Integrating Body Surface Area, Renal Function, and Pharmacokinetic Parameters

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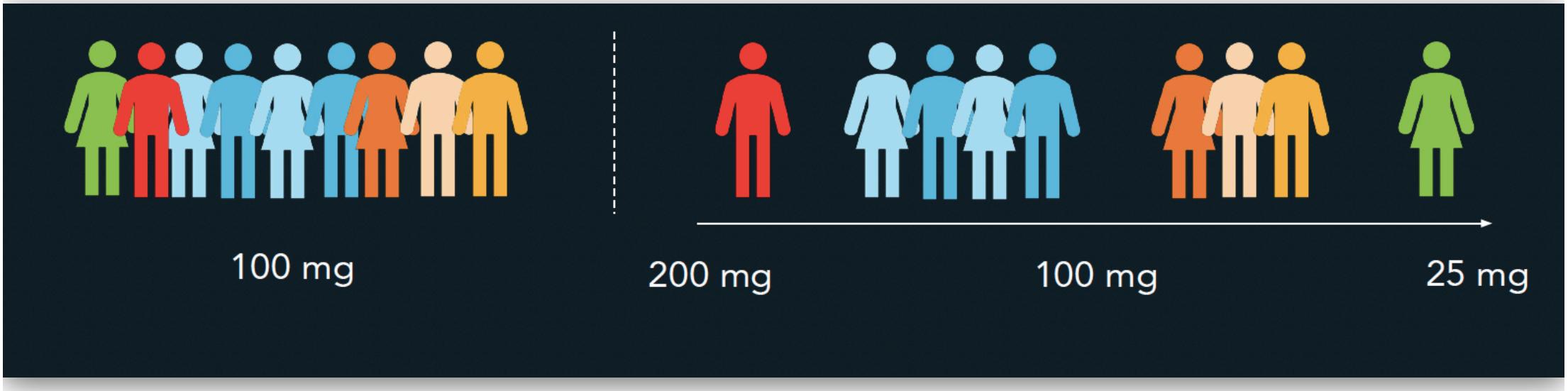
Disampaikan pada acara:
PIT HISFARSI
Pekan Baru, 26 Juni 2026

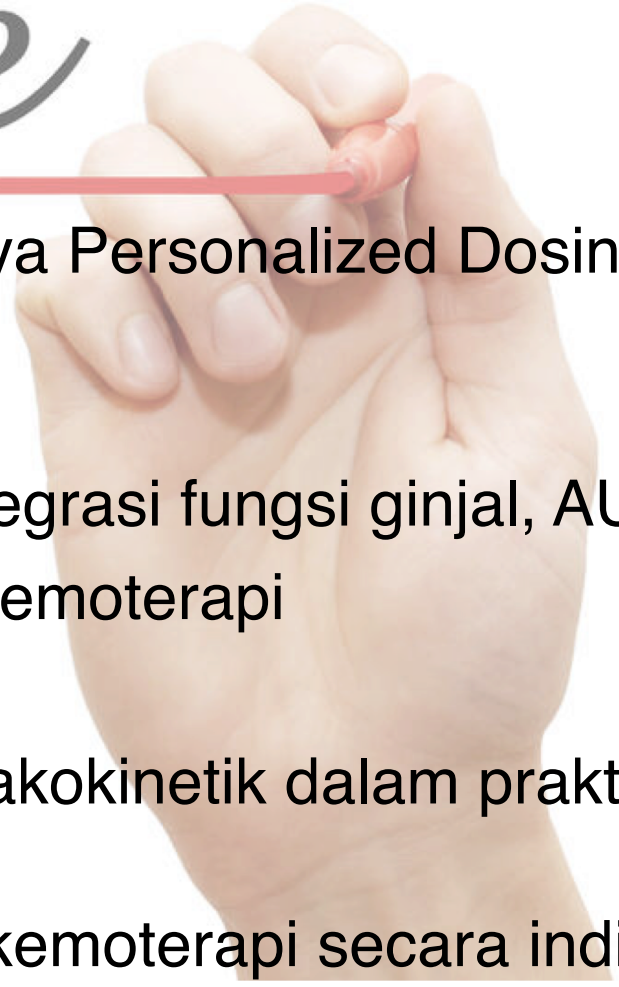
Personalized Chemotherapy Dosing

Beyond “One Dose Fits All”



Precision in oncology is not only about choosing the right drug — it is about delivering the right exposure.

Outline



1. Pendahuluan: Pentingnya Personalized Dosing di Onkologi
2. Dosis berbasis BSA, Integrasi fungsi ginjal, AUC dalam pemilihan dosis kemoterapi
3. Penerapan prinsip farmakokinetik dalam praktik onkologi
   - ✓Optimalisasi regimen kemoterapi secara individual

Mengapa PERSONALIZED DOSING Penting?

Chemotherapy → Narrow Therapeutic Index

Underexposure	Optimal Exposure	Overexposure
Therapeutic failure	Maximum efficacy	Severe toxicity
Resestance	Disease control	Hospitalization
Relaps	Better survival	Treatment discontinuation

