Pharmacogenomics of Chemotherapy induced nausea & vomiting

Dr. Sandip Mukhopadhyay
MD, NFPM
Assistant Professor, Pharmacology
Burdwan Medical College, India

MASCC/ISOO
Annual Meeting on Suppportive Care in Cancer • June 21-23, 2019
#MASCC19 • Follow us on Twitter: @CancerCareMASCC

Dr Sandip Mukhopadhyay

- **MBBS**, Burdwan University (1995) **Gold medal in Pharmacology**
- **MD in Pharmacology, Christian Medical College-Ludhiana**
- **Fellowship in Palliative Medicine** – IPM-Calicut

- *Assistant Professor of Pharmacology & Coordinator of Pharmacovigilance at Burdwan Medical College*
- ***Research interest of supportive Oncology***
- *Received **8 international awards in last five years***
- ***"Young Investigator" 2017** by the "**Multinational Association of Supportive Care in Cancer (MASCC)"** **in Washington DC, USA** to receive his award*
- ***"MASCC Ambassador" for India** 2017-18 for Supportive care*

Conflict of interest

- None

Overview

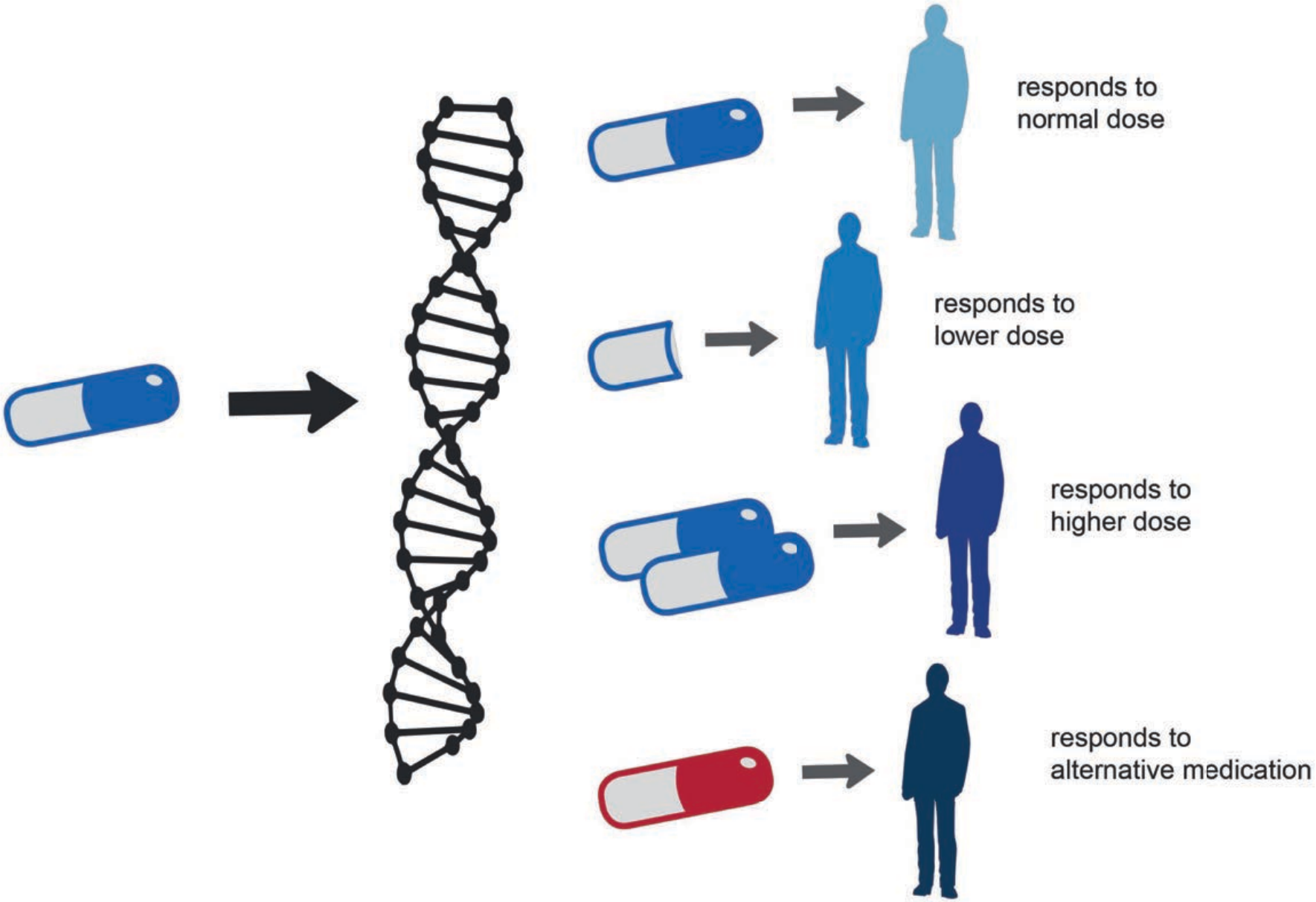
- Introduction
- Pharmacogenomic angles in CINV
  - Background sensitivity
  - PGx of antiemetics
  - PGx of chemotherapy drugs
  - PGx of Opioids
- Implementing PGx strategies
  - Success of PGx in CINV
  - The grey areas
  - Barriers in implementation
- Future direction
- Conclusions

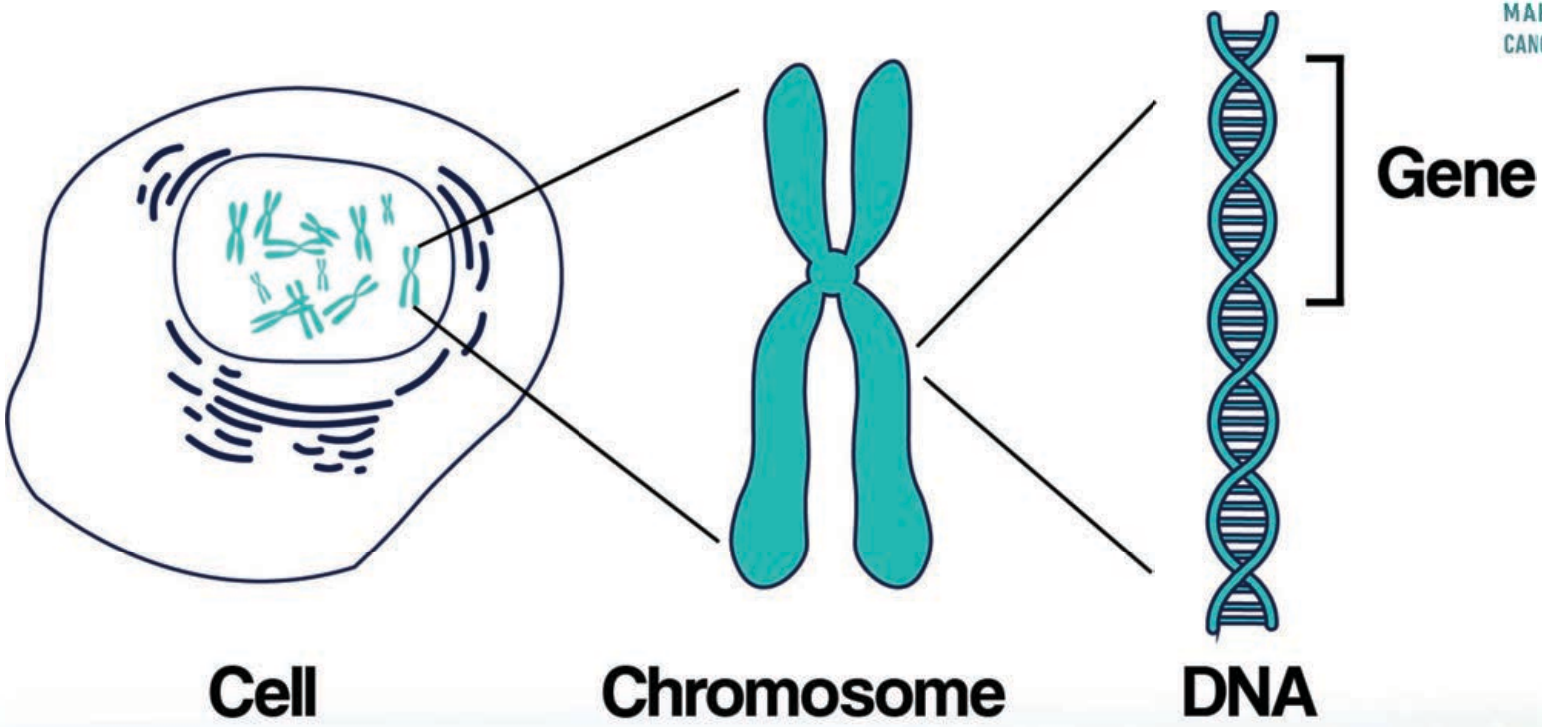
"Here's my sequence..."

