Health Technology Assessments of Radiotheranostic Practices in Cancer Care: Considerations and Challenges

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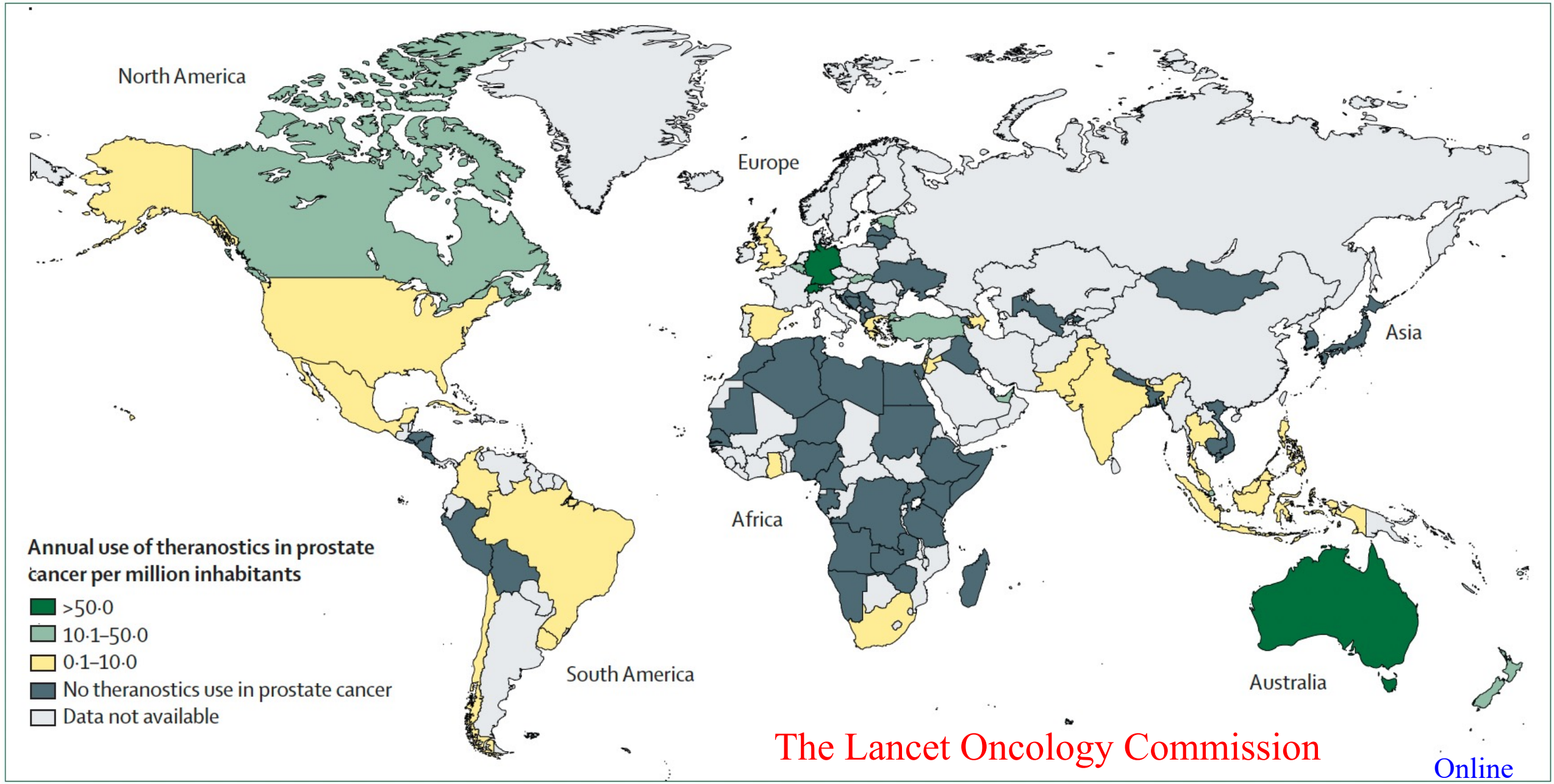
RadioTheranostics

- A.k.a: Targeted Molecular Radionuclide Therapy, Targeted Radiopharmaceutical Therapy, Nuclear Theranostics
- It is the pairing of radiolabeled diagnostic biomarkers with radiolabeled therapeutic agents that share a specific target in diseased cells or tissues
- May involve radionuclides as radiotracers or radiolabeled biological molecules, e.g. radiopharmaceuticals

Clinical Applications for Cancer Control

- Unconjugated Radionuclides
  - I-131, Y-90, Ra-223, Sm-153…
- Radionuclide-Conjugated Cancer-Specific Vectors
  - Peptides
  - Small Molecules (PSMA, I-131 MIBG)
  - Antibodies
  - Nanoparticles



The Lancet Oncology Commission

Online

Figure 10: Use of [^{177}Lu]PSMA and [^{225}Ac]PSMA in prostate cancer

https://doi.org/10.1016/S1470-2045(24)00407-8 30 Sept 2024

Health Technology Assessment (HTA)

- HTA is a multidisciplinary process that uses explicit methods to determine the value of a **health technology** at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system.