Faktanya.....,

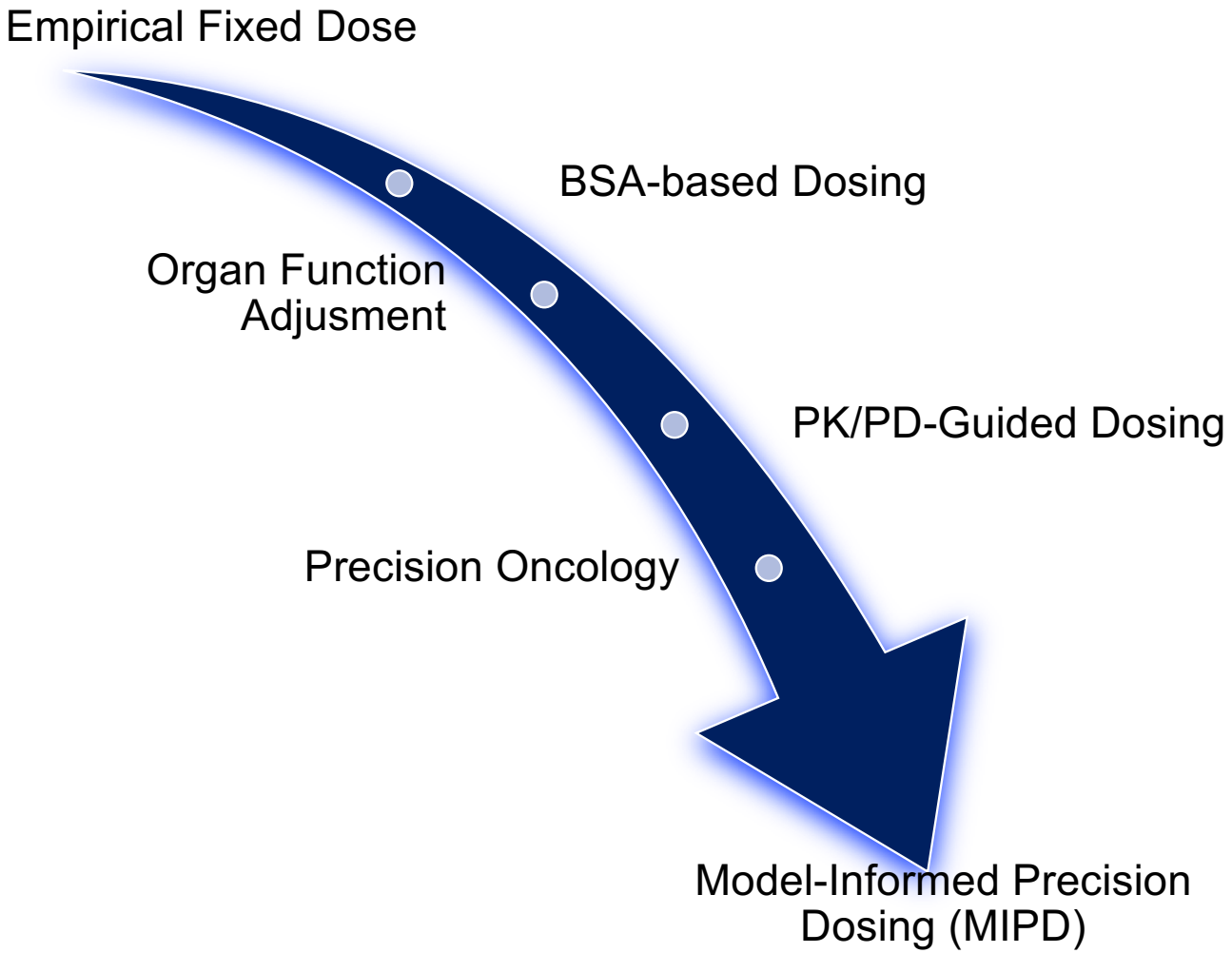
Dosis **sama**, Apakah.....

- ✓ Konsentrasi obat dalam darah
- ✓ Profil toksisitas
- ✓ Outcome

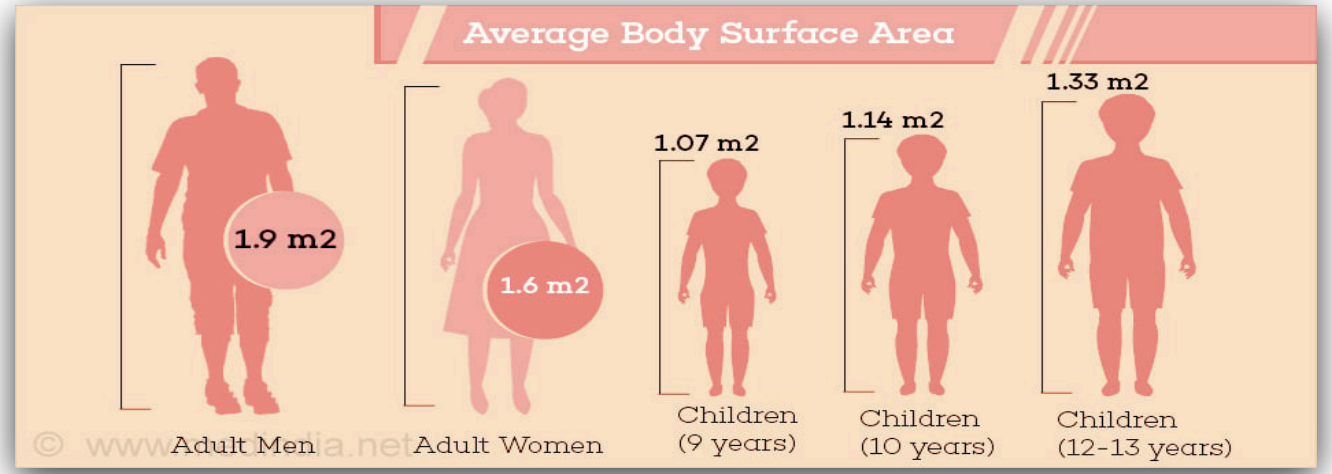
SAMA ?

- ❑Klirens obat
- ❑Fungsi organ
- ❑Farmakogenomik

EVOLUTION OF CHEMOTHERAPY DOSING



Body Surface Area



Formula BSA

Mosteller Formula: $\sqrt{(\text{Height} \times \text{Weight}/3600)}$

DuBois Formula: $0.007184 \times \text{Height(cm)}^{0.725} \times \text{Weight(kg)}^{0.425}$

Haycock Formula: $0.024265 \times \text{Height}^{0.3964} \times \text{Weight}^{0.5378}$

Gehan & George: $0.0235 \times \text{Height}^{0.42246} \times \text{Weight}^{0.51456}$

Mengapa BSA menjadi Standard?

- ✓Korelasi antara BSA dg karakteristik tertentu pasien :
  - ❑laju filtrasi glomerulus (GFR),
  - ❑volume darah
  - ❑laju metabolisme basal (BMR)

- ✓Dosis awal kemoterapi pada studi fase I awalnya ditentukan berdasarkan berat badan atau BSA dari model hewan.