New Yorker, 2000

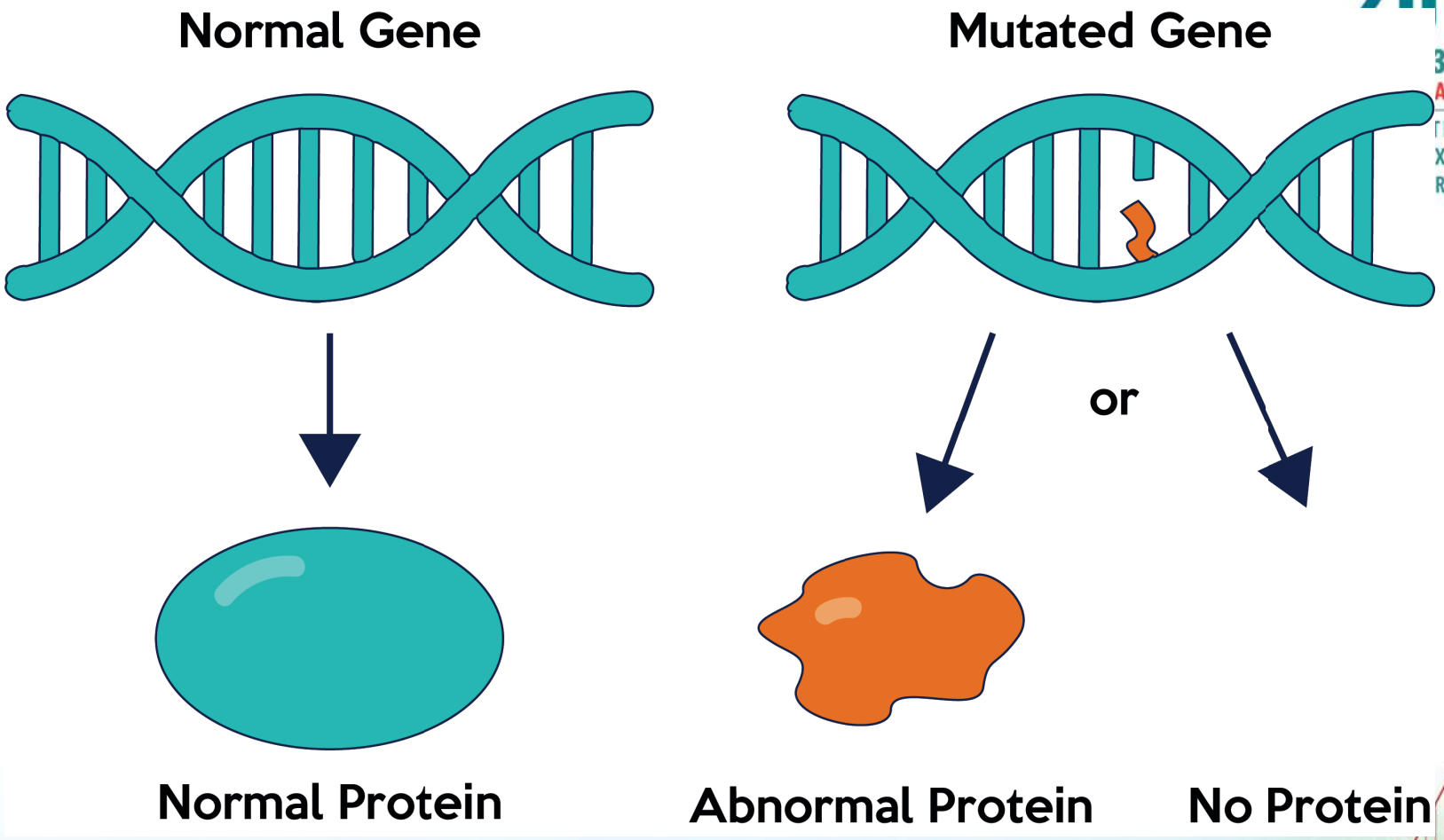
- **Pharmacogenetics** - alteration of drug action due to single gene
- **Pharmacogenomics** - alteration of drug action due to effect of number of genes (genome)

- Because drug responses - determined by multiple proteins, rather than single proteins
  - Recent trends - ***shifted from pharmacogenetics to pharmacogenomics***.

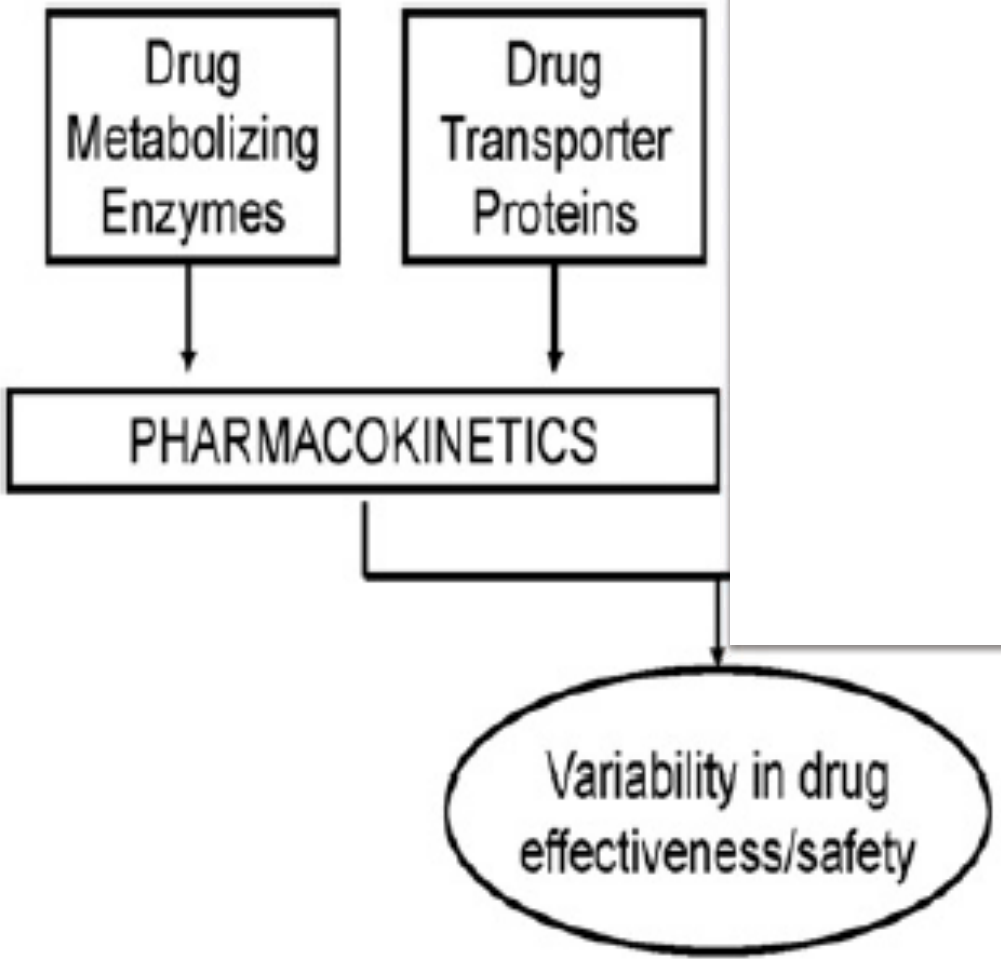

responds to
normal dose
responds to
lower dose
responds to
higher dose
responds to
alternative medication



