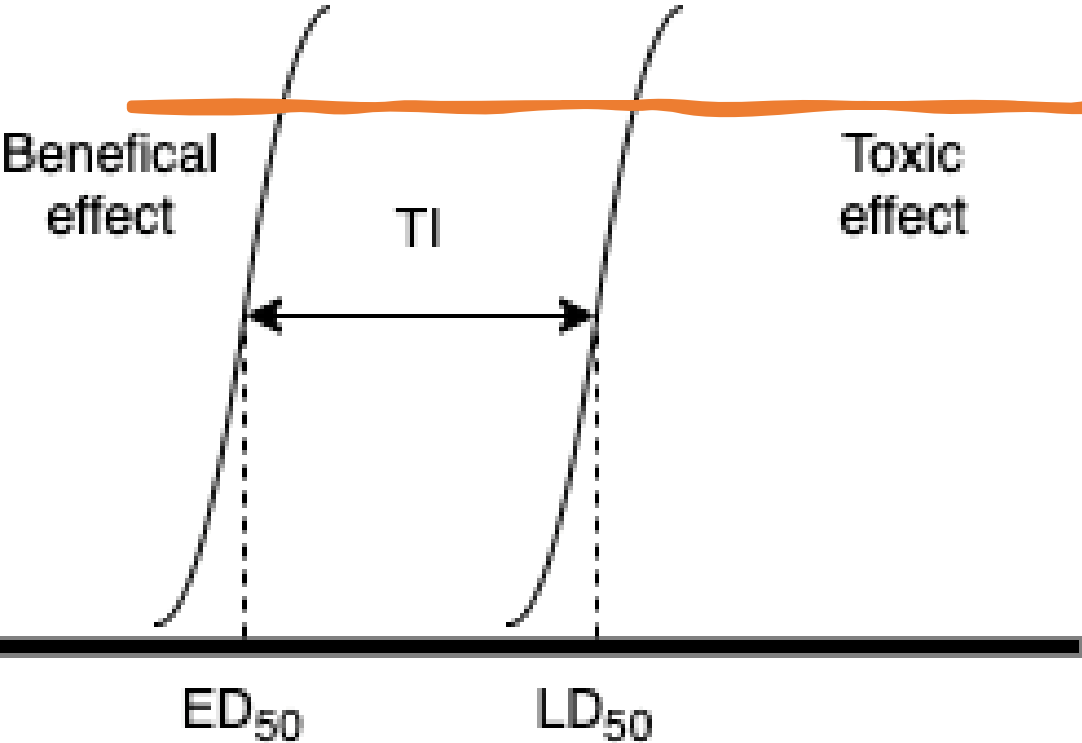
Treat the man not a disease

To make progress we need to reach into the past :

Each patient needs his ‘Doctor / Quarterback’

**Solutions: Give Physicians Back their time to truly practice medicine
Technology to alleviate other bureaucratic burdens, streamline processes**