Contoh Perhitungan

CASE 1

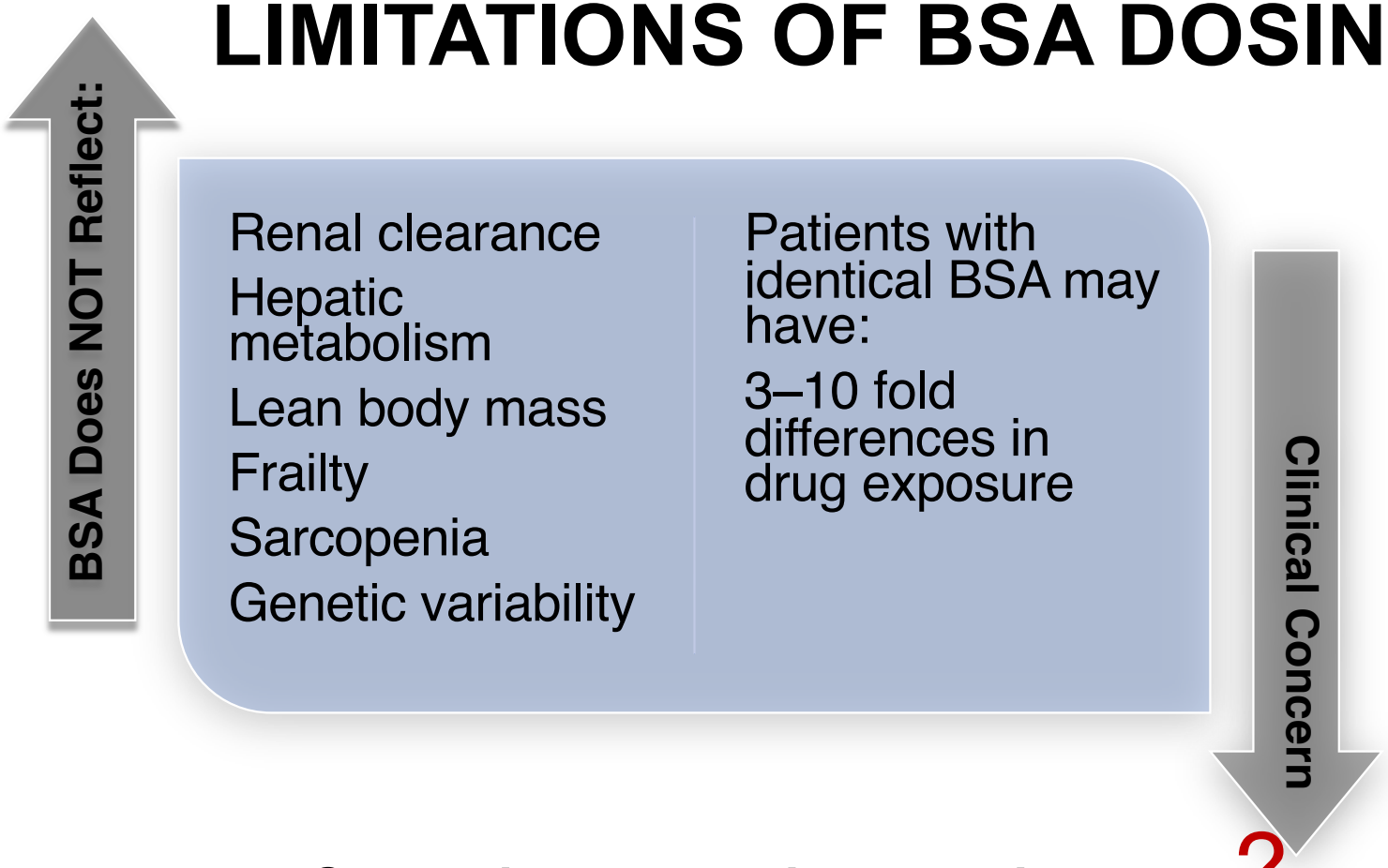
Mr Z, colorectal carcinoma , chemotherapy protocol XELOX.

Height= 168 cm; weight 57 kg.

XELOX	
Oxaliplatin 130 mg/m^2	D1
Capecitabine 1000 mg/m^2 bid po	D1-14

Step 1. Hitung BSA
Step 2. Regimen standard
Step 3. Hitung dosis

LIMITATIONS OF BSA DOSING



Apakah BSA masih relevan di onkologi modern ?

RENAL FUNCTION IN ONCOLOGY

Many anticancer drugs are renally eliminated:

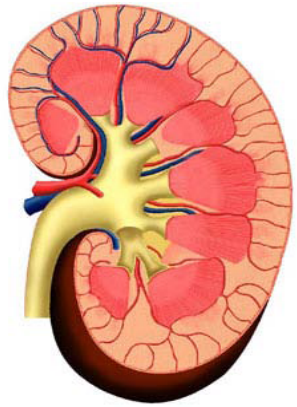
Drug	Clinical Concern
Carboplatin	Myelosuppression
Cisplatin	Nephrotoxicity
Methotrexate	Delayed elimination
Capecitabine	Toxic metabolite accumulation

GFR, ESTIMATION OF RENAL FUNCTION

Important information prior to starting chemotherapy

Glomerular filtration rate (GFR→ renal function

Creatinin Clearance, Serum Creatinin



Penilaian Fungsi Ginjal

Creatinine Clearance (CrCl)

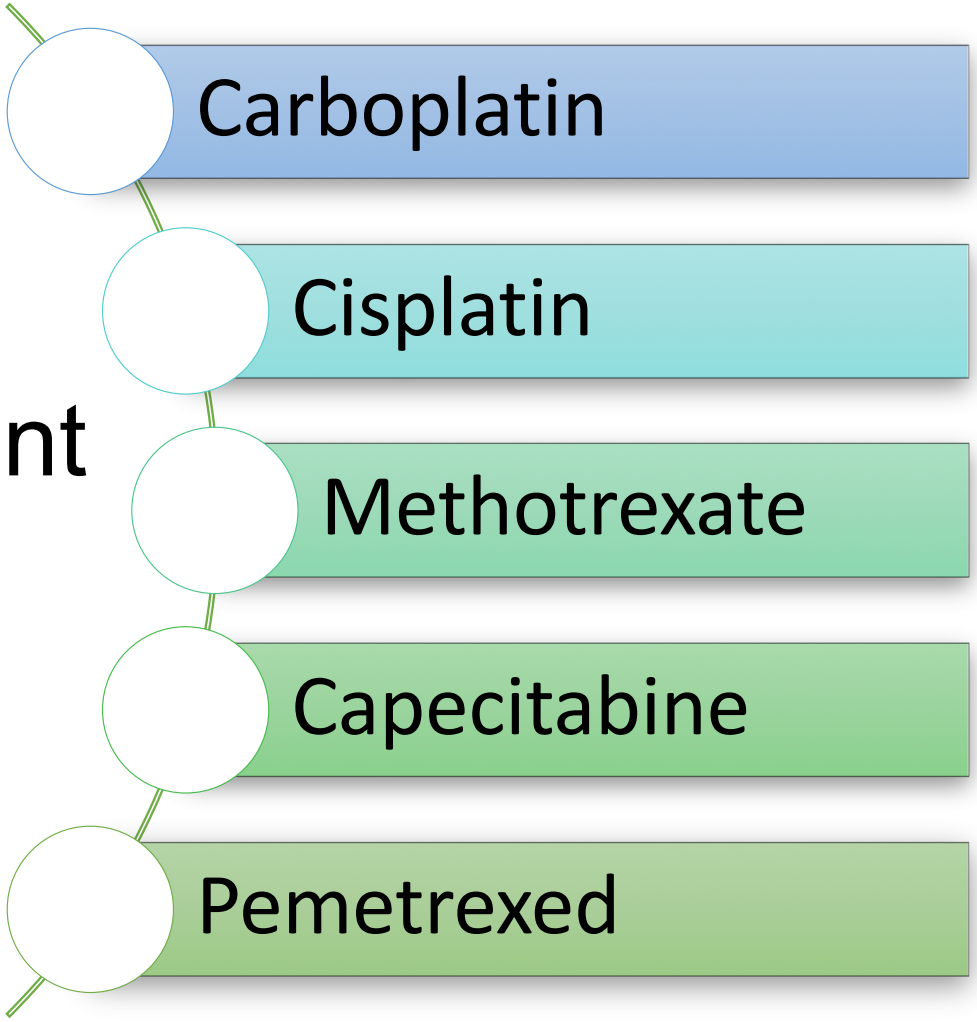
eGFR (CKD-EPI / MDRD)