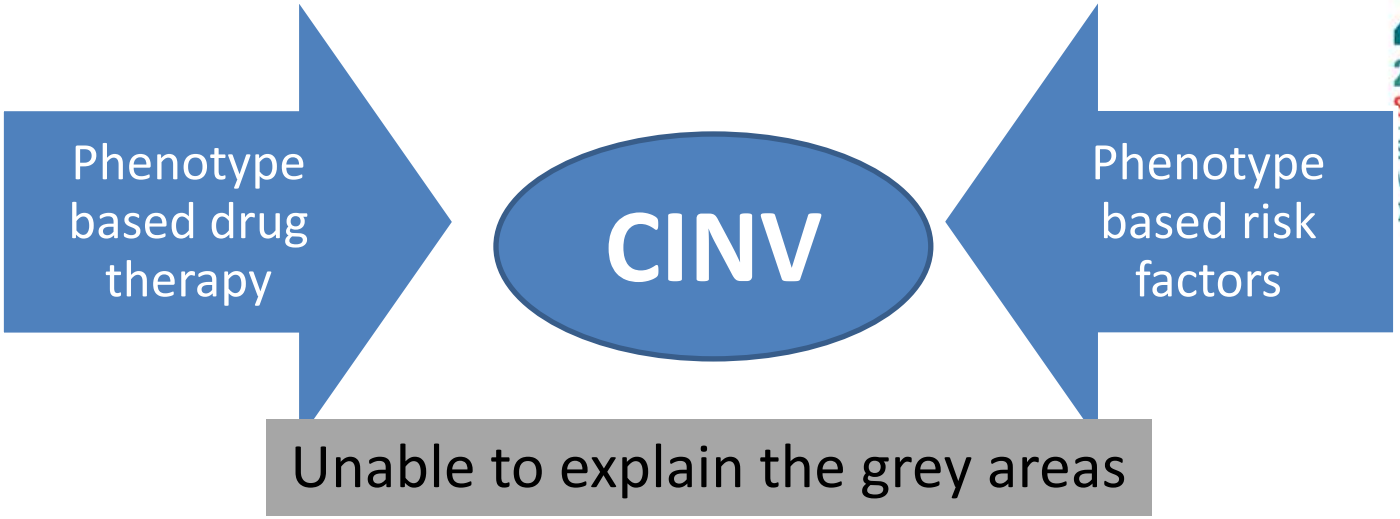
https://kintalk.org/genetics-101/



https://kintalk.org/genetics-101/

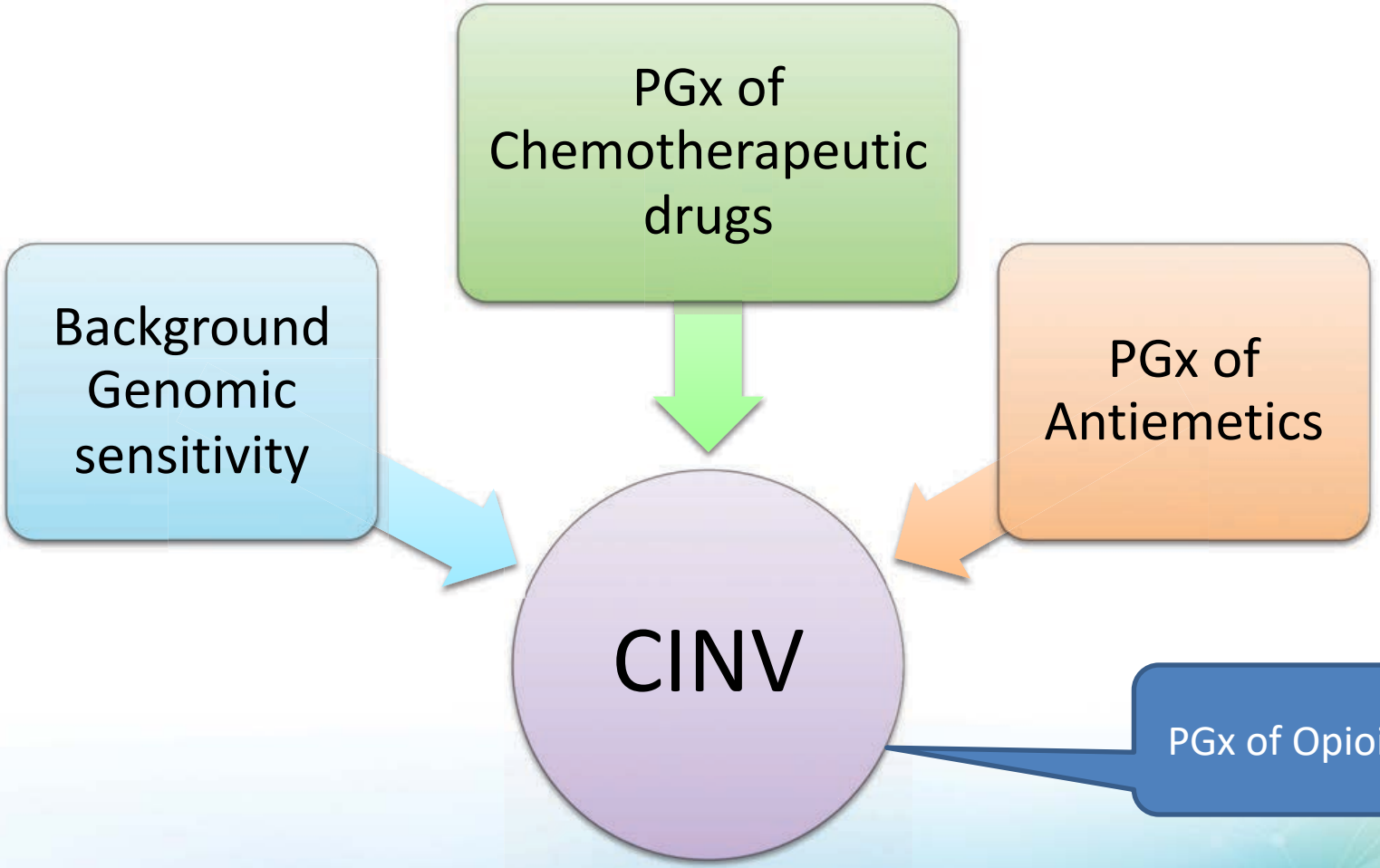

Drug Metabolizing Enzymes
Drug Transporter Proteins
PHARMACOKINETICS
Variability in drug effectiveness/safety

Why?



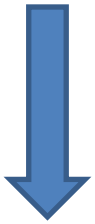
- Growing research in genomics - now explained many areas in the health including cancer treatment
- Genomic input - possible in supportive care/ **CINV**

Pharmacogenetic angles in CINV



Background genomic sensitivity

- BRCA gene mutation
- Low expression of BRCA gene protein

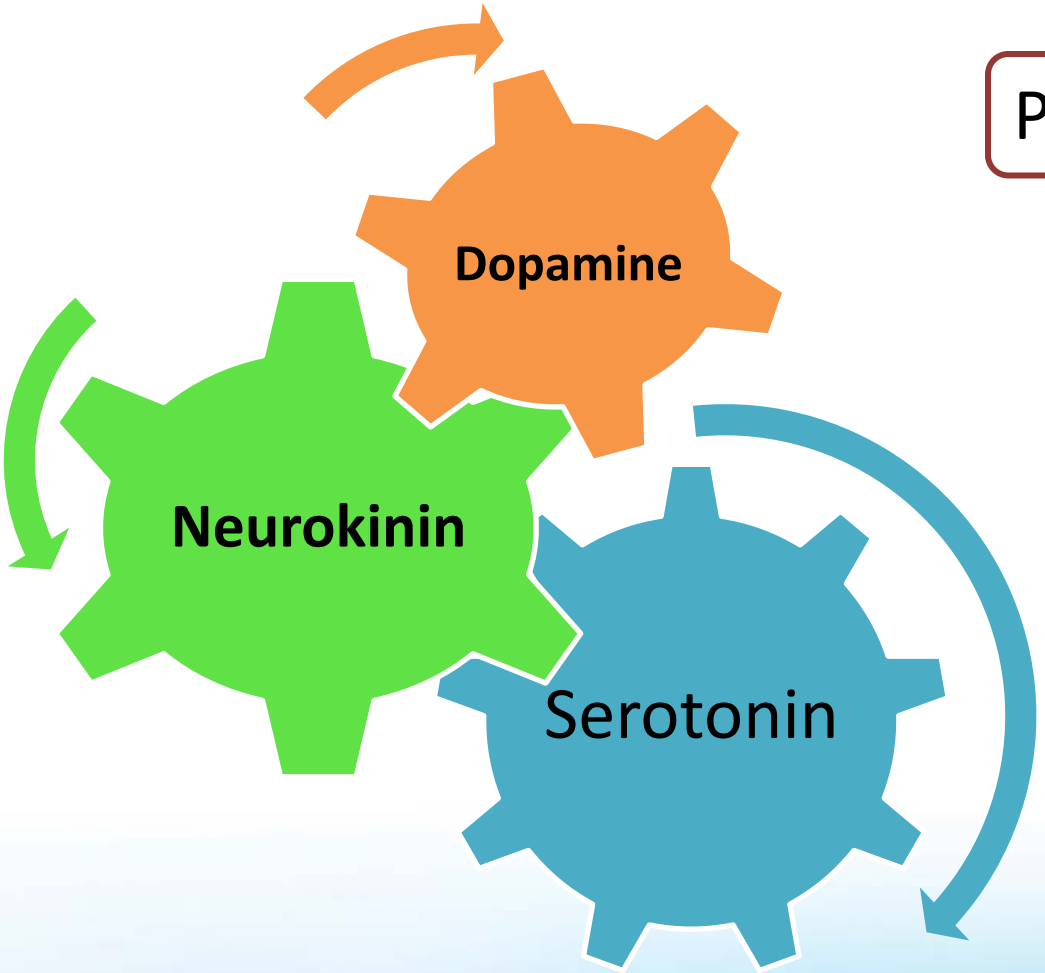


Less CINV

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Pharmacogenomics of Antiemetic drugs