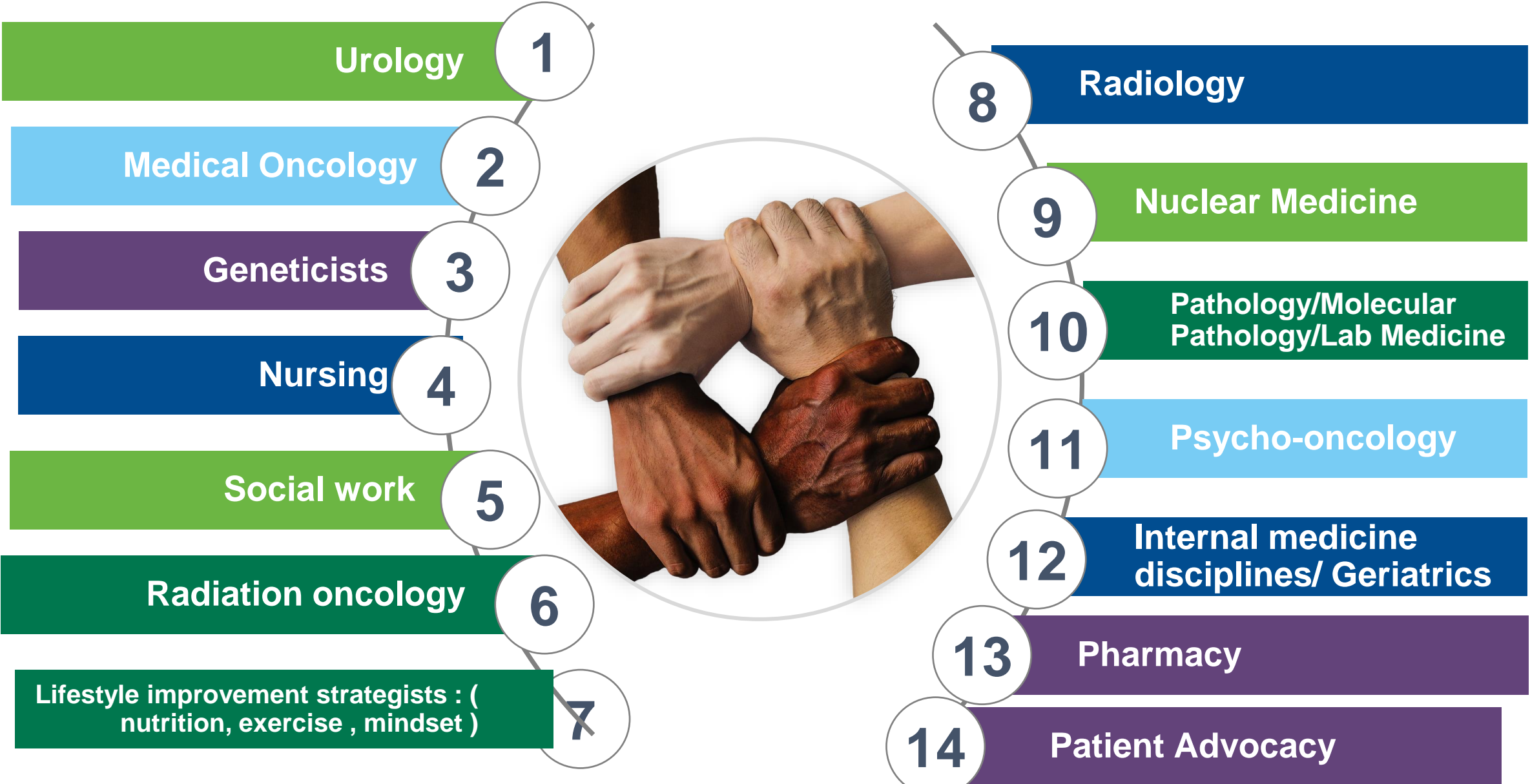
How to Maximize “Therapeutic Index” – Dose our “therapeutic strategy” towards the most Efficacious and least toxic for our specific patient



Therapeutic Index :
Efficacy / Safety

**Achieving the balance between
Overtreatment and
Undertreatment**

A HealthCare “Corporation” to treat each man



The Elephant in the room....

Does Precision Medicine Pursuit serve Population Health Objectives



What is our goal as a community : Individual Health or Public Health ?
Are we depriving Public Health of resources on our endeavor ?

The Vision : A Patient in charge of his health management

Patient-Centered Care





‘Science is not cold and unfeeling.

In scientific investigation one becomes emotionally contained in his problem.

Head, heart and hand – the three H’s of experimentation – all are involved in creativity in the medical sciences.

The combination enables us to recognize a solvable problem.’

Charles B. Huggins

Dogmas / Conventions/ Absolute Purism should not govern our research practice

Adaptation to an evolving therapeutic paradigm is of paramount importance

We are here to all work together and make progress