- A **health technology** is an intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program, or system.

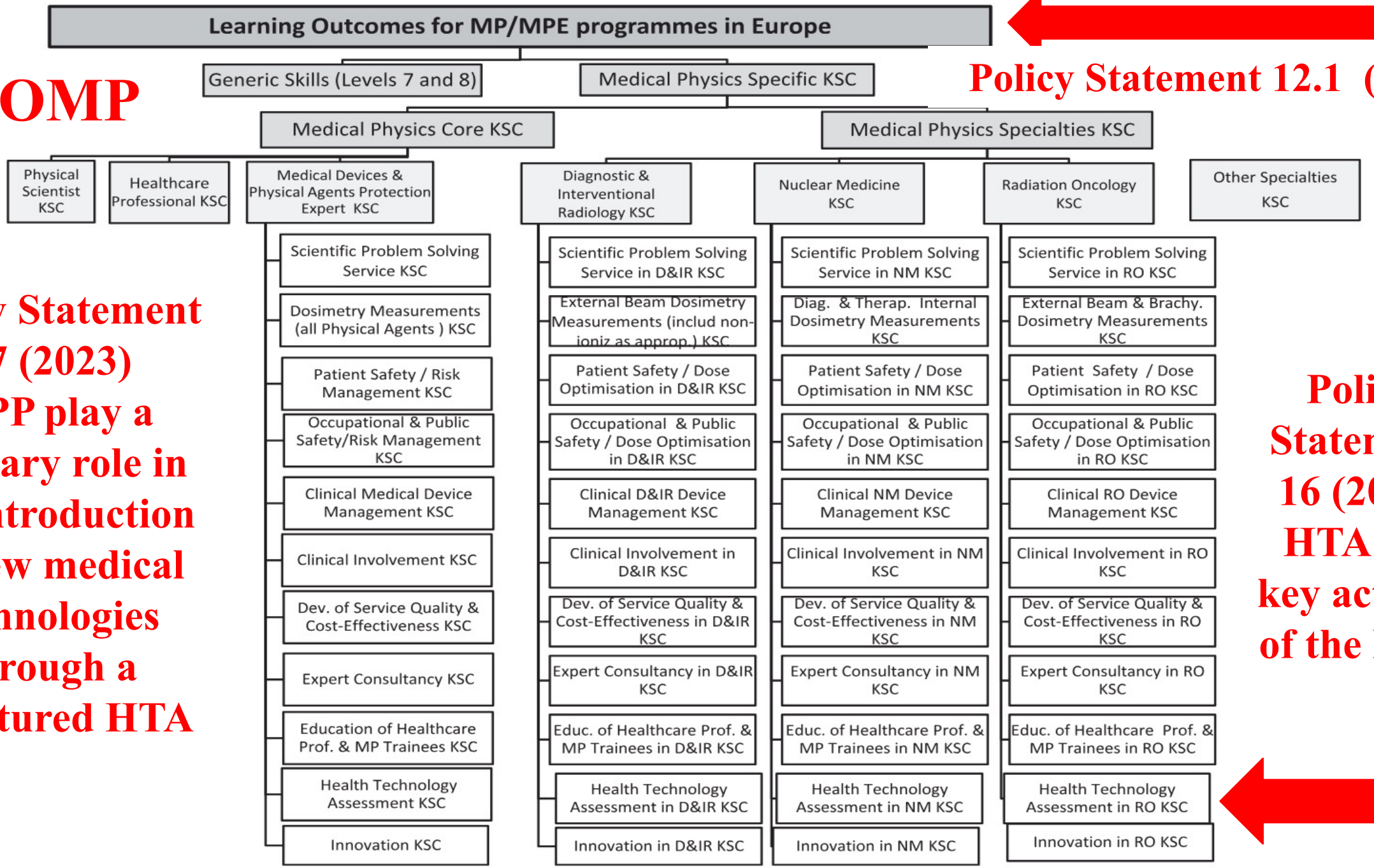
(O'Rourke *et al.*, 2020 – adopted by INAHTA and HTAi)

International Network of Agencies for Health Technology Assessment (INAHTA)

ACE * AETS * AETSA * Agenas * AHRQ * AHTA * AIHTA * ANS * AOTMiT * AP-HP * AQuAS * ASERNIP-S * AVALIA-T * C2H * CADTH * CDE * CONITEC * DHQI * DIGEMID * FinCCHTA * G-BA * GOG * HAD-Uruguay * HAS * HIQA * HIS * HTAIn * HTW * IACS * IECS * IETS * IHE * INEAS * INESSS * IQWiG * KCE * MaHTAS * NECA * NICE * NIHO * NIHR * NIPH * PHARMAC * OH * OSTEBA * RER * SK-NRCHD * SBU * SFOPH * UVT * ZIN * ZonMw

EFOMP

Policy Statement 12.1 (2014)



Policy Statement 17 (2023) MPP play a primary role in the introduction of new medical technologies through a structured HTA

