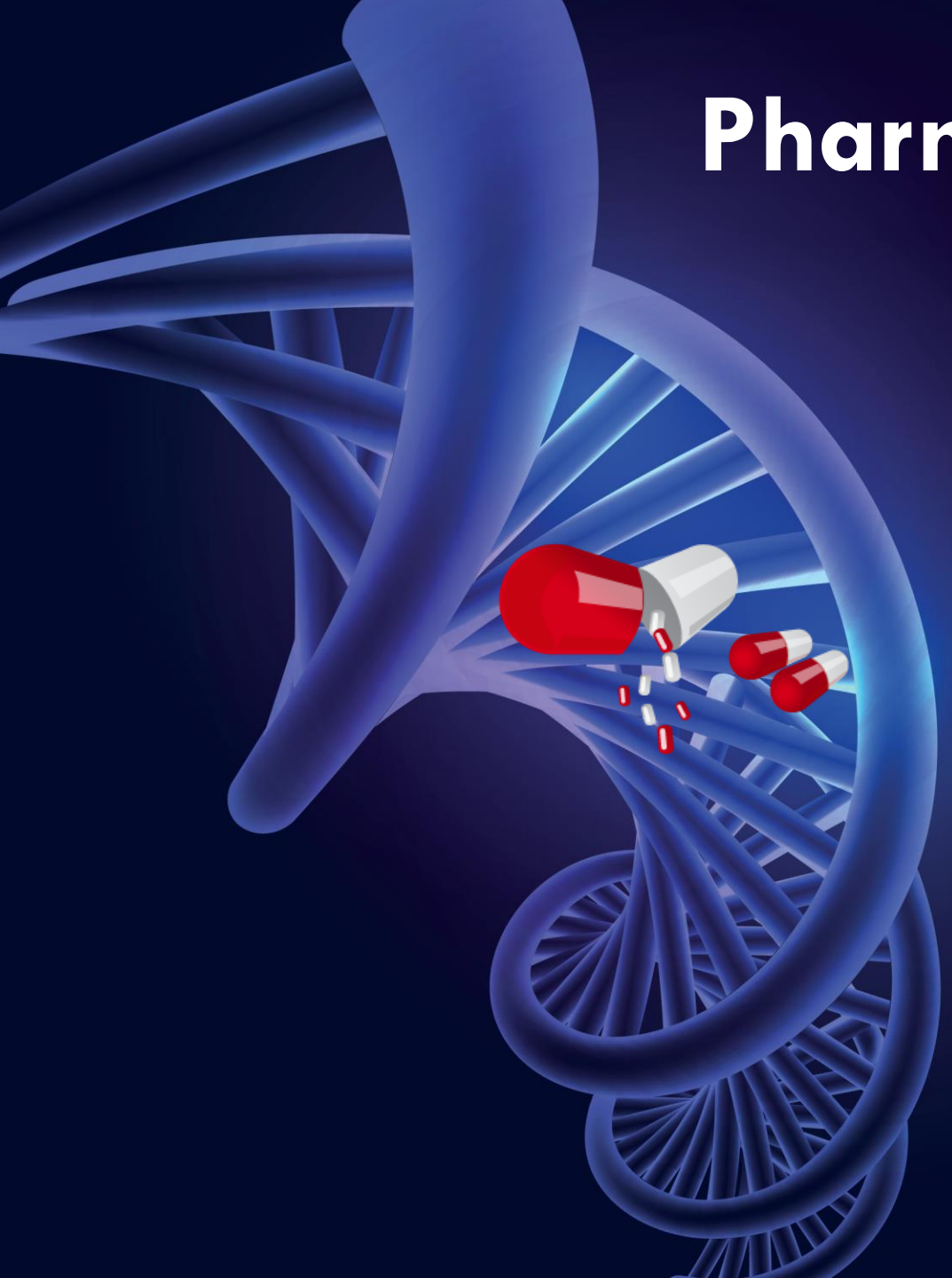


# Pharmacogenomics in Oncology

**Luis A. Quiñones, PhD.**

May 16, 2024

Regional Meeting

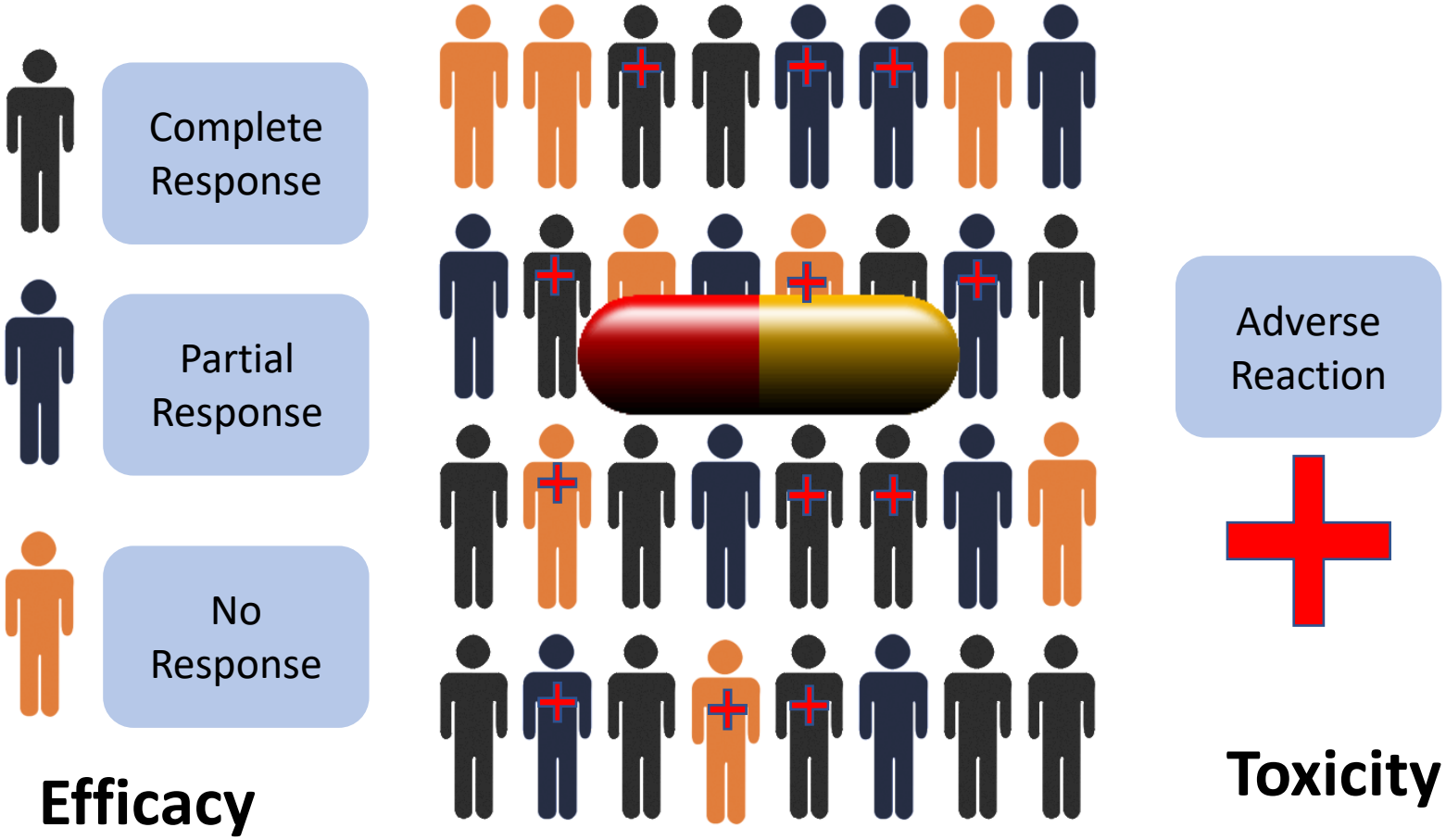
**Human Genomics for Health:**
**Enhancing the Impact of Effective Research**