Antiemetic drugs acts commonly on



Possible PGx angles

- Receptors
- Transporters
- Metabolizing enzymes

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

A. Pharmacogenetic prediction from metabolizing enzyme

Biotransformation

2019
21-23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

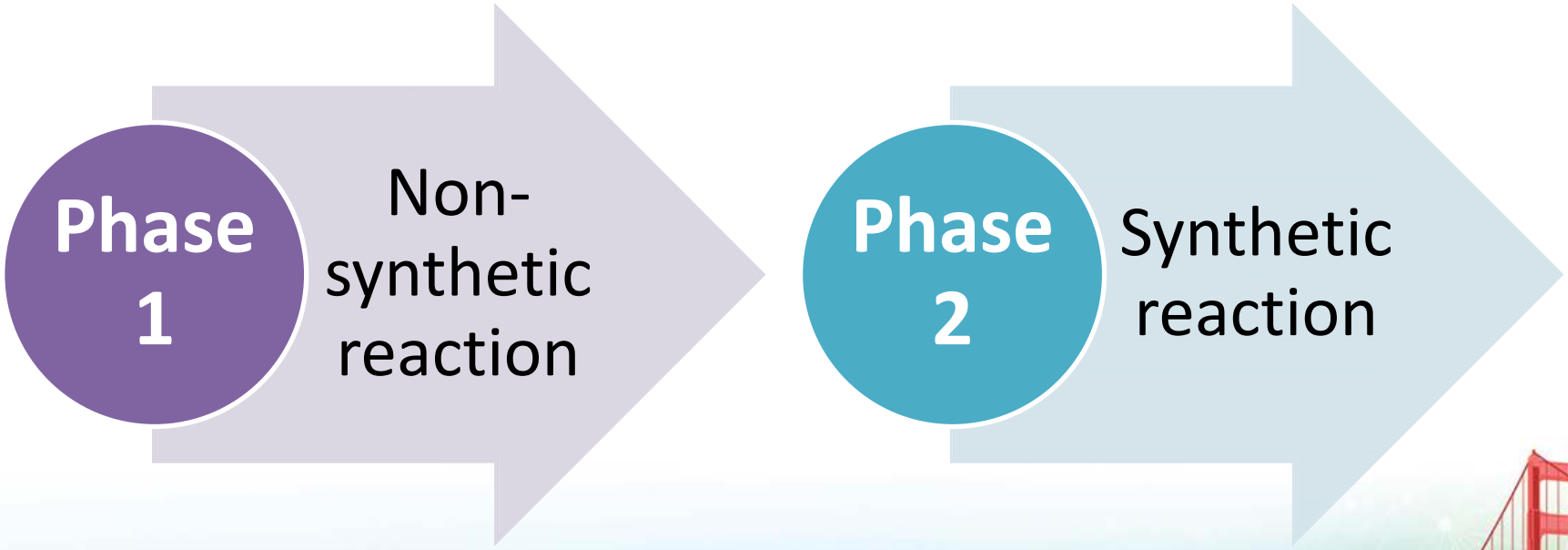
Inactive drug → **Active drug**

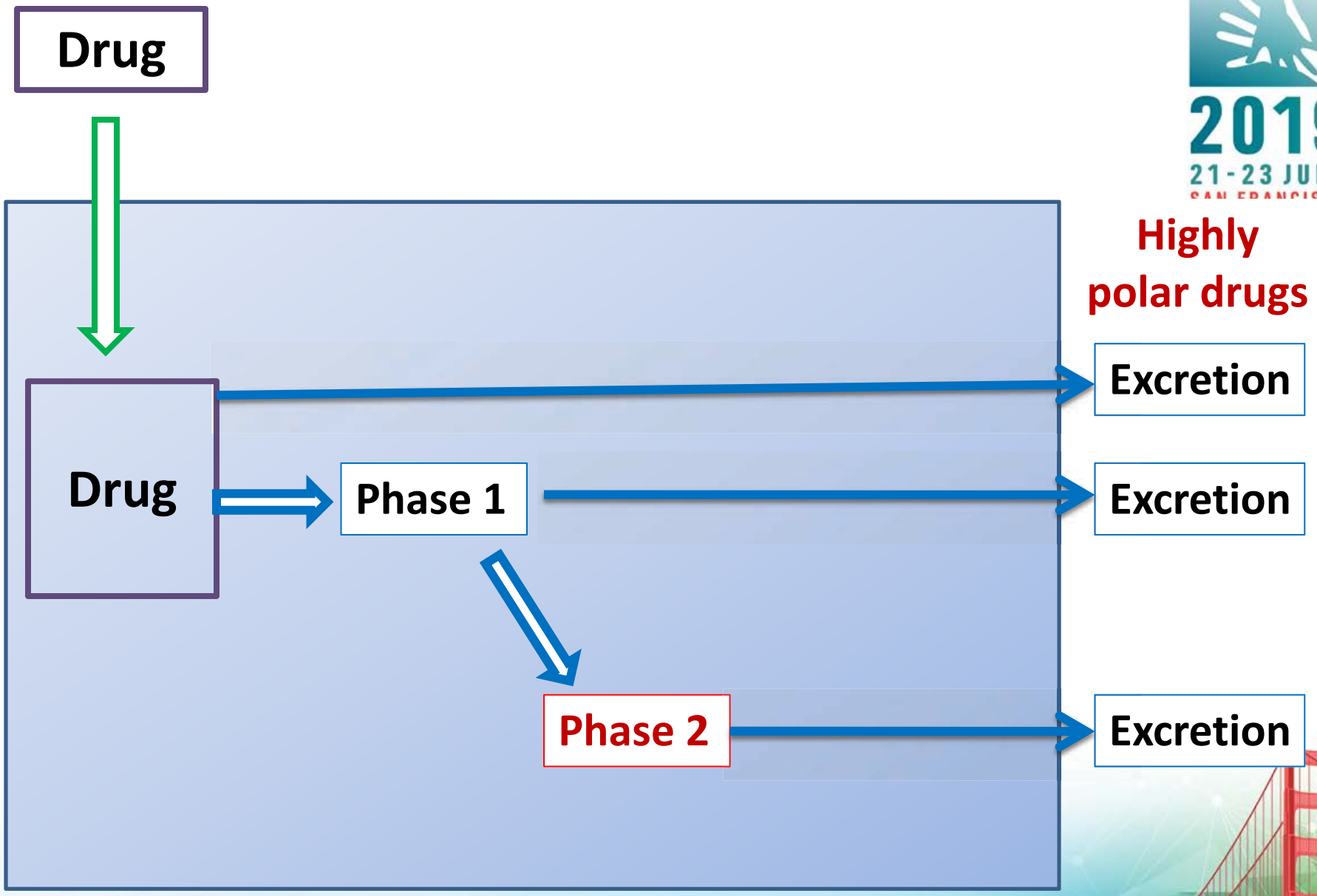
Active drug → Inactive drug

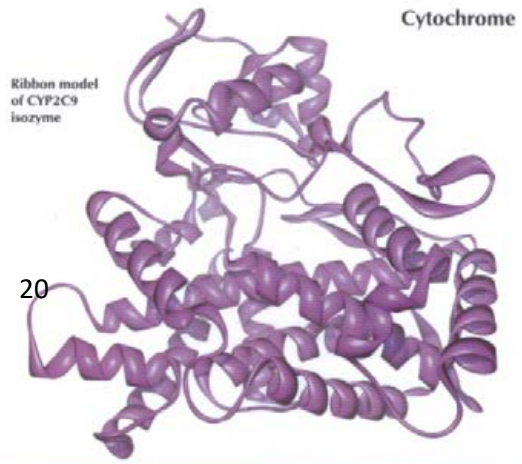
Active drug → **Active metabolite**

.....Biotransformation

Phases of biotransformation

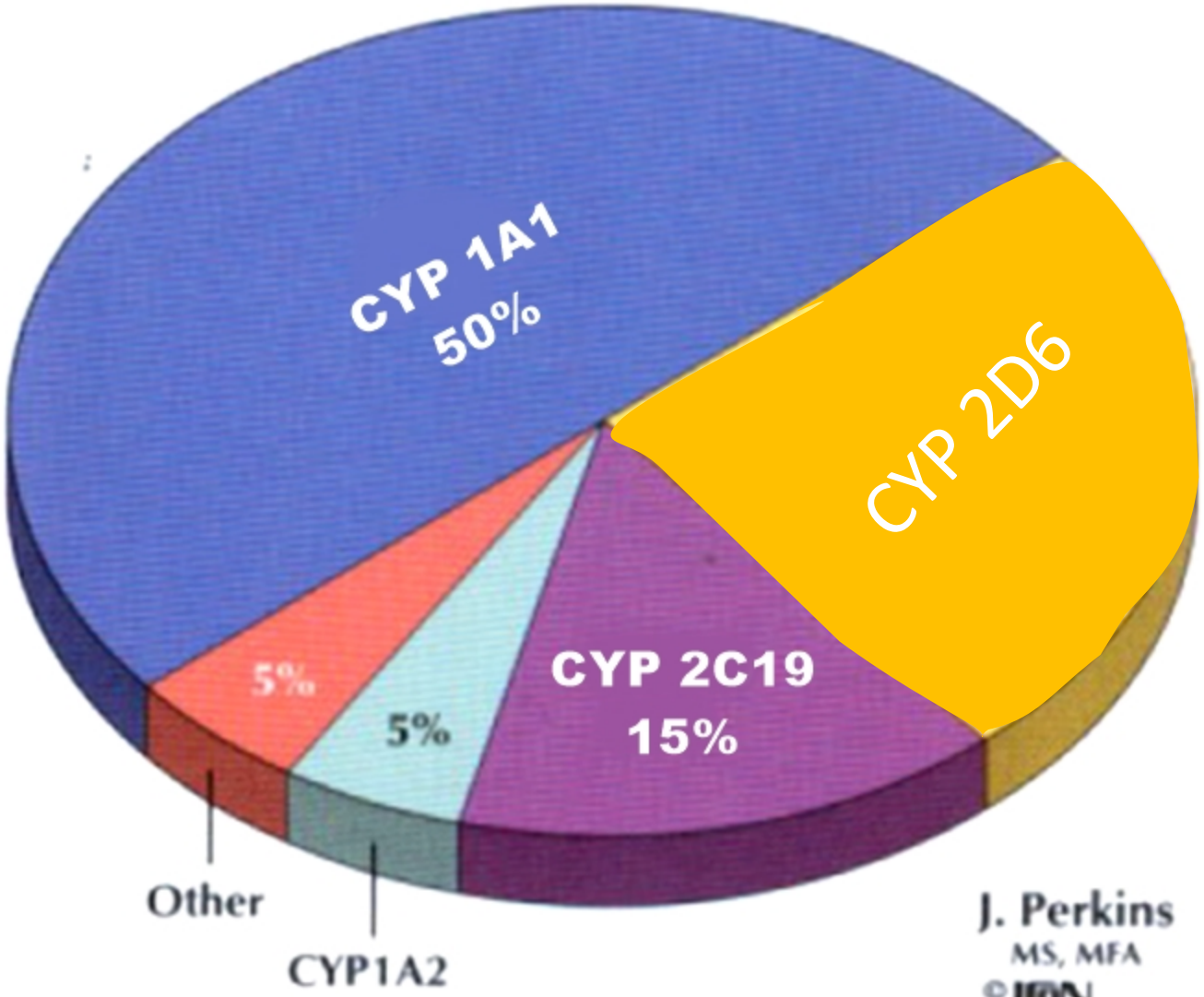



Drug
Drug
Phase 1
Phase 2
Highly polar drugs
Excretion
Excretion
Excretion



CYP isoenzymes

- CYP 3A4
- CYP 1A1
- CYP2D6
- CYP2C9
- CYP 2C19
- CYP2E1



5HT3RA metabolism by CYP

$5HT_3$-RA	Major P450(s)	Minor P450(s)
Dolasetron (a prodrug, must be converted to reduced dolasetron by carbonyl reductase)	CYP2D6	CYP3A4
Granisetron	CYP3A	
Ondansetron	No dominant P450	CYP1A1, CYP1A2, CYP2D6, CYP2E1, CYP3A4
Palonosetron	CYP2D6	CYP3A, CYP1A2
Ramosetron	CYP1A2, CYP2D6	