Policy Statement 16 (2018) HTA is a key activity of the MPP

HTA Historical Dates

- World Health Assembly Resolution 67.23 (2014): Health intervention and technology assessment in support of universal health coverage
- The Regulation (EU) 2021/2282 on health technology assessment (HTAR) contributes to improving the availability for EU patients of innovative technologies in the area of health, such as medicines and certain medical devices. It ensures an efficient use of resources and strengthens the quality of HTA across the Union
- As of January 2025, the EU's Regulation on HTA enters full effect for new cancer medicines and advanced therapy medicinal products (ATMPs)

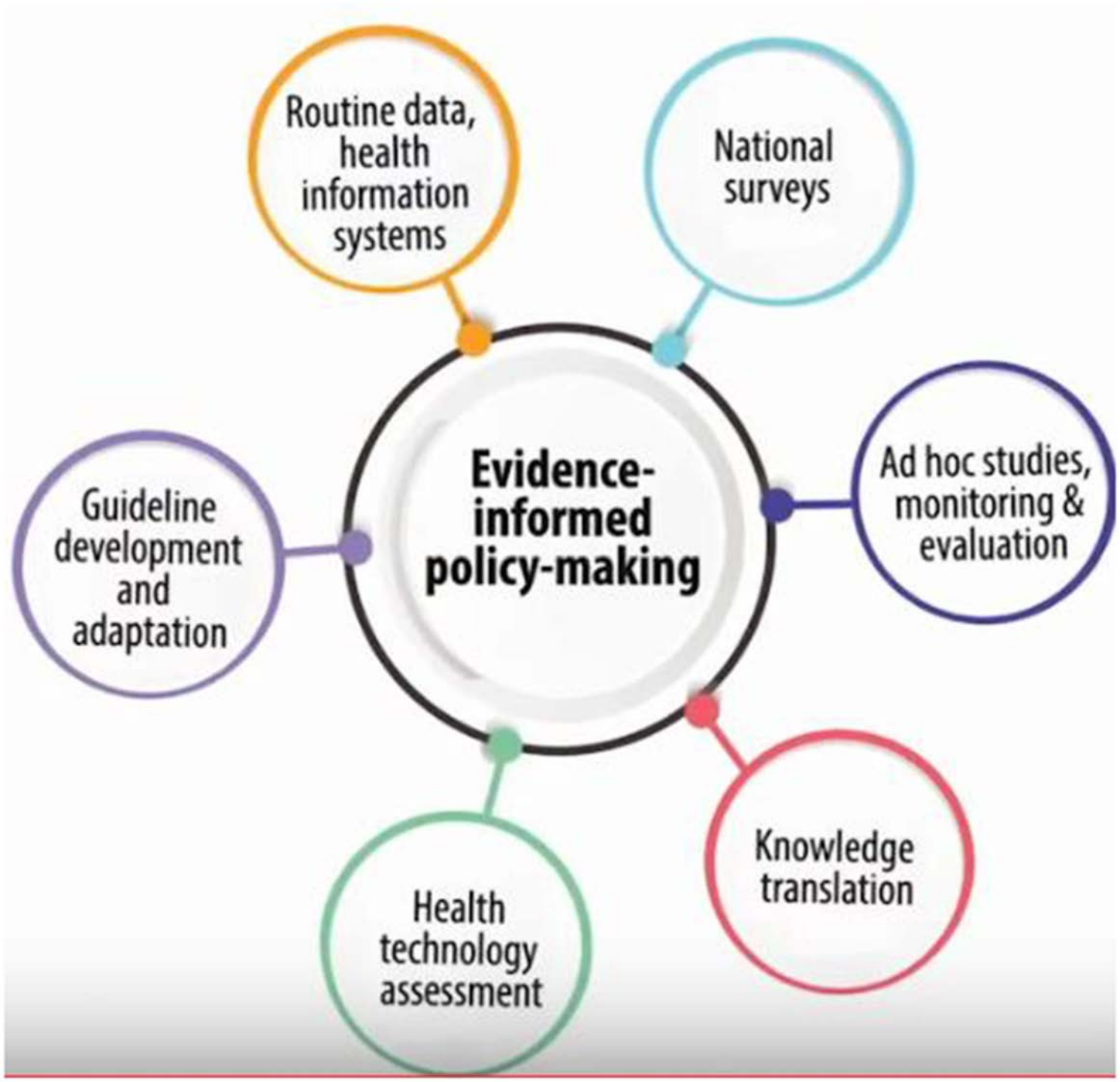
HTA Basic Concepts

Term	Definition
Safety	Effect > Risk
Efficacy	Effect in Ideal Conditions
Effectiveness	Effect in Practical Conditions
Analysis Cost-Effectiveness	Compares Costs of Equally Effective HT
Usefulness	Improved Quality of Life due to HT
Analysis Cost-Usefulness	Compares Costs with Survival adjusted by Quality of Life