# Pharmacogenomics:
## Personalized/Precision Medicine

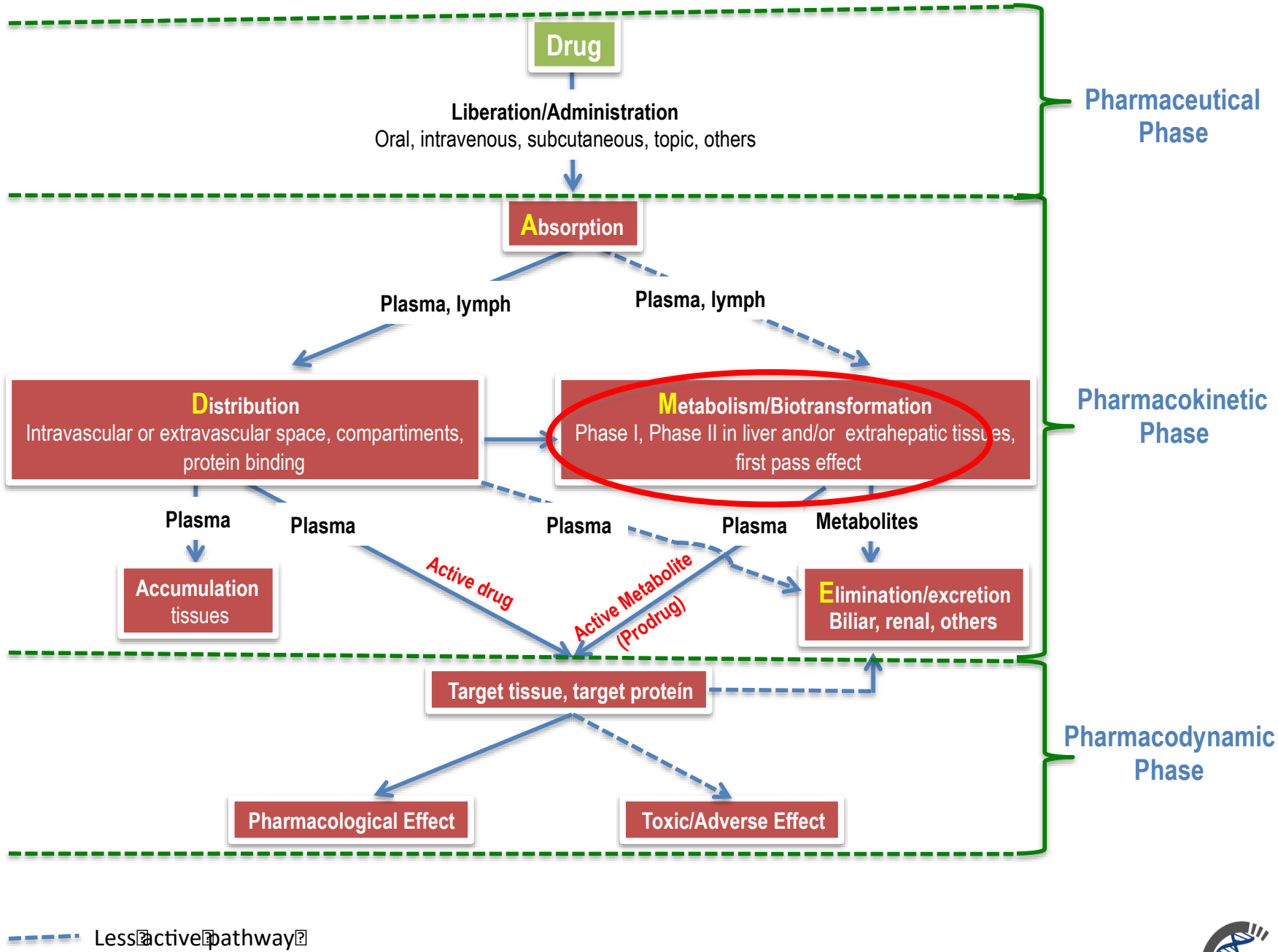
- **Why does someone need twice the standard dose of a drug for it to be effective?**
- **Why does this drug work for you but not for me?**
- **Why do I experience side effects and you don't?**
- **Why do some people develop cancer while others do not?**

*Luis Quiñones S.*

# Pharmacological variability



# The life of a drug in the body




Less active pathway

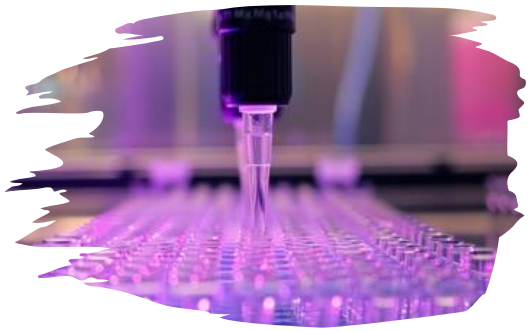
***In: Relationship between pharmacokinetics and pharmacogenomics, and its impact on drug choice and dose regimens***. *Matías F. Martínez, Luis A. Quiñones. In In: ADME processes and their impact on pharmaceutical sciences, Ed. Talevi A. Ed. Springer, 2019*