Tropisetron	CYP2D6	

Trammel, et al, 2013

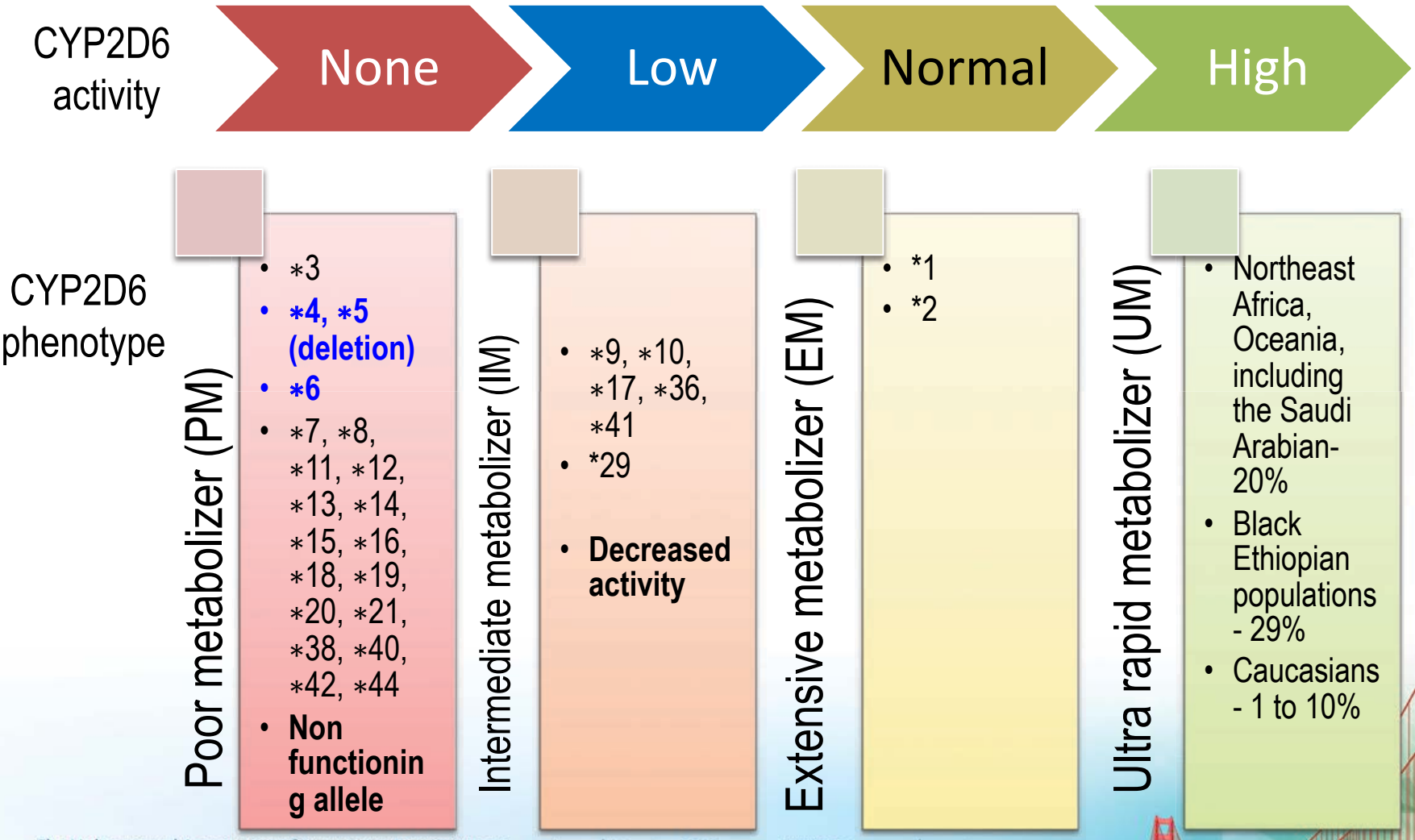
CYP 2D6 genetic variation

- 100+ documented alleles
- number of variants more common in different ethnicities

- Duplications, deletions, or rearrangement constitutes a major source of interindividual variation in the human genome

- Normal Function- CYP2D6*1, *2

https://www.pharmvar.org/gene/CYP2D6


CYP2D6 activity
None
Low
Normal
High
CYP2D6 phenotype
Poor metabolizer (PM)
• ∗3
• ∗4, ∗5 (deletion)
• ∗6
• ∗7, ∗8, ∗11, ∗12, ∗13, ∗14, ∗15, ∗16, ∗18, ∗19, ∗20, ∗21, ∗38, ∗40, ∗42, ∗44
• Non functioning allele
Intermediate metabolizer (IM)
• ∗9, ∗10, ∗17, ∗36, ∗41
• *29
• Decreased activity
Extensive metabolizer (EM)
• *1
• *2
Ultra rapid metabolizer (UM)
• Northeast Africa, Oceania, including the Saudi Arabian- 20%
• Black Ethiopian populations - 29%
• Caucasians - 1 to 10%

Patient-Tailored Antiemetic Treatment With 5-Hydroxytryptamine Type 3 Receptor Antagonists According to Cytochrome P-450 2D6 Genotypes

Rolf Kaiser, Orhan Sezer, Anja Papies, Steffen Bauer, Claudia Schelenz, Pierre-Benoit Tremblay...