HT Incorporation Process to Clinical Practice

- Development of "Product"
- Clinical Trial*
- Regulation Submission and Approval
- HTA Process and Final Recommendations
- Clinical Guidance

* Patient cohorts may not reflect the diverse population physicians see in clinics, particularly those with poor performance status, limited life expectancy, or significant comorbidities



Alkhaldi et al, 2022

Patient biological response

Scanner and activity calibration

Multiple time-point imaging

Quantitative imaging

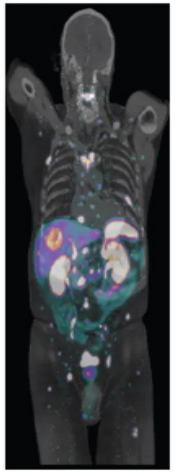
Registration and Segmentation

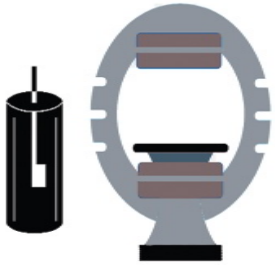
Time integrated Activity (TIA)

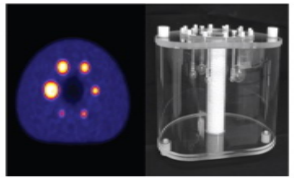
Dose calculation

Treatment Response

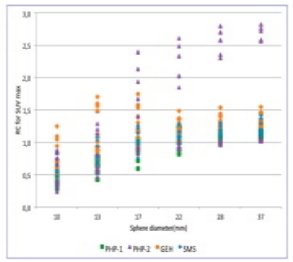
PET/CT



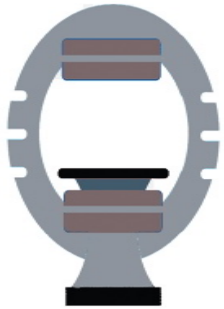




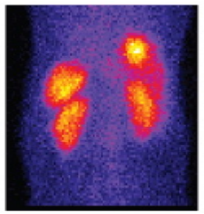
Reconstructions



SPECT/CT



T1



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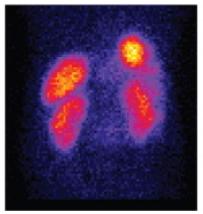

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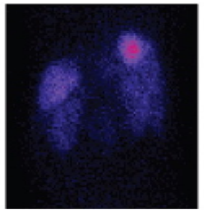
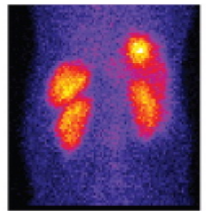
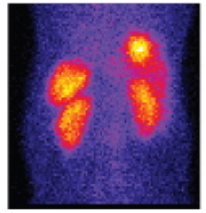