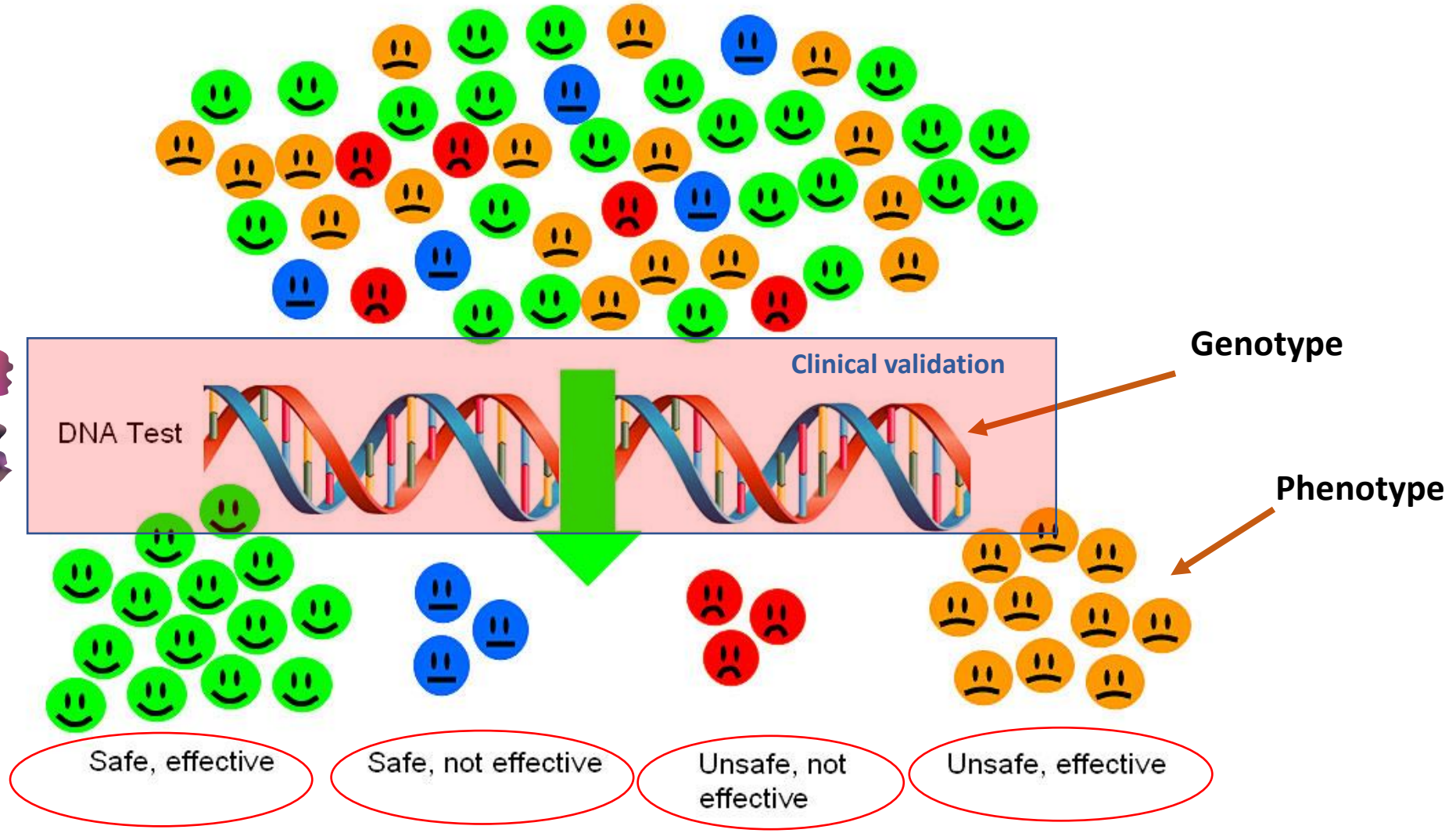
# CYP Variability


Luis Quiñones S.