Cockcroft-Gault equation

Cachexia and low serum creatinine pitfalls

METHOD	FORMULA	
Cockroft and Gault (ml/min)	$\frac{(140 - \text{age}) \times \text{Wt (kg)}}{72 \times \text{SCr (mg/dl)}}$	Female = malex0.85
MDRD	$3277 \times (\text{Cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \times \text{sex})$	Male =0 Female =1

Renal Dose Adjustment



MEDICAL ONCOLOGY

Chemotherapy Dose Adjustment in Renal Dysfunction for Adults*[1,2]

	CrCL(ml/min)				Comments
	90-50	50-30	30-10	<10	
Bleomycin[3]	100%	75%		50%	For package insert adjustment: See LEXI recommendation
Capecitabine	100%	75%	Omit	Omit	
Carboplatin	AUC-based dose determined by the Calvert formula = AUC X (CrCl +25), Maximum GFR 125ml/min				
Carmustine	100%	80% CrCL 60-46 75% CrCl 45-31	Consider alternative		Recommend dose reduction, no guideline
Cisplatin	100%	75%		50%	Other: administer 75% CrCl 60-46, 50% CrCl 45-30, alternative <30ml/min Repeat courses if Scr <1.5mg/dl (133µmol/L) and/or BUN <25mg/dl
	TCF regimen: 50% if CrCl 60-40, omit if CrCl <40ml/min				
Cyclophosphamide	100%	75%		50%	Other: administer 75% dose when CrCl <10ml/min Controversial, adjustment is not recommended by several authors
Cytarabine	100%	60% CrCl 60-45 50% CrCl 45-30	Consider alternative		This recommendation for High dose only
Dacarbazine		80-70% CrCl 60-30			
Daunorubicin			50%		administer 50% when Scr>3mg/dl (265mmol/L)
Epirubicin					Adjust if Scr >5mg/dl (445mmol/L)
Etoposide	100%	75%		50%	Recommend dose reduction, no guideline
Fludarabin	80% CrCl 70-30 (USA) 50% CrCl 70-30 (UK)		Avoid	Avoid	Different product recommendation between US and UK Oral: administer 80% if CrCl 30-70mL/min: 50% if <30 mL/minute
Fluorouracil		50% CrCl <50ml/min			Recommend dose reduction, no guideline
Gemcitabine					Discontinue if severe renal toxicity or HUS, no guideline
Hydroxyurea	100%	50%		20%	Recommend dose reduction, no guideline
Ifosfamide	100%			75%	Recommend dose reduction, no guideline
Lomustin	100%	75%		50-25%	Recommend dose reduction, no guideline
Melphalan	100%	75%		50%	Other: 50% of if BUN >30mg/dl (10.7mmol/L), or Scr <1.5mg/dl (133µmol/L)
Methotrexate	100%	50%		Omit	Recommend dose reduction, no guideline
Mitomycin	100%			75%	other: do not give if Scr >1.7mg/dl (150µmol/L)
Oxaliplatin	100%		Omit CrCL <20ml/min (USA), <30ml/min (Canadian)		
Pemetrexed		Hold if CrCl ≥45ml/min			
Temozolomide					No data in sever renal dysfunction

* the percentage is reflecting % of dose administered

HUS hemolytic uremic syndrome

Fatma Maraiki, Pharm D, BCOP 03/2011

Reference:

1. Solimando DA. Drug Information Handbook Oncology. 9th ed. Hudson (OH):Lexi-Comp; 2011

Comparing Different GFR Formula

	GFR formula producing least bias and most precise estimates	GFR formula producing most bias and least precise estimates
GFR (ml/min)		
< 50	Jelliffe	Wright
50–100	MDRD/Cockcroft–Gault	Jelliffe/Wright
>100	Cockcroft–Gault	MDRD/Jelliffe
Age (years)		
< 40	Jelliffe	Wright
40 to < 70	Cockcroft–Gault	Jelliffe
70 +	Wright	Jelliffe
BMI		
< 18.5	Cockcroft–Gault	Wright/MDRD
18.5 to < 25	MDRD/Cockcroft–Gault	Wright
25 to < 30	Cockcroft–Gault	MDRD/Jelliffe
30 +	Wright	MDRD/Jelliffe

Ainsworth et. al. Annals of Oncology 2012;23: 1845–53

Menghitung GFR

Ny. Wati 37 tahun, BB = 65 kg, TB = 170 cm

Hasil pemeriksaan lab

JENIS PEMERIKSAAN	TGL PERIKSA 11 April 2009	NILAI NORMAL
Ureum	21.1 mg/dl	10 – 50 mg/dl
Kreatinin	1,27 mg/dl	0.6 – 1.1 mg/dl
Asam urat	4 mg/dl	2.3 – 6.1 mg/dl

- Estimated GFR!