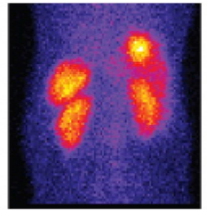
Scanner units

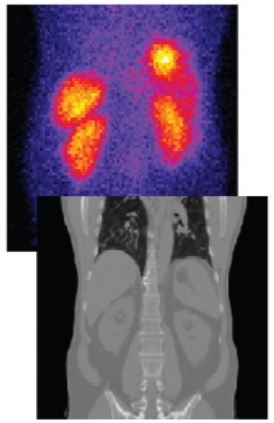


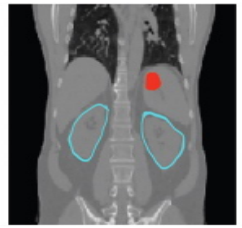
kBq/mL

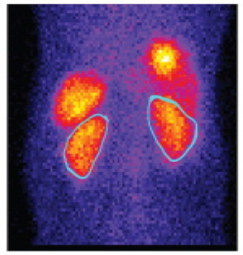


SUV

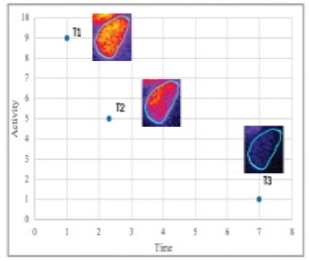




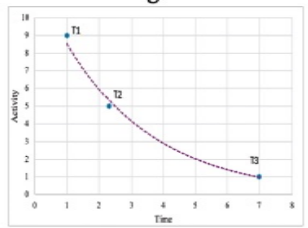




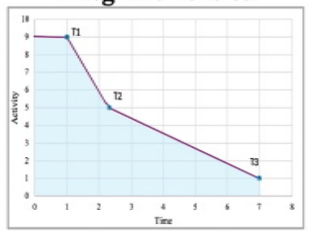
ROI Time Points

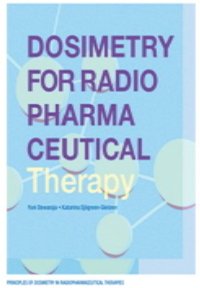


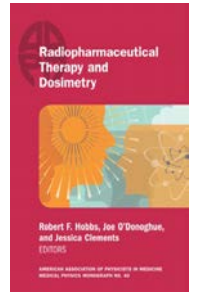
Fitting curve



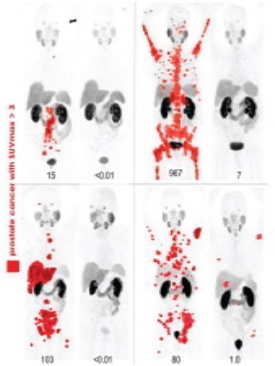
Integration choice

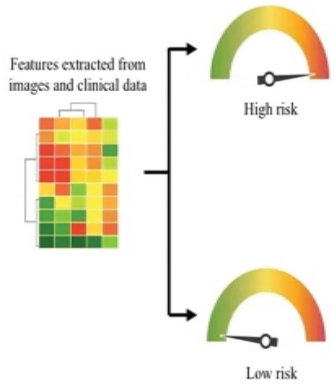






Biological differences

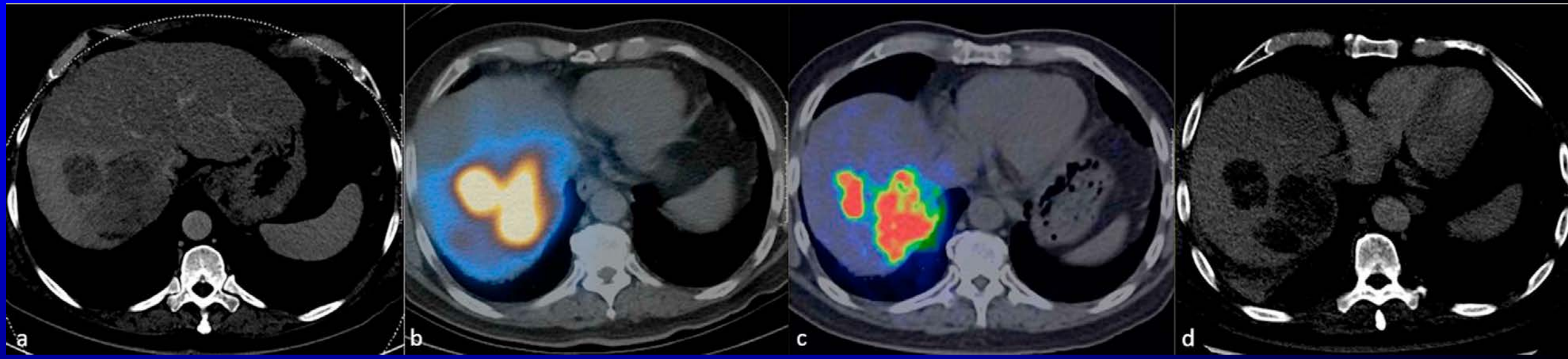




Radiotheranostics Workflow

(adapted from A. M. Marques da Silva, 2025)

^{90}Y Selective Internal Radiation Therapy (SIRT)



Pre-treatment CT

^{99m}Tc-MAA SPECT/CT

^{90}Y PET/CT

Post-Treatment CT

A.KT. Tong et al in C. Borrás & M. Stabin eds. Radiotheranostics: A Primer for Medical Physicists. CRC Press 2024

Radiotheranostics HTA Effectiveness Considerations

- The effectiveness of a therapeutic intervention is often assessed by either progression-free (PFS) or overall survival (OS), but this ignores the impact of disease on the patient and those within their social network
- Is overall survival a good effectiveness end point, when it may involve a lot of suffering by the patient? Patients may fear morbidities such as pain and xerostomia more than death!
- Pain can be
  - severe but episodic and relieved by opiate medication or
  - low-grade but continuous and resistant to analgesia
- Different patients may rate one or the other as more debilitating

Radiotheranostics HTA Quality of Life Considerations

- Effectiveness should include quality-adjusted life years (QALYs)
- A temporary but marked reduction in QOL can be acceptable to patients
  - if the treatment meaningfully prolongs their life
  - and even more so if they are cured
- However, if a treatment is not curative, there is a tipping point between the prolongation of life and the severity of symptoms related to the disease itself or to the enduring complications of the treatment