| P450 gene | Polymorphisms |
|---|---|
| CYP1A1 | *1,*2A,*2B,*2C,*3,*4, *5, *6, *7, *8, *9,*10, *11, *12,*13. |
| CYP1A2 | *1A, *1B, *1C, *1D, *1E, *1F, *1G, *1H, *1J,*1K, *1L*1M*1N,*1P, *1Q, *1R, *1S, *1T, *1U, *1V, *1W, *2, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19,*20, *21. |
| CYP1B1 | **1, *2, *3, *4, *5, *6, *7,*8, *9, *10,*11, *12, *13, *14, *15, *16, *17, *18, *19, *20,*21,*22,*23, *24,*25, *26. |
| CYP2A6 | *1A, *1B1, *1B2, *1B3, *1B4, *1B5, *1B6, *1B7, *1B8, *1B9, *1B10, *1B11, *1B12, *1B13, *1B14, *1B15, *1B16, *1B17, *1C,*1D,*1E, *1F, *1G, *1H, *1J, *1K, *1L, *1X2A, *1X2B, *2, *3, *4A, *4B, *4C, *4D, *4F, *4G, *4H, *5,*6, *7, *8, *9A, *9B, *10,*11,*12A, *12B, *12C,*13, *14,*15, *16, *17, *18A, *18B, *18C, *19, *20, *21, *22,*23, *24A, *24B, *25, *26, *27, *28A,*28B, *29, *30, *31A, *31B, *32,*33, *34, *35A, *35B, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45 |
| CYP2A13 | *1A, *1B, *1C, *1D, *1E,*1F, *1G, *1H, *1J, *1K, *1L, *2A, *2B, *3, *4, *5, *6, *7, *8, *9, *10. |
| CYP2B6 | *1A, *1B, *1C, *1D, *1E, *1F, *1G, *1H, *1J, *1K, *1L,*1M, *1N, *2A, *2B, *3,*4A, *4B, *4C, *4D, *5A, *5B,*5C,*6A,*6B, *6C, *7A, *7B, *8, *9, *10, *11A, *11B, *13A, *13B, *14, *15A, *15B, *16, *17A, *17B, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34 |
| CYP2C8 | *1A, *1B, *1C, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14. |
| CYP2C9 | *1A, *1B, *1C, *1D, *2A, *2B, 2C, *3A, *3B, *4, *5, *6, *7, *8, *9, *10, *11A, *11B, *12, *13, *14, *15, *16,*17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60. |
| CYP2C19 | *1A, *1B,*1C, *2A, *2B, *2C, *2D, *2E, *2F, *2G, *2H, *2J, *3A, *3B, *3C, *4A, *4B, *5A, *5B, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34. |
| CYP2D6 | *1A, *1B,*1C, *1D, *1XN, *2A, *2B, *2C, *2D, *2E, *2F, *2G, *2H, *2J, *2K, *2L, *2M, *2XN, *3A, *3B, *4A, *4B, *4C, *4D, *4F, *4G, *4H,*4J, *4K, *4L, *4M, *4N, *4P, *4X2, *5, ,*6A,*6B, *6C, *6D, *7, *8, *9, *10A,*10B, *10C, *10D, *10X2, *11, *12, *13, *14A,*14B, *15, *16, *17, *17XN, *18, *19, *20, *21A, *21B,*22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35A, *35B, *35X2, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45A, *45B, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56ª, *56B, *57, *58, *59, *60, *61, *62, *63, *64, *65, *66, *67, *68A, *68B, *69, *70, *71, *72, *73, *74, *75, *76, *77, *78, *79, *80, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *92, *93, *94A, *94B, *95, *96, *97, *98, *99, *100 *101, *102, *103, *104, *105. |
| CYP2E1 | *1A, *1B,*1C, *1CX2 *1D, *2, *3, *4, *5A, *5B, *6, *7A, *7B, *7C, |
| CYP2F1 | *1, *2A, *2B, *3, *4, *5A, *5B, *6 |
| CYP2J2 | *1, *2, *3, *4, *5, *6, *7,*8, *9, *10. |
| CYP2R1 | *1, *2. |
| CYP2S1 | *1A, , *1B, *1C, *1D, *1E,*1F, *1G, *1H, *2, *3, *4, *5A, *5B |
| CYP2W1 | *1A, *1B, *2, *3, *4, *5, *6. |
| CYP3A4 | *1A,*1B,*1C,*1D,*1F,*1G,*1H,*1J,*1K,*1L,*1M,*1N,*1P,*1Q,*1R,*1S,*1T,*2,*3,*4,*5,*6,*7,*8,*9,*10,*11,*12,*13,*14,*15A,*15B,*16A,*16B,*17,*18A,*18B,*19,*20,*21,*22,*23,*24,*25,*26 |
| CYP3A5 | *1A, *1B, *1C, *1D, *1E, *2, *3A, *3B, *3C, *3D, *3E,*3F, *3G, *3H, *3I, *3J, *3K, *3L, *4, *5, *6, *7, *8, *9, *10, *11. |
| CYP3A7 | *1A, *1B, *1C, *1D, *2, *3. |
| CYP3A43 | *1A, *1B, *2A, *2B, *3. |
| CYP4A11 | *1 |
| CYP4A22 | *1, *2, *3A, *3B, *3C, *3D, *3E, *4, *5, *6, *7, *8, *9, *10, *11, *12A, *12B. *13A, *13B, *14, *15 |
| CYP4B1 | *1, *2A, *2B, *3, *4, *5, *6, *7. |
| CYP4F2 | *1, *2, *3. |
| CYP5A1 | *1A, *1B, *1C, *1D, *2, *3, *4, *5, *6, *7,*8, *9 |
| CYP8A1 | *1A, *1B, *1C, *1D, *1E, *1F, *1G, *1H, *1J, *1K, *1L, *2, *3, *4. |
| CYP19A1 | *1, *2, *3, *4, *5 |
| CYP21A2 | *1A, *1B, *2, *3, *4, *5, *6, *7, 8, *9, *10,*11, *12, *13, *14, *15, *16, *17, *18, *19, *20A, *20B, *20C, *20D, *20E, *20F, *20G,*20H, *20J, *20K, *20L, *20M, *20N, *20P, *20Q, *20R, *20S, *20T, *20U, *20V, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37, *38, *39, *40, *41, *42, *43, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *60, *61, *62, *63, *64, *65, *66, *67, *68, *69, *70, *71, *72, *73, *74, *75, *76, *77, *78, *79, *80, *81, *82, *83, *84, *85, *86, *87, *88, *89, *90, *91, *92, *93, *94, *95, *96, *97, *98, *99, *100 *101, *102, *103, *104, *105, *106, *107, *108, *109, *110, *111, *112, *113, *114, *115, *116, *117, *118, *119, *120, *121, *122, *123, *124, *125, *126, *127, *128, *129, *130, *131, *132, *133, *134, *135, *136, *137, *138, *139, *140, *141, *142, *143, *144, *145, *146, *147, *148, *149, *150, *151, *152, *153, *154, *155, *156, *157, *158, *159, *160, *161, *162, *163, *164, *165, *166, *167, *168, *169, *170, *171, *172, *173, *174, *175, *176, *177, *178, *179, *180, *181. |
| CYP26A1 | *1, *2, *3, *4. |

# Your DNA Affects Your Response to Drugs






*Adapted from: https://es.slideshare.net/shaikhazaroddin/pharmacogenomics-by-vaiibhavi#12*