$$GFR = \frac{(140 - age) \times Wt\ (kg)}{72 \times SCr\ (mg/dl)} \times 0.85$$

$$= \frac{(140 - 37) \times 65}{72 \times 1.27} \times 0.85$$

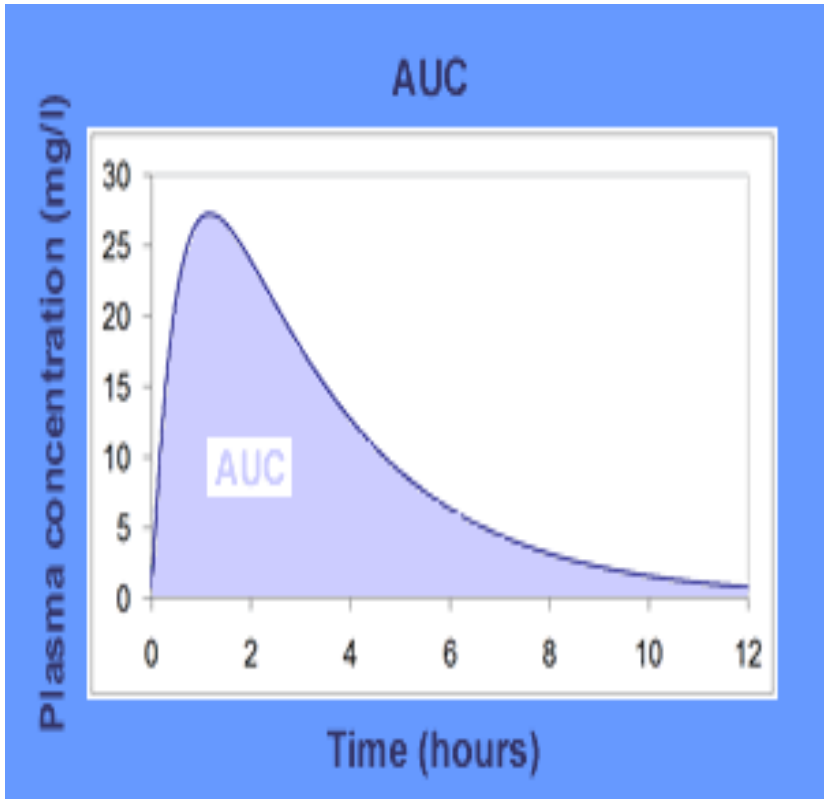
$$= 62.23\ ml/menit$$

Tahap Penyakit Ginjal Kronis

Stadium	GFR	Gambaran
1	≥90	Normal
2	60-89	Fungsi ginjal sedikit berkurang
3	30-59	Penurunan fungsi ginjal sedang, ± bukti kerusakan lain
4	15-29	Penurunan fungsi ginjal berat
5	<15	Kegagalan ginjal

AUC-BASED DOSING, CARBOPLATIN

1. • Myelotoxicity and clinical efficacy of carboplatin correlate with the clearence of the drug , which is correlated to the glomerular filtration rate (GFR), **renal function**
2. • **AUC** is used to determine carboplatin doses
3. • **AUC** is the area under curve when the concentration of a drug in plasma is plotted against time.
4. • Target **AUC** → 4 to 7 mg/ml/minute



Dose = AUC . Clcr

Calvert Formula

Total Carboplatin Dose (mg) = (target AUC) X (GFR + 25)

AUC-BASED DOSING, CARBOPLATIN

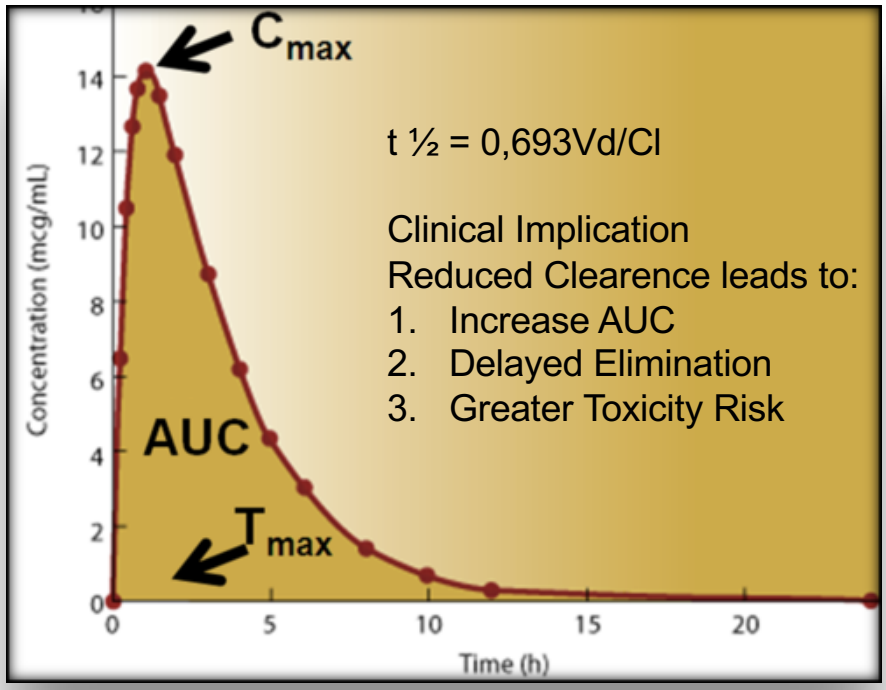
Calvert Formula

Total Carboplatin Dose (mg) = (target AUC) X (GFR + 25)

- Ny AD 53 tahun, ca. Ovarium, mendapatkan kemoterapi carboplatin, BB = 50 kg, TB = 160 cm, GFR = 70 ml/min, target AUC 6. Hitung dosis carboplatin !

PHARMACOKINETICS (PK) IN ONCOLOGY

Parameter	Clinical Meaning
• Clearance (Cl) • Volume distribusi (Vd) • t1/2 • AUC	• Eliminasi obat • Distribusi jaringan • Durasi • Total Exposire