Journal of Clinical Oncology
An American Society of Clinical Oncology Journal

- Prospective cohort study
- N= 270, five emetogenic level
- CINV prophylaxis with Ondansetron & tropisetron

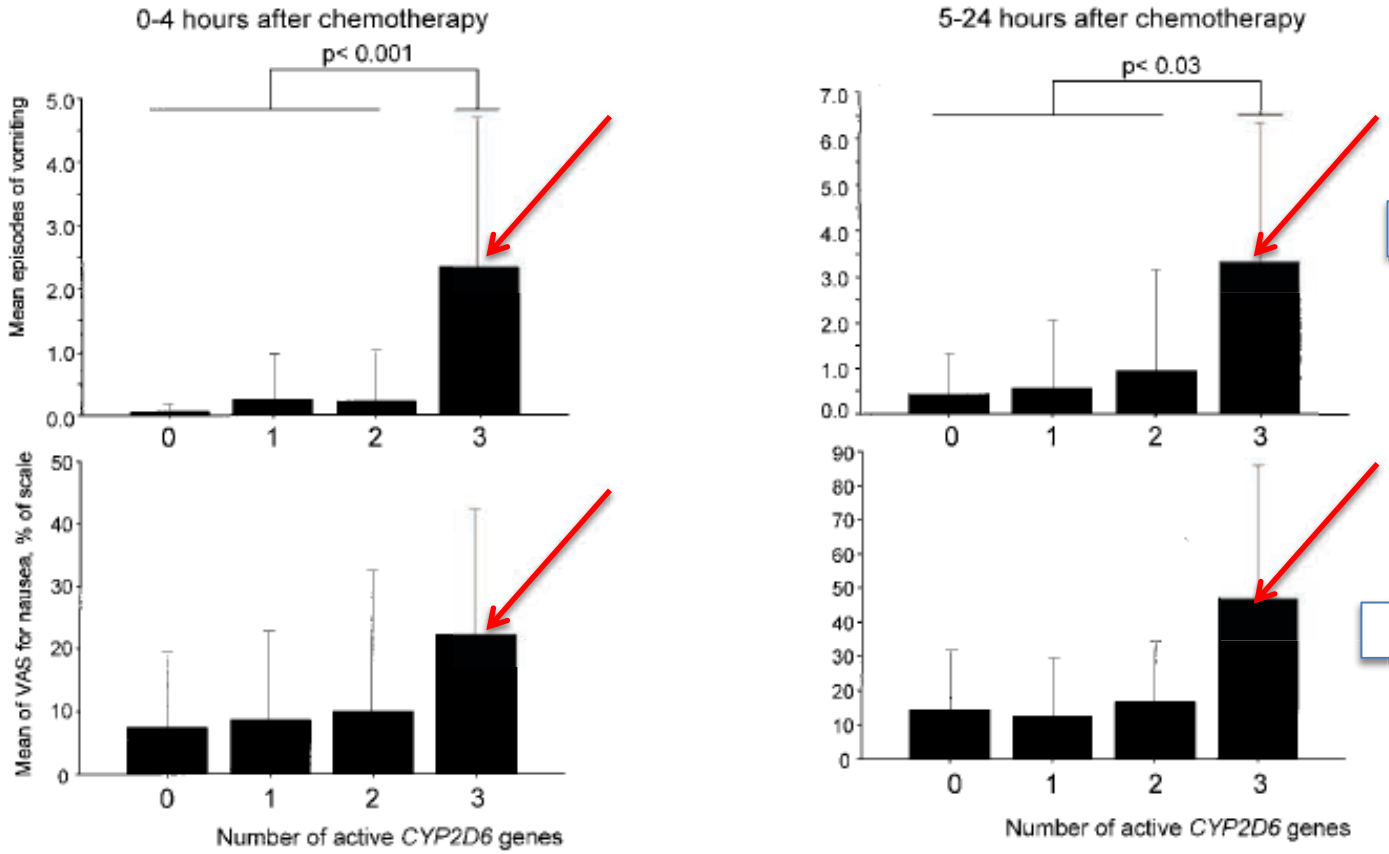
level 1, (n 2)
level 2 (n 55)
level 3 (n 22)
level 4 (n 95)
level 5 (n 96)

- CYP2D6 genotyping
- Plasma tropisetron concentration
- Acute emesis (0-24 hours)
  - Two time frames

Journal of Clinical Oncology, Vol 20, No 12, 2002: pp 2805-2811

- ***CYP2D6 genotyping***
  - Poor metabolizer - (7.8%)- No functional allele
    - ***Tropisetron*** **serum conc.** (6 hours after administration) ↑↑
  - Extensive metabolizers – (58.1%)- two active alleles
  - Ultra rapid metabolizer- (1.58%) - **3 alleles**

Mean values (SD) of vomiting as function of number of active *CYP2D6 genes*

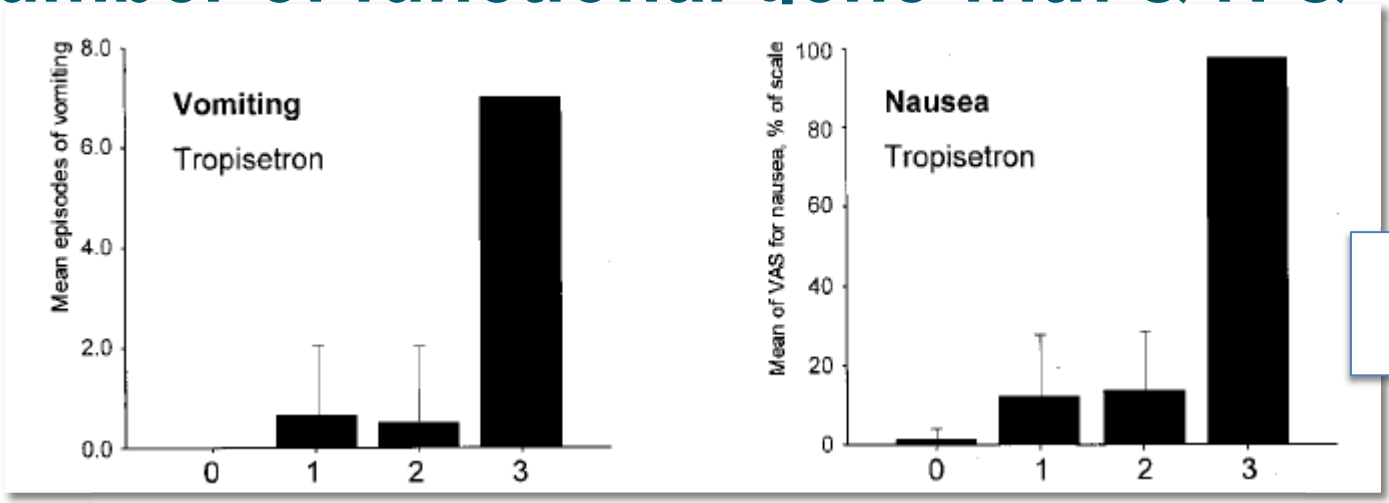


Vomiting

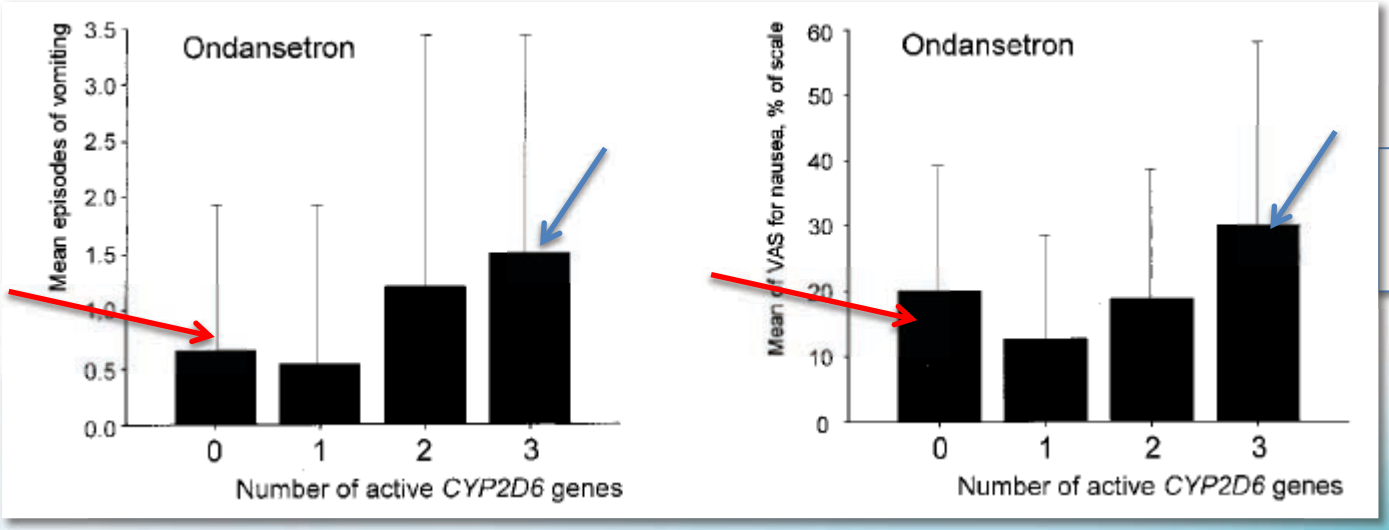
Nausea

***Patients* with three active genes had significantly more vomiting at both observation periods than all other patients (*P < .001, P < .03*)**

Tropisetron Vs. Ondansetron (Number of functional gene with & N & V)



Tropisetron



Ondansetron

- Ondansetron
- Partly metabolized by CYP3A4

  -CYP 3A4 - relatively more stable

- "Because of the low frequency (1.5% to 2%) of genetically defined UM in the German population, it would be necessary to ***genotype approximately 50 patients*** for CYP2D6 ***to prevent one case*** of severe vomiting or nausea"

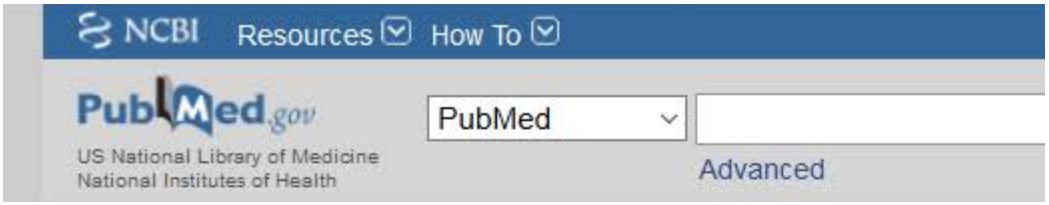
- Higher proportion of UM other regions - may influence the efficacy of antiemetic treatment in cancer patients

- **Genotyping for *CYP2D6***
- *before start of the chemotherapy* or
- use of **alternative** antiemetic drugs not metabolized by CYP2D6

  - may further ↓ CINV

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

CYP3A4 pharmacogenetics



2019

Asian Pac J Cancer Prev. 2011;12(1):185-91.