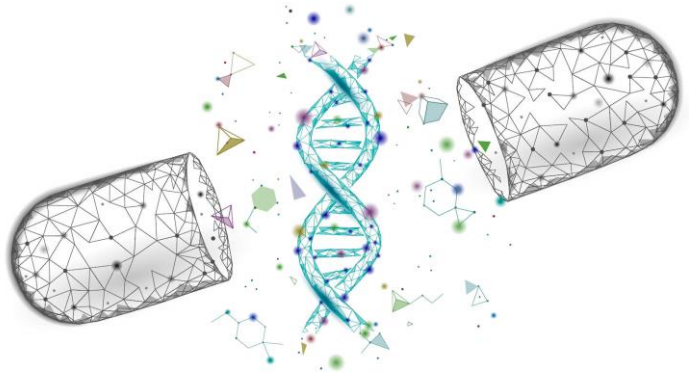
# EVOLUTION OF THE IMPLEMENTATION OF PHARMACOGENOMIC TESTING AROUND THE WORLD

**2006. *TPMT* variant for thiopurines (azathioprine or mercaptopurine - myelosuppression)**

**2006. Pharmacogenetic dosing system for warfarin (*CYP2C9* & *VKORC1*)**

**2008. *HLA-B*5701* variant for abacavir (hypersensitivity syndrome)**

**2011. *IL-28* variant (rs12979860) for interferon + ribavirin (hepatitis C - persistence**



**2012. Pharmacogenetic dosing system for acenocoumarol (*CYP2C9* & *VKORC1*)**

**2013. *CYP2C19* variant for clopidogrel (avoid in poor metabolizers)**

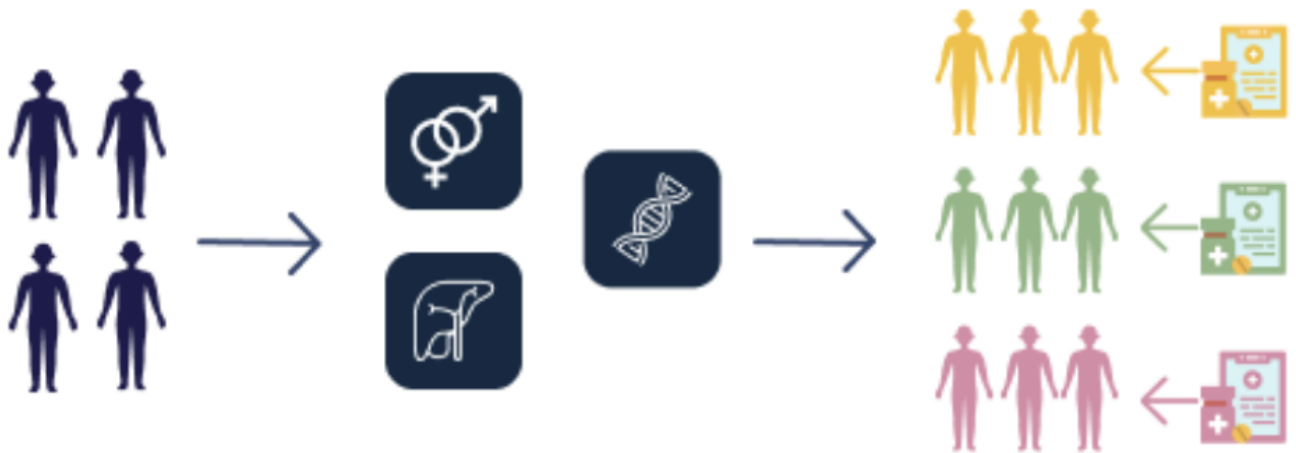