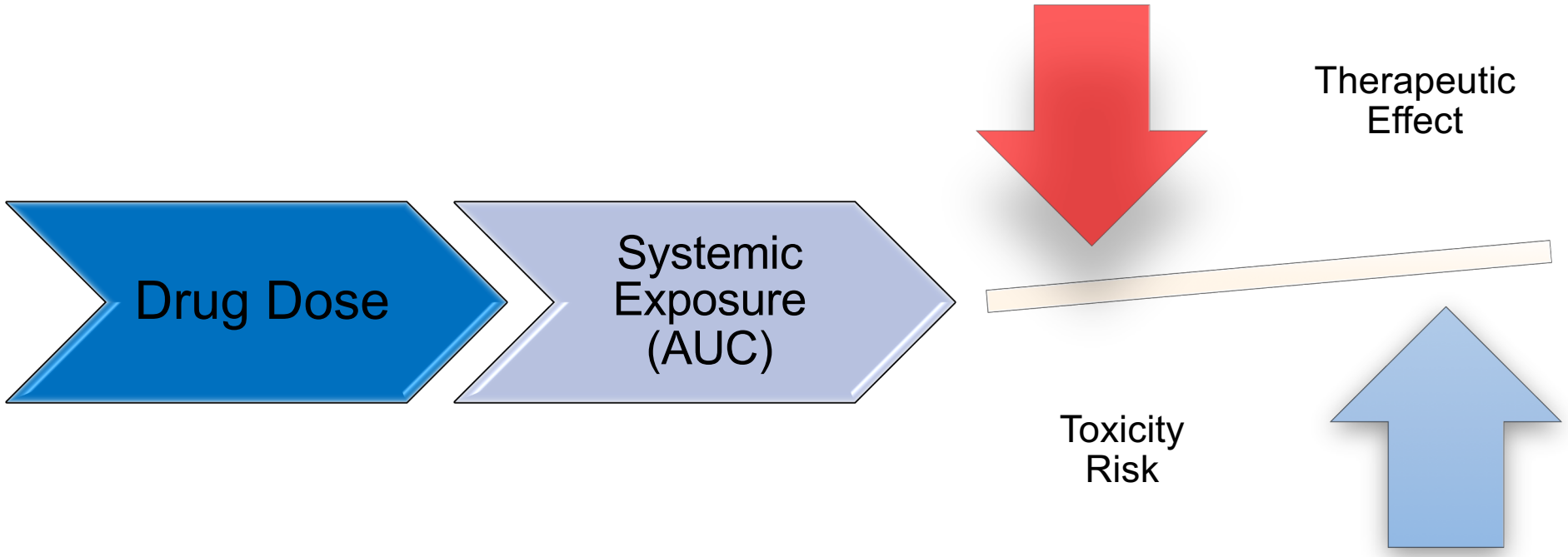


t ½ = 0,693Vd/Cl

Clinical Implication
Reduced Clearence leads to:

1. Increase AUC
2. Delayed Elimination
3. Greater Toxicity Risk

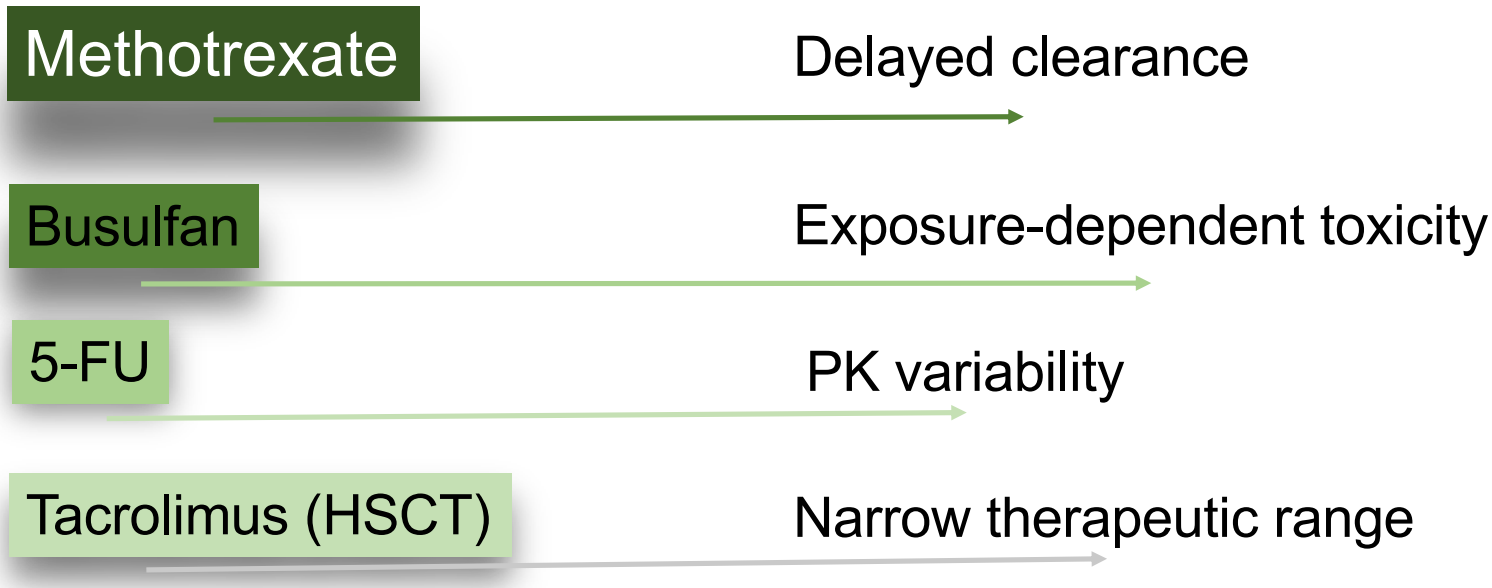
EXPOSURE-TOXICITY RELATIONSHIP



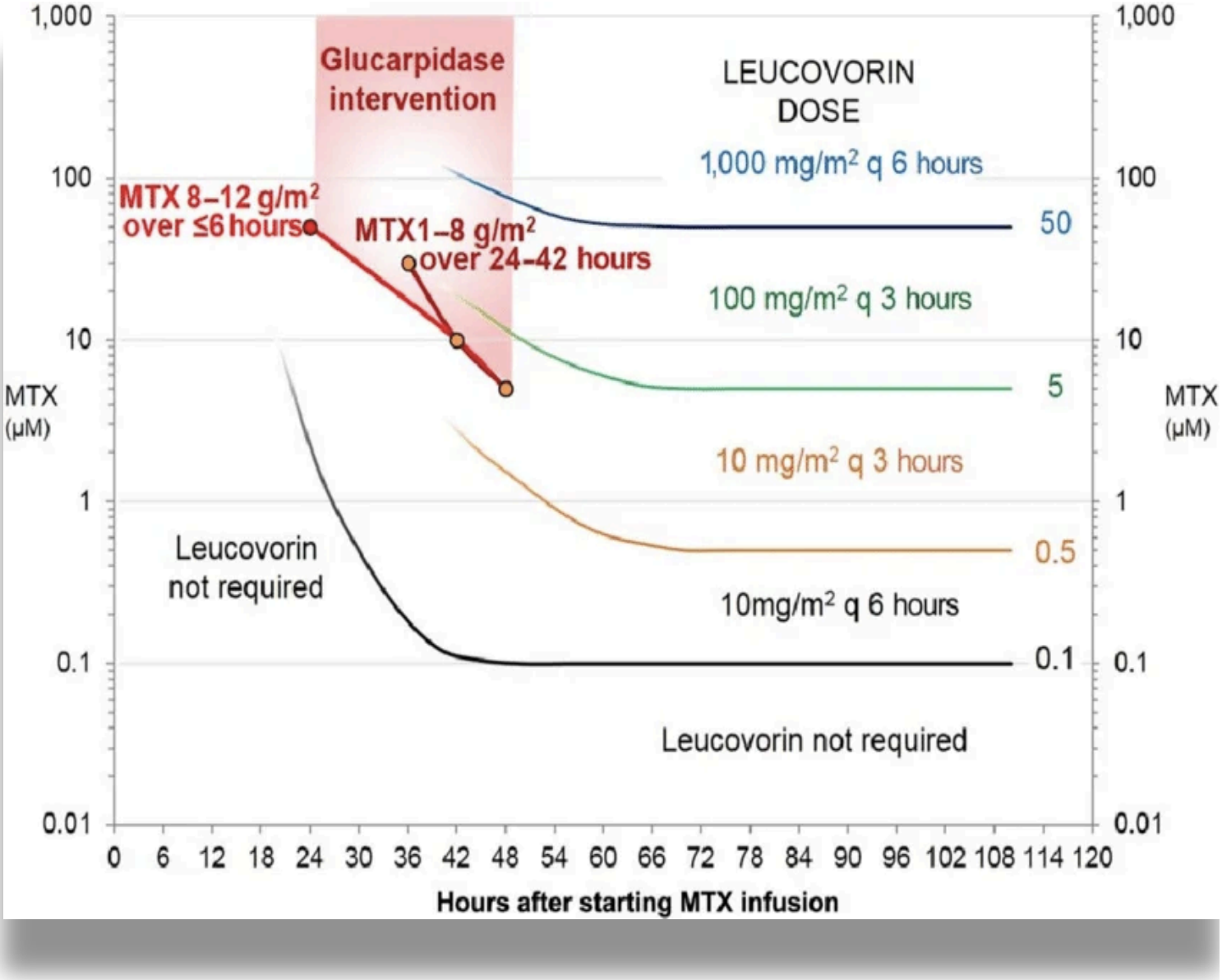
THERAPEUTIC DRUG MONITORING (TDM)

TDM-Supported Oncology Drugs

Why Monitor?



MTX, Kapan mulai Leucovorin Rescue?



PRECISION DOSING IN SPECIAL POPULATIONS

Obesitas

- ASCO recommends full weight-based dosing for curative intent
- Underdosing worsens survival

Elderly

Challenges:

- Reduced GFR
- Frailty
- Polypharmacy
- Sarcopenia

Pediatri

Challenges:

- Organ maturation
- Enzyme expression
- Age dependent-clearence
- Toxicity profile berbeda dg dewasa

Lainnya

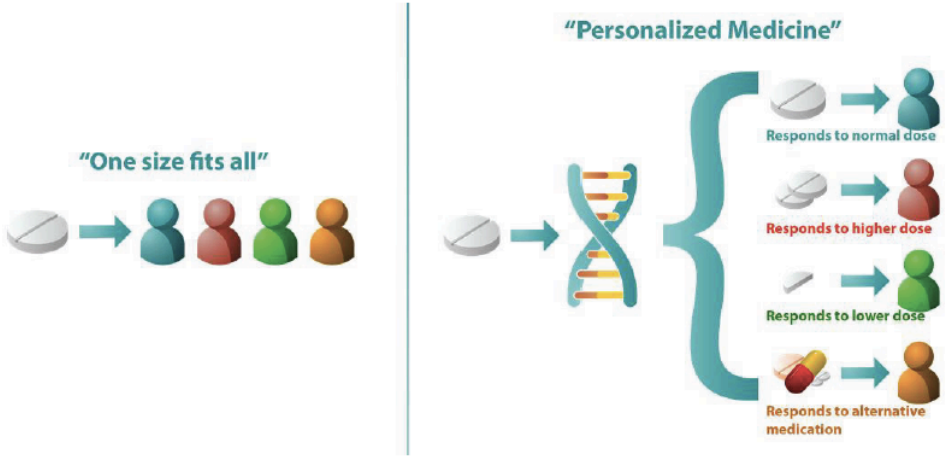
Hypoalbuminemia

Increases free fraction of:

- Paclitaxel
- Etoposide
- Methotrexate

PHARMACOGENOMICS

The Future of Precision Oncology



Gen	Nama Obat	Outcome
DPYD	5-FU	Severe toxicity
UGT1A!	Irinotecan	Neutropenia
TPMP	Thiopurine	Myelosupresi


Modern Approach to Oncology Dosing
✓Fungsi organ
✓Farmakokonetik
✓Farmakogenomik
✓Judgement Klinis
Precision Chemotherapy Dosing