Patient and Social Aspects
HTA Core Model contains 8 HTA Assessments

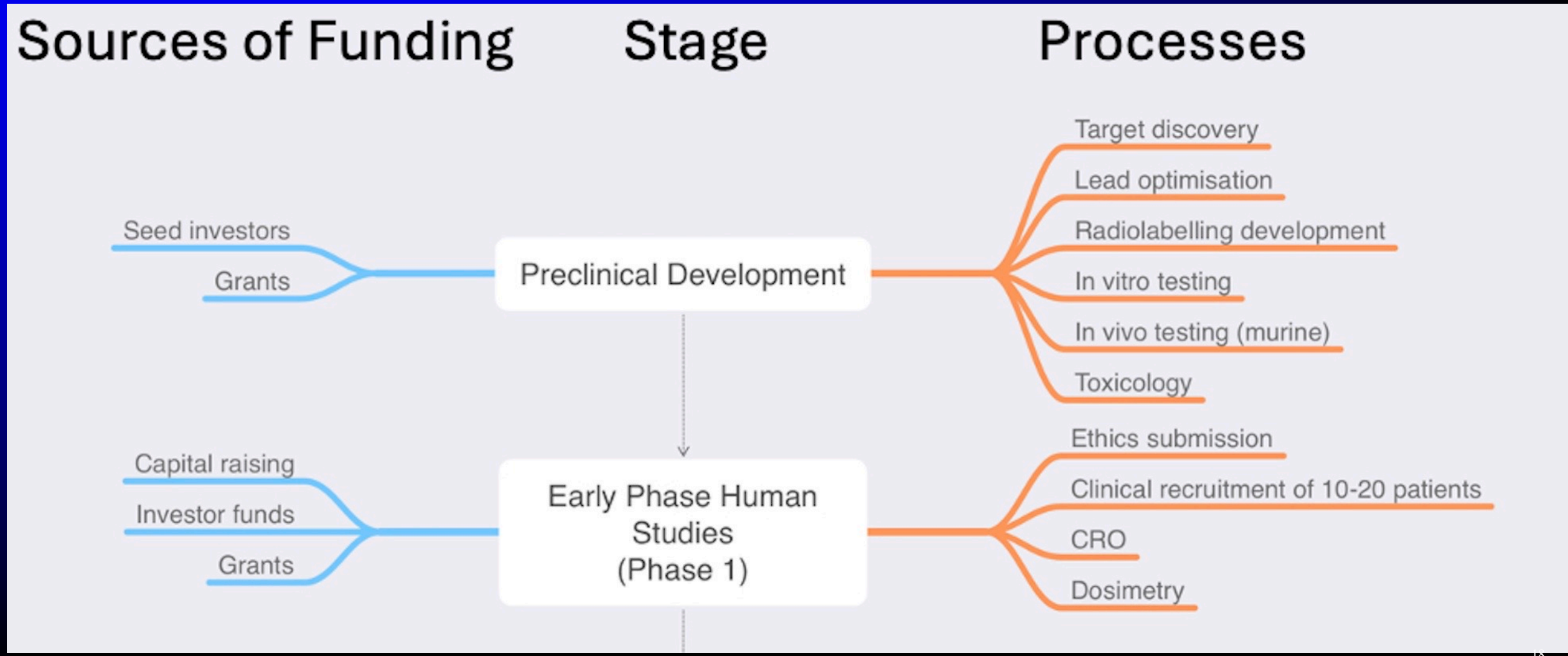
Topic	Assessment elements
Patients' perspectives	What are the experiences of living with the condition?
	What expectations and wishes do patients have regarding the technology and what do they expect to gain from it?
	How do patients perceive the technology under assessment?
	What is the burden on caregivers?
Social group's aspects	Are there groups of patients who currently don't have good access to available therapies?
	Are there factors that could prevent a group or person from gaining access to the technology?
Communication aspects	How are treatment choices explained to patients?
	What specific issues may need to be communicated to patients to improve adherence?