**2014. Actionable *DPYD* variants for fluorouracil, capecitabine, or tegafur (severe adverse reactions in complete or partial deficiency)**

**2015. *CYP2D6* variants for opioids (severe toxicity or inefficacy)**

**2020. *CYP2C9*3* variant for siponimod (severe toxicity due to high plasma levels)**

# Precision Oncology:

## Tackling PK Variability in Cancer Chemotherapy



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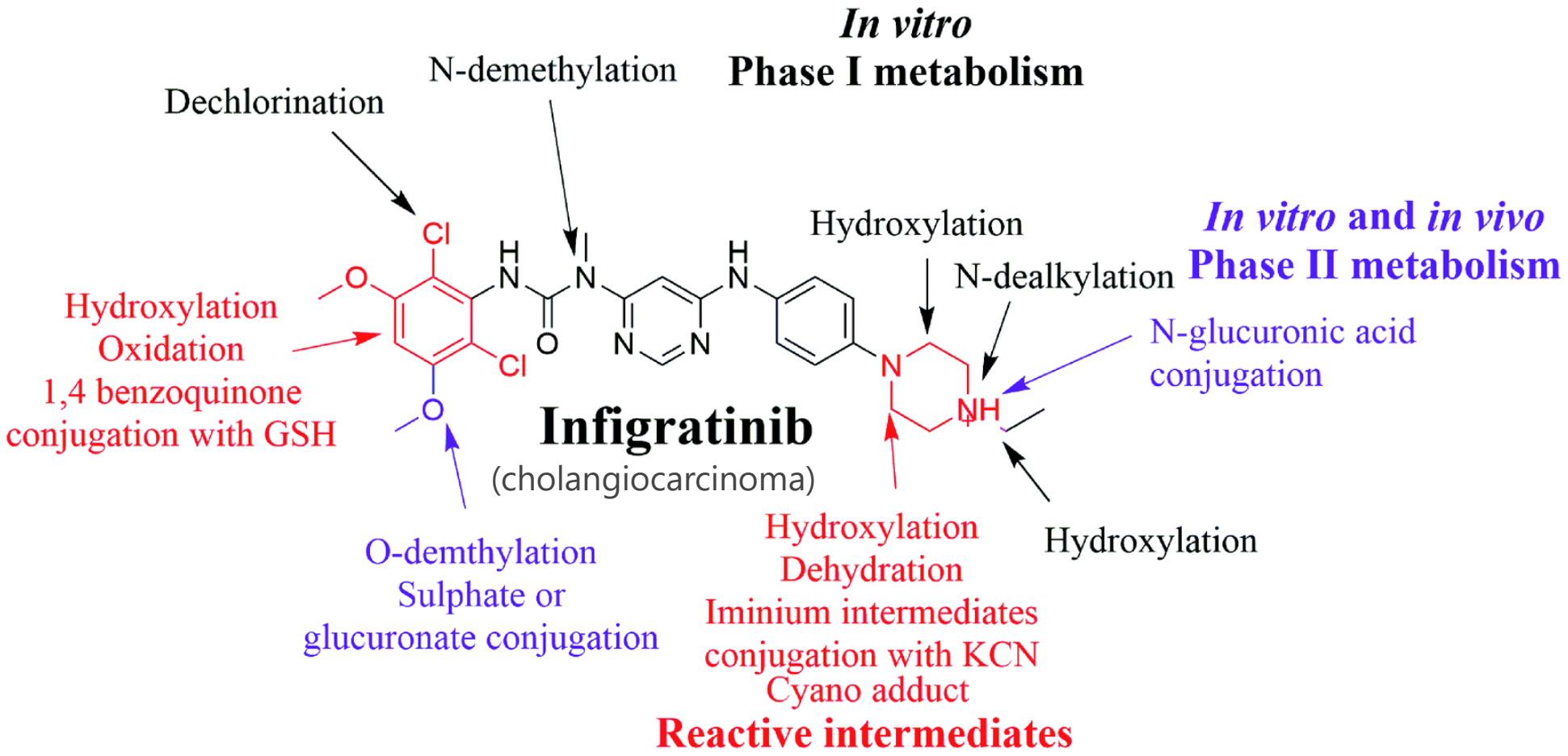
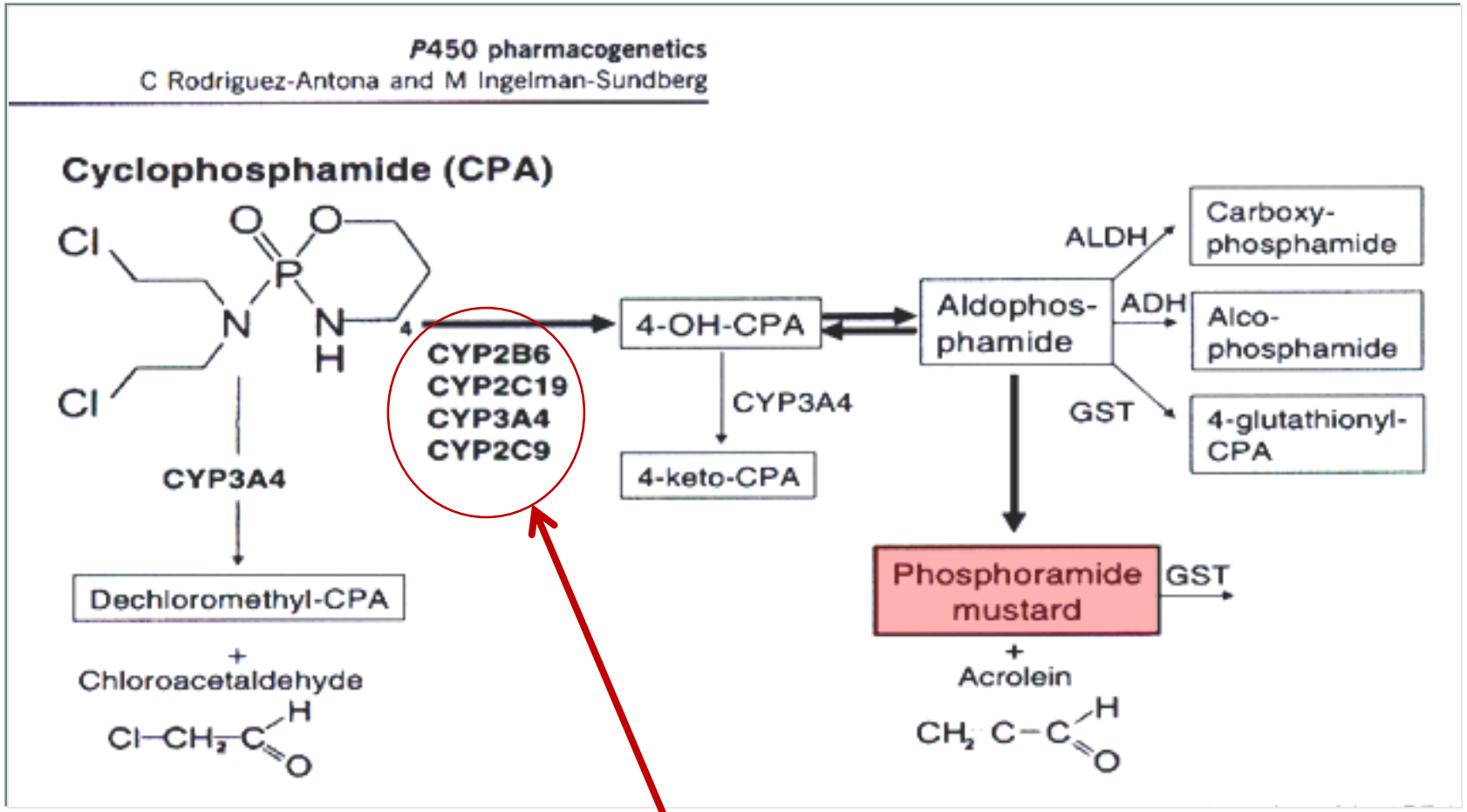
# DRUG METABOLISM