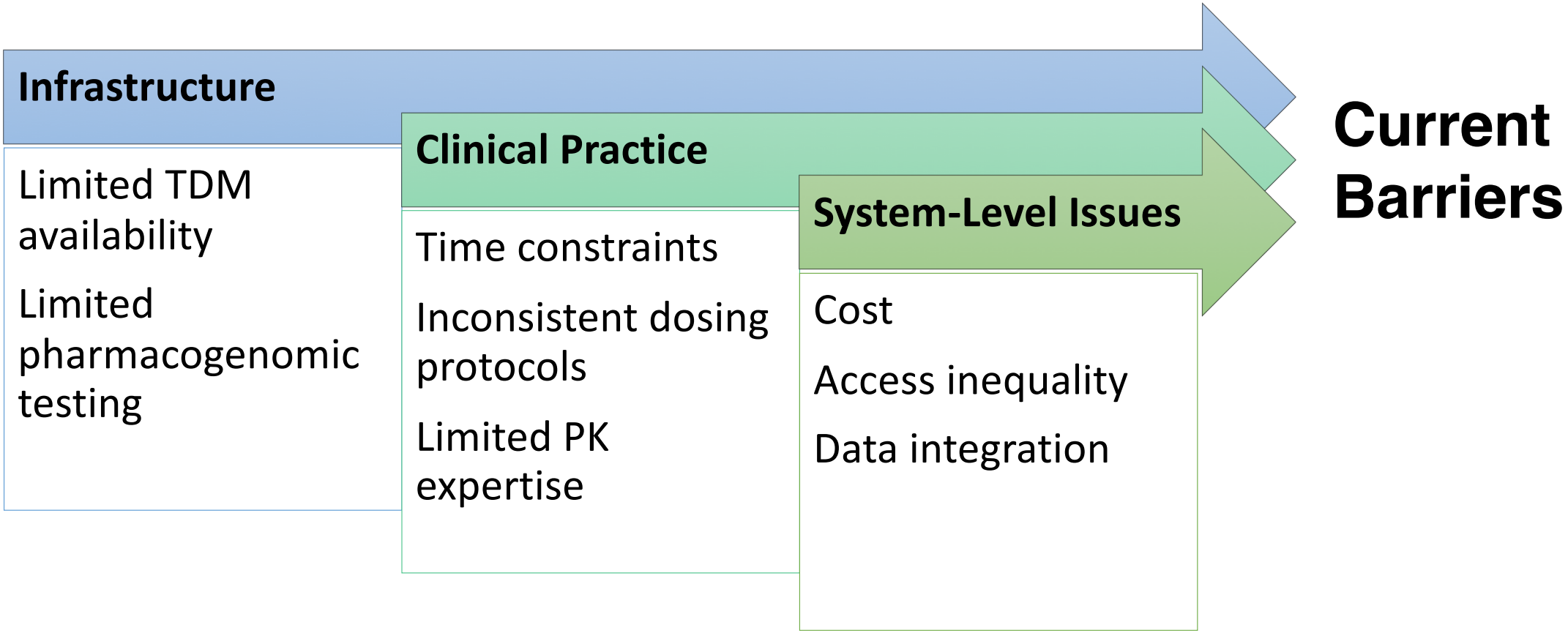
ROLE OF THE CLINICAL PHARMACIST

Oncology Pharmacist as Precision Medicine Partner

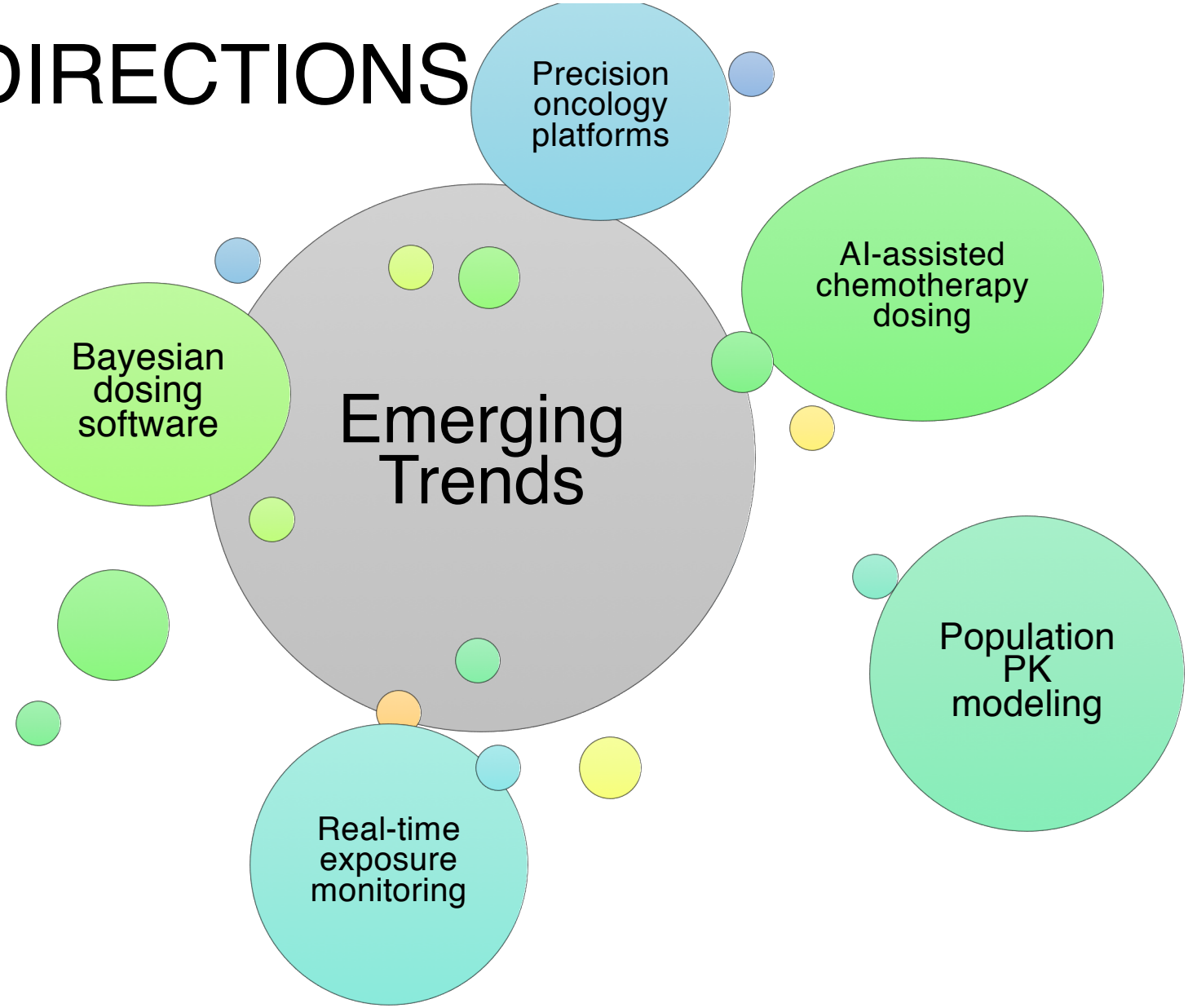
Core Responsibilities

- Chemotherapy verification
- Dose optimization
- Renal/hepatic adjustment
- PK interpretation
- Toxicity monitoring
- Interprofessional collaboration
- Patient counseling

IMPLEMENTATION CHALLENGES



FUTURE DIRECTIONS



TAKE-HOME MESSAGES

BSA alone is insufficient
Renal function strongly influences exposure
AUC-based dosing improves precision
PK/PD integration enhances safety
Personalized dosing improves patient outcomes
Pharmacists are central to precision oncology

TERIMA KASIH

“Precision oncology is not merely selecting the right drug — it is engineering the right exposure for the right patient.”