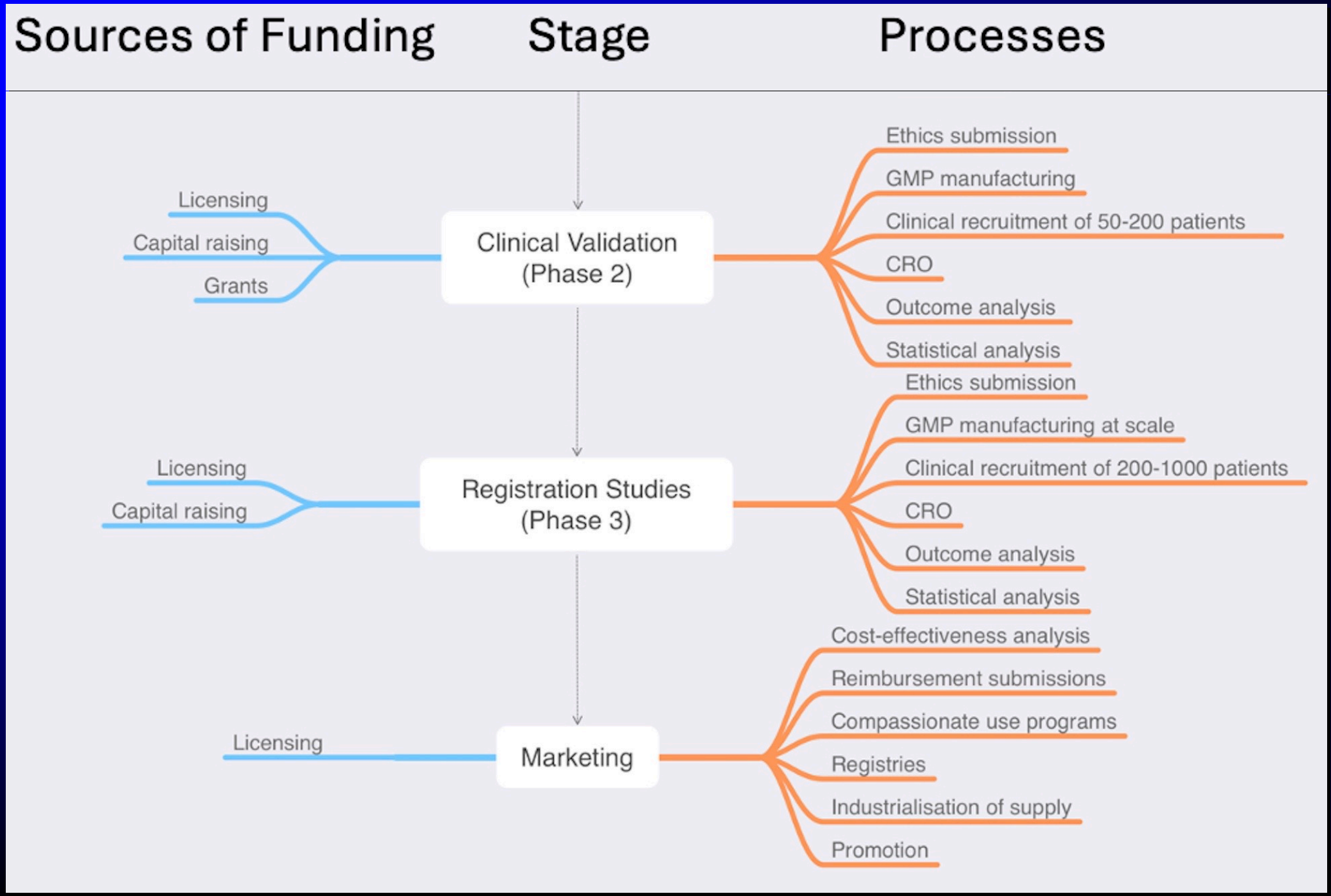
EUnetHTA, 2016

Radiotheranostics HTA Cost Considerations

- TRNTs are currently seldom curative and often treat diseases that have already failed multiple lines of treatment, which themselves can irreparably damage normal tissues - are treatments for long-term toxicities included in the costs?
- Longer survival with marked debility may be more expensive than premature death due to ongoing medical and hospice care costs
- Costs are not only medical expenses, but should also include the extra financial burdens of living with the disease for the patient and their family and the loss of income from premature death
- The time spent by caregivers has a direct impact on their own QOL and impacts productivity if they need to take time away from work

The Funding, Development, and Processes of Theranostic Agent Development (R. Hicks, 2025)




Sources of Funding
Stage
Processes
Licensing
Capital raising
Grants
Clinical Validation (Phase 2)
Ethics submission
GMP manufacturing
Clinical recruitment of 50-200 patients
CRO
Outcome analysis
Statistical analysis
Licensing
Capital raising
Registration Studies (Phase 3)
Ethics submission
GMP manufacturing at scale
Clinical recruitment of 200-1000 patients
CRO
Outcome analysis
Statistical analysis
Licensing
Marketing
Cost-effectiveness analysis
Reimbursement submissions
Compassionate use programs
Registries
Industrialisation of supply
Promotion

Radiotheranostics Costs

- Radionuclide and Radiopharmaceutical Development
- Commercialization
- Regulatory Approval of Novel Diagnostic and Therapeutic Radiotheranostic Agents
- Clinical Trials
- Clinical Implementation
  - Facility, Equipment and Supplies
  - Staff
  - Procedures

Reimbursement?

Health System Models

- Bismarck model
  - Named for Prussian Chancellor – private providers and private payers
- Beveridge model
  - Named after a British economist favoring government provided service, which is similar to other infrastructure services
- National Health Insurance model
  - National payment system is government run, but providers are private
- Out-of-pocket personal payment model
  - Individuals purchase care on the open market and pay ‘cash’