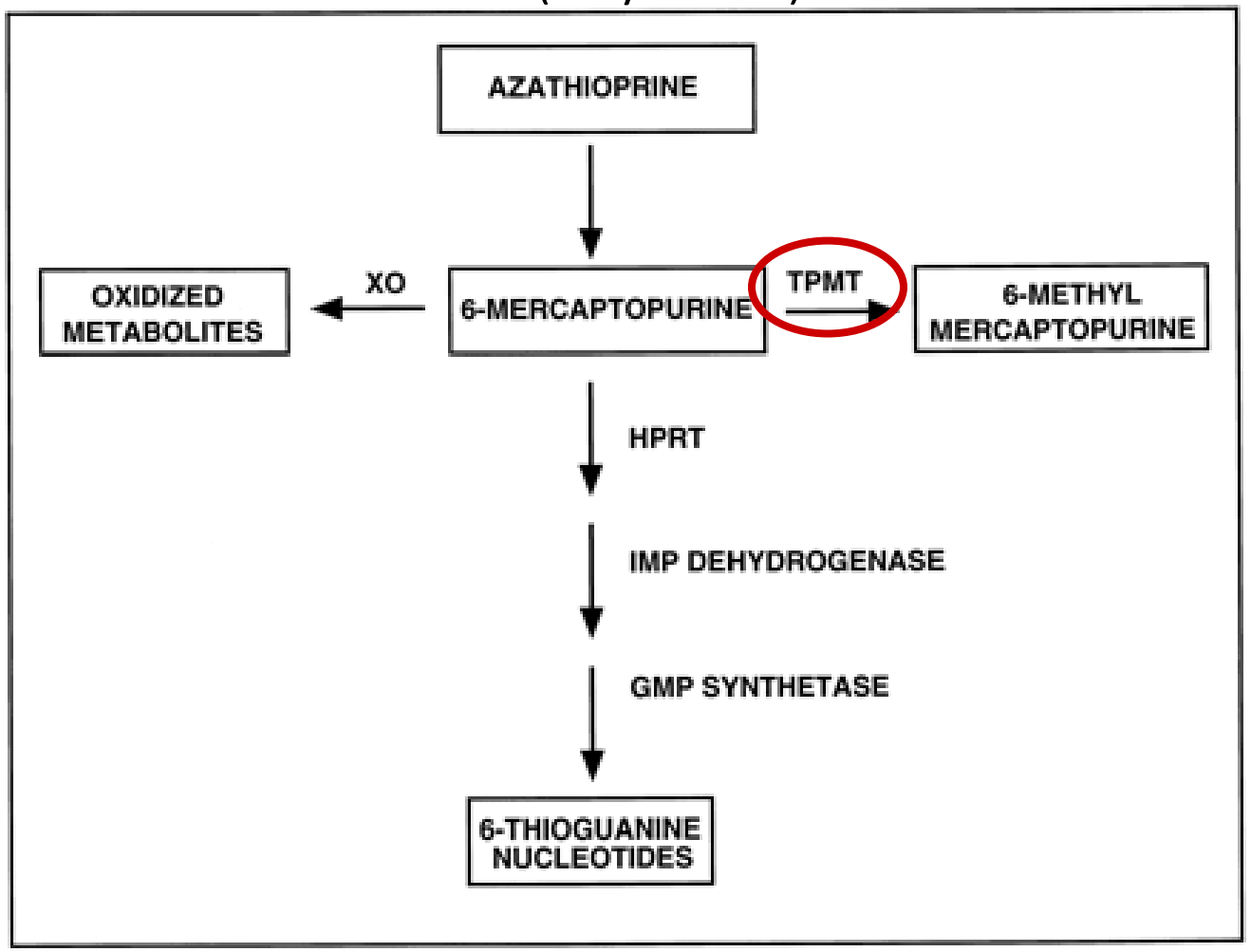
# Cyclophosphamide Bioactivation




**Genetic variants?**

# 6-MP Inactivation

Weinshilboum (Mayo Clinic) 2001




**PharmGKB -- http://www.pharmgkb.org/**

International Journal of *Molecular Sciences*

MDPI

*Review*

# State of Art of Cancer Pharmacogenomics in Latin American Populations

Andrés López-Cortés [1], Santiago Guerrero [2], María Ana Redal [3], Angel Tito Alvarado [4] and Luis Abel Quiñones [5,*]

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 19 May 2021

# Preliminary pharmacogenomic-based predictive models of tamoxifen response in hormone-dependent Chilean Breast Cancer patients

Carla Miranda[1], Macarena Galleguillos[1], Roberto Torres.[2], Karla Tardón S. [2], Dante D. Cáceres[3], Kuen Lee[1,4], Nelson M. Varela[1,5*], Luis A. Quiñones[1,5*]

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 08 March 2019

# Association Study Among Candidate Genetic Polymorphisms and Chemotherapy-Related Severe Toxicity in Testicular Cancer Patients

*María A. Lavanderos[1], Juan P. Cayún[1], Ángela Roco[1,2], Christopher Sandoval[1], Leslie Cerpa[1], Juan C. Rubilar[1], Roberto Cerro[1], Sebastián Molina-Mellico[1], Cesar Celedón[1], Berta Cerda[3], Elena García-Martín[4], José A. G. Agúndez[4], Cristián Acevedo[1,5], Karina Peña[6], Dante D. Cáceres[1,7], Nelson M. Varela[1*] and Luis A. Quiñones[1*]*

Cordova-Delgado *et al. BMC Cancer* (2021) 21:1030
https://doi.org/10.1186/s12885-021-08745-0

BMC Cancer

RESEARCH Open Access

# A case-control study of a combination of single nucleotide polymorphisms and clinical parameters to predict clinically relevant toxicity associated with fluoropyrimidine and platinum-based chemotherapy in gastric cancer

Miguel Cordova-Delgado[1,2,3], María Loreto Bravo[3], Elisa Cumsille[2], Charlotte N. Hill[2,4], Matías Muñoz-Medel[3], Mauricio P. Pinto[3], Ignacio N. Retamal[5], María A. Lavanderos[6,7,8], Juan Francisco Miquel[9], Maria Rodriguez-Fernandez[10], Yuwei Liao[11,12], Zhiguang Li[12,13], Alejandro H. Corvalán[3,14], Ricardo Armisén[15], Marcelo Garrido[3], Luis A. Quiñones[6,7*] and Gareth I. Owen[2,3,4,14*]

*Current Oncology*

MDPI

*Article*

# Genetic Polymorphisms and Tumoral Mutational Profiles over Survival in Advanced Colorectal Cancer Patients: An Exploratory Study

Juan Pablo Cayún [1,2], Leslie Carol Cerpa [1,2], Alicia Colombo [3,4], Dante Daniel Cáceres [5], José Luis Leal [6], Felipe Reyes [6], Carolina Gutiérrez-Cáceres [1,7], Susan Calfunao [1,2,8], Nelson Miguel Varela [1,2,*] and Luis Abel Quiñones [1,2,7,*]

*Curr. Oncol.* 2024, 31, 274-295. https://doi.org/10.3390/curroncol31010018

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 10 March 2021

# Pharmacogenetics–Based Preliminary Algorithm to Predict the Incidence of Infection in Patients Receiving Cytotoxic Chemotherapy for Hematological Malignancies: A Discovery Cohort

OPEN ACCESS

*Matías F. Martínez[1,2,3*], Enzo Alveal[1], Tomas G. Soto[1,4], Eva I. Bustamante[5], Fernanda Ávila[6], Shrikant I. Bangdiwala[7,8], Ivonne Flores[9], Claudia Monterrosa[9], Ricardo Morales[9], Nelson M. Varela[1,2], Alison E. Fohner[9] and Luis A. Quiñones[1,2*]*

The Pharmacogenomics Journal
https://doi.org/10.1038/s41397-019-0102-4

CONSENSUS STATEMENT

# Pharmacogenomics, biomarker network, and allele frequencies in colorectal cancer

Andrés López-Cortés[1,2,3] · César Paz-y-Miño[1] · Santiago Guerrero[1,4] · Gabriela Jaramillo-Koupermann[5] · Ángela León Cáceres[6] · Dámaris P. Intriago-Baldeón[7,8] · Jennyfer M. García-Cárdenas[1] · Patricia Guevara-Ramírez[1] · Isaac Armendáriz-Castillo[1] · Paola E. Leone[1] · Luis Abel Quiñones[3,9] · Juan Pablo Cayún[3,9] · Néstor W. Soria[10]