Genetic polymorphisms in the three malaysian races effect granisetron clinical antiemetic actions in breast cancer patients receiving chemotherapy.

Hassan BA[1], Yusoff ZB.

- **Aim:** to clarify ***genetic polymorphism effects*** in the three main races in Malaysia i.e., ***Malay, Chinese and Indian***, on the clinical **antiemetic effects** of granisetron
- prospective observational study, breast cancer patients
- n-=158
- CINV in the first 24 hours after chemotherapy administration

- High CINV in Chinese- linked to CYP3A4 polymorphism

.....CYP3A4 pharmacogenetics

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

"…**Chinese patients** with breast cancer should be ***treated with a different type of 5-HT3RA***

such as tropisetron and dolasetron,

since they are predominantly metabolized by CYP2D6 only" (Hassan et al, 2011)

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

B. Pharmacogenetic prediction from transport proteins

ABCB1 transporter

Author	Gene	Findings
Babaoglu et al., 2005	ABCB1 transporter	3435C > T associated with treatment efficacy
He et al., 2014	ABCB1 transporter	3435C > T associated with **higher risk for CINV**
Perwitasari et al., 2011	ABCB1 transporter	CTG haplotype associated with **higher delayed phase CINV**
Zoto et al., 2015	ABCB1 transporter	3435TT variant with **significantly less CINV**

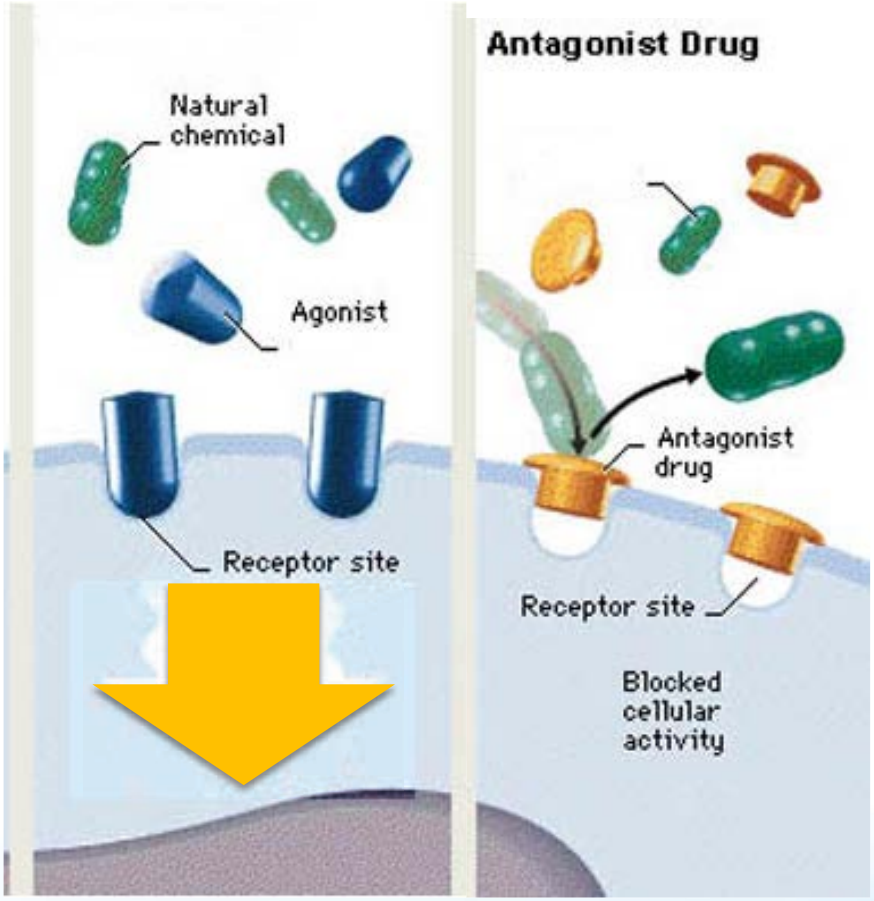
OCT1

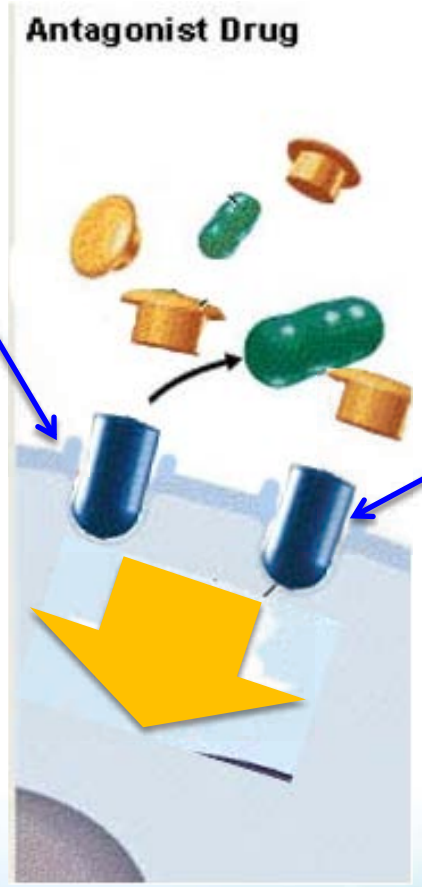
Author	Gene	Findings	
Tzvetkov et al., 2012	OCT1	May increase efficacy of tropisetron (Navoban®) by limiting hepatic uptake	

Present status:
No validated chip available for routine clinical use for transporters

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

C. Pharmacogenetic prediction from CINV- the Pharmacodynamic angle





Genetic variation of receptor

Codes for 5HT receptors

Normal receptor function

MAKES EXCELLENT CANCER CARE POSSIBLE

Abnormal 5HT receptors

No antagonist function

CINV

Author	Drug	Gene	Findings
Kaiser et al. (2004)	Tropisetron (n=242)	5-HT3A receptor	21 polymorphism No significant association with CINV
	Same	**5-HT3B** gene	13 polymorphism 30% of the patients suffered from CINV
Fasching et al. (2008),	Ondansetron (n=120)	**5-HT3C receptor**	Variant genotype of K163 N was associated with vomiting (RR = 2.62)
Tremblay et al. (2003)	Ondansetron & tropisetron (n=286)	**5-HT3B gene**	**5-HT3B receptor gene may serve as genetic predictor** for anti-emetic therapy with ***the _AAG deletion variant (OR = 32).*** after adjusted with other risk factors of emesis.

Author	Drug	Gene	Finding
Hammer et al. (2010)	Ondansetron n-=110 Ca Breast (EC/ E chemo-Rx)	HTR3A, HTR3B, HTR3D and HTR3E	Along with previously identified HTR3 polymorphisms, the **HTR3D polymorphism** may be a **predictor of CINV.** **G allele of *HTR3D p.G36A - over-represented in nonresponders*** - individual risk predictions
Ward et al., 2008	Dolasetron or tropisetron (n=70)	5-HT3C 5-HT3B CYP 2D6	**No SNPs significant** One patient with polymorphism and higher CINV

NK1 receptor gene

- *TACR1 gene*
  - *t*achykinin receptor 1 (also known as neurokinin 1 receptor or substance P receptor *)*
- ***Not been examined*** *in relation to CINV*

- Laugsand *et al.*
  - *genotyped ten SNPsHowever,* ***none*** *of the investigated SNPs was significantly* ***associated with nausea and vomiting***

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Pharmacogenetics of anticancer drugs- partial linkage

Pharmacogenetics of opioid-induced nausea & vomiting during chemotherapy : Needs further evaluation

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Implementing PGx strategies in CINV

- The clinical implementation process has 3 distinct phases:
  - pre-implementation,
  - developmental, and
  - clinical implementation stage.
- Research and finding solutions to challenges:
  - required within each phase
- In addition, suitable and feasible solutions are required to overcome education, ELSI, reimbursement, and scientific barriers

Success

- Acute emesis link
  - 5HT3B gene – Pharmacodynamic modulation
  - CYP2D6 – Metabolism modulation
  - CYP3A4 – Metabolism modulation
  - ABCB1 (Pgp) - Transporter

- Data about all 1st generation 5HT3RA (ondansetron, tropisetron, dolasetron, granisetron)

The grey areas

- Little or no data
  - Delayed emesis
  - Dopamine receptor & CINV
  - Palonosetron
  - NK1 antagonist
  - Olanzapine
- Studies- mostly on candidate gene approach
- Small study population
- Isolated patients (e.g. breast cancer)
- Animal models- difficult pre-cllinical research