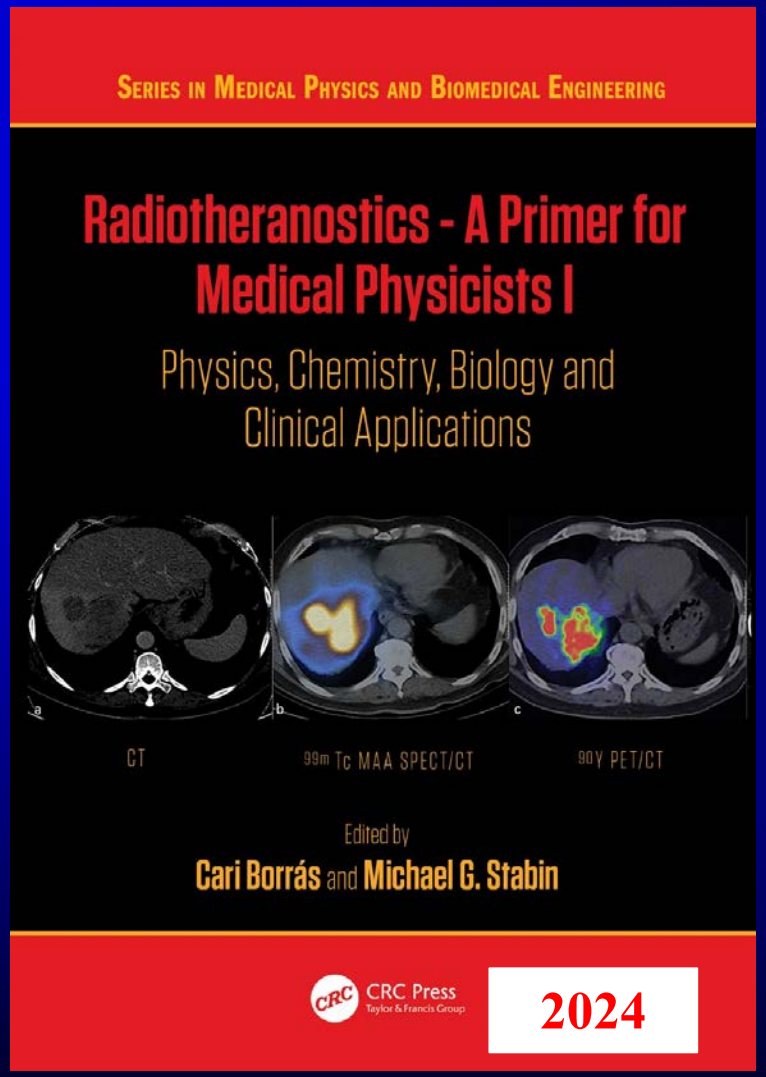
HTA Ethical Issues re Equity and Access – Fair Distribution across Populations and Countries

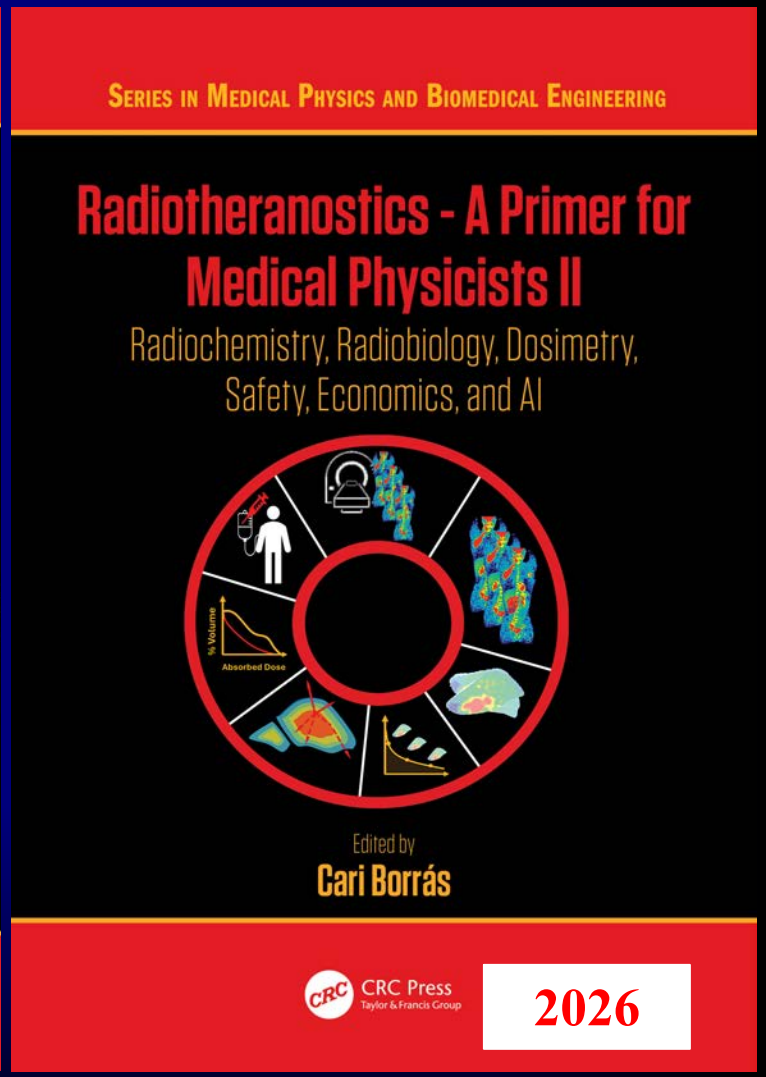
- Equitable access to healthcare may require rationing of resources. As a consequence, individual patients may be denied optimal care

- The larger the population of eligible patients, the greater the degree to which costs can be amortized over time. Such considerations work in favor of common cancers, like prostate cancer, but against rare malignancies, like NET

Acknowledgement

Thanks to Rodney J. Hicks, AM, MB BS (Hons), MD, FRACP, FICIS, FAHMS. University of Melbourne, St Vincent's Hospital, Fitzroy, Victoria, Australia, on whose chapter "The Economics of Theranostics" in *Radiotheranostics: A Primer for Medical Physicists II* is mainly based this presentation, and who inspired the organization of this Special Symposium





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