# Biomarkers

| Drug | Therapeutic type | PGx Biomarker | Reference sub-group |
|---|---|---|---|
| Amitryptiline | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Capecitabine | Oncology | *DPYD* | DPD deficiency |
| Cisplatin | Oncology | *TPMT* | TPMT Poor or intermediate Metabolizer (PM or IM) |
| Citalopram | Psychiatry | *CYP2C19* | CYP2C19 Poor Metabolizer (PM) |
| | | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Clozapine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Codeine | Anesthesiology | *CYP2D6* | CYP2D6 Ultrarapid Metabolizer (UM) |
| Desipramine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Diazepam | Psychiatry | *CYP2C19* | CYP2C19 Poor Metabolizer (PM) |
| Doxepine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| | | *CYP2C19* | CYP2D6 Poor Metabolizer (PM) |
| Fluorouracil (5-FU) | Oncology | *DPYD* | DPD deficiency |
| Fluoxetine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Fluvoxamine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Iloperidone | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Imipramine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Irinotecan | Oncology | *UGT1A1* | UGT1A1*28 carriers |
| Mercaptopurine | Oncology | *TPMT* | TPMT Poor or intermediate Metabolizer (PM or IM) |
| Modafinilo | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Nefazodone | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Nilotinib | Oncology | *UGT1A1* | UGT1A1*28 (TA)7/(TA)7 genotype |
| Nortriptiline | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Pazopanib | Oncology | *UGT1A1* | UGT1A1*28 (TA)7/(TA)7 genotype |
| Rasburicase | Oncology | *G6PD* | G6PD deficiency |
| | | *CYB5R1-4* | NADH cytochrome b5 reductase deficiency |
| Risperidone | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Tamoxifen | Oncology | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Thioguanine | Oncology | *TPMT* | TPMT Poor or intermediate Metabolizer (PM or IM) |
| Tramadol | Analgesia | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Trimipramine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |
| Venlafaxine | Psychiatry | *CYP2D6* | CYP2D6 Poor Metabolizer (PM) |

## Kits

| Gene | Drug | Consequence |
|---|---|---|
| *TPMT* | 6MP | Toxicity |
| *CYP2D6* | Tamoxifen | Decreased Efficacy |
| *UGT1A1* | Irinotecan | Toxicity |
| *CYP2D6* | Codein | Ineffective analgesia |

Luis Quiñones S.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

2024. 36 Clinical Guidelines for drug/gene pairs

CPIC UPDATE

# Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update

Ursula Amstutz[1], Linda M. Henricks[2], Steven M. Offer[3], Julia Barbarino[4], Jan H.M. Schellens[2,5], Jesse J. Swen[6], Teri E. Klein[4], Howard L. McLeod[7], Kelly E. Caudle[8], Robert B. Diasio[3,9] and Matthias Schwab[10,11,12]

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 00 NUMBER 00 | MONTH 2017

CQF

*Luis Quiñones S.*


# RELIVAF

**Red Latinoamericana de implementación y validación de guías clínicas Farmacogenómicas**

***111 Participants from 16 countries**

https://cyted.org/web_redes.php?id_rede=138

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TYPE Original Research
PUBLISHED 11 May 2023
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# An updated examination of the perception of barriers for pharmacogenomics implementation and the usefulness of drug/gene pairs in Latin America and the Caribbean

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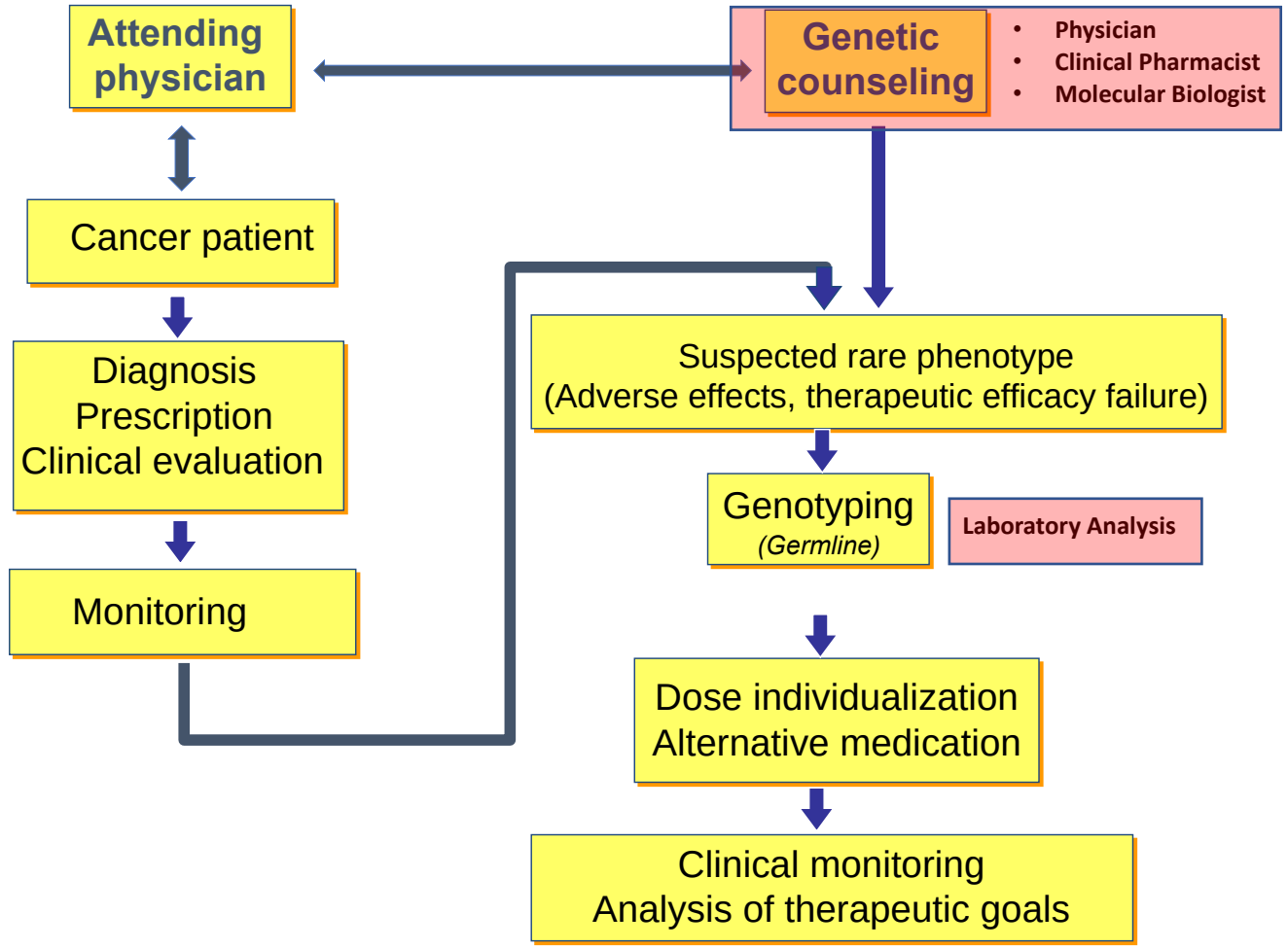


**Proposed Oncological Pharmacogenetic Algorithm for Implementation in the Chilean Healthcare System**
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