Barriers for Clinical Implementation of PGx

IT infrastructure
(infrastructure, IT PGx integration)

Scientific
(e.g. turnaround time of PGx test, gene-drug pair selection)

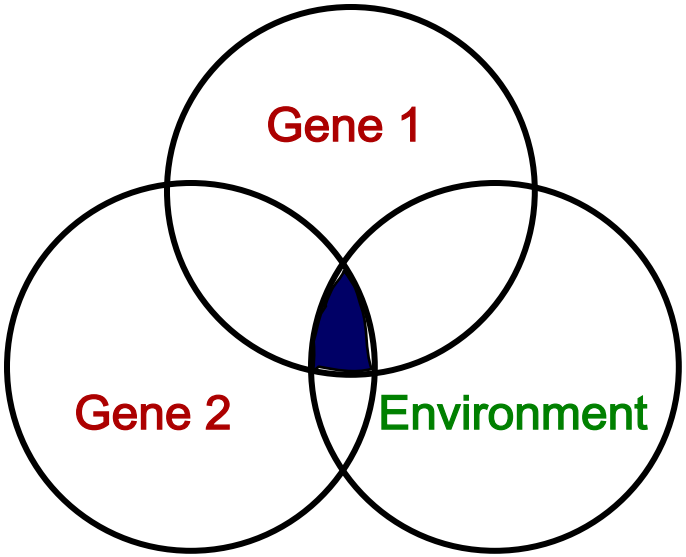
Educational
(awareness)

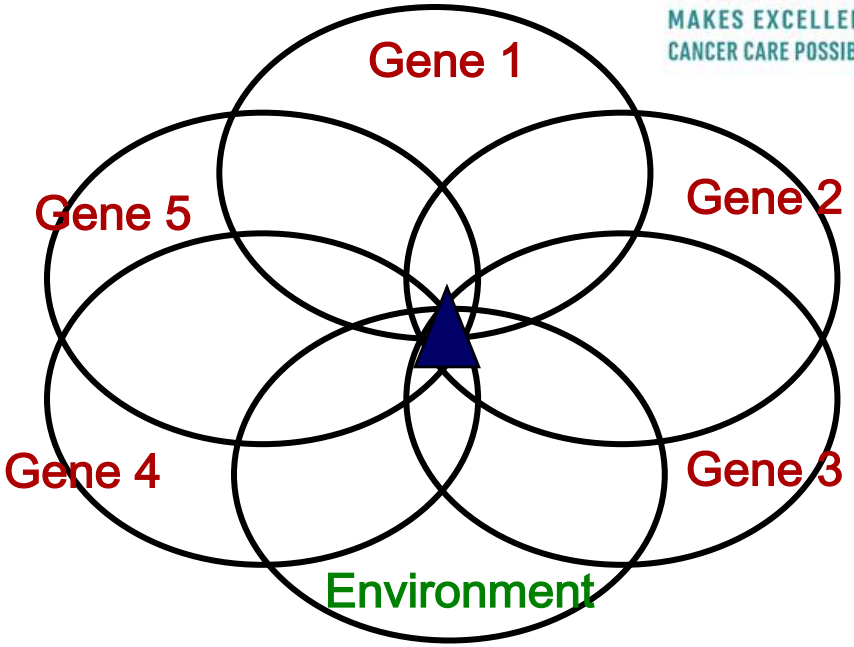
Ethical, regulatory, legal issues

….Barriers for Clinical Implementation

- Translation of data in to clinical practice
- Cost
- Availability of test facility
- No valid tests for transporters and receptors for routine use
- High expectations

Complex Phenotypes – What Can We Expect?



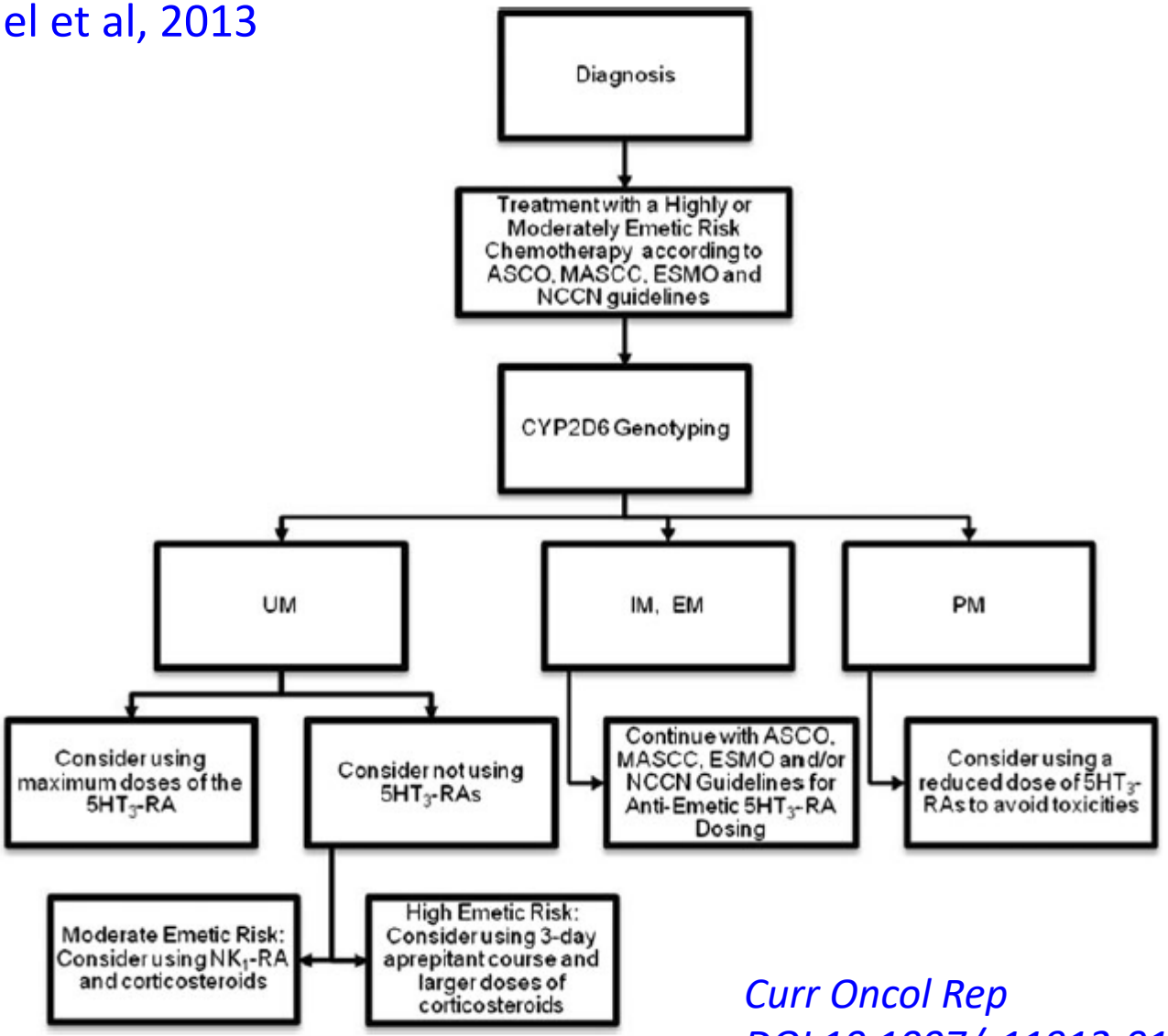


Few genes and environmental factors each contributing a large risk

Many genes and environmental factors each contributing a small risk

An individualized antiemetic treatment algorithm using the cytochrome P450 (CYP) 2D6 genotype

Trammel et al, 2013



Curr Oncol Rep
DOI 10.1007/s11912-013-0312-x

2019
21-23 JUNE
SAN FRANCISCO

IVE CARE
CCELLENT
E POSSIBLE

Proposed

Future perspective

- Interindividual differences in susceptibility to CINV-partly explained
- Tech support- Next-generation DNA sequencing- **revolutionary**
- Necessary to shift the research paradigm in CINV from a **candidate gene approach** to **GWAS (Genome wide association studies)**
  - Number of genes in the human genome exceeds 20,000, and the number of SNPs might be hundreds to thousands times larger

Conclusion

Advances in pharmacogenetics and pharmacogenomics related to CINV will contribute to future personalized cancer therapy strategies

2019
21 - 23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Thank you

MASCC/ISOO

Your Partners in

SUPPORTIVE CANCER CARE

MASCC™
Multinational Association of Supportive Care in Cancer

ISOO
INTERNATIONAL SOCIETY of ORAL ONCOLOGY

Join MASCC/ISOO today and enjoy the benefits

- Collaboration with global experts
- Subscription to Supportive Care in Cancer
- Society Newsletter & Member Directory
- Discounted meeting registration fees
- Scholarship and award opportunities
- Online access to practice guidelines & tools

Supportive Care Makes Excellent Cancer Care Possible

Join Today at www.mascc.org