Pharmacogenomics: Implications for Palliative Care Practice

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THE UNIVERSITY OF ADELAIDE AUSTRALIA

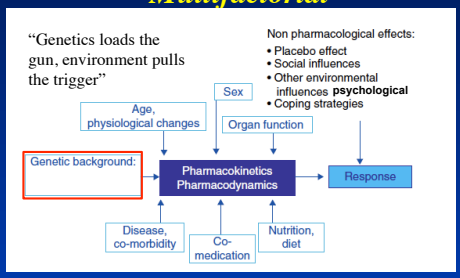
Centre for Palliative Care Research and Education

Queensland Government

Declaration

- Mundipharma
  - 2007: Chair Transdermal Buprenorphine Advisory Group
  - 2010: Consultancy-Targin PBS Submission
- TGA: ACNM- Advisory Committee on NonPrescription Medicines
- AMH: Board Director & Editorial Advisory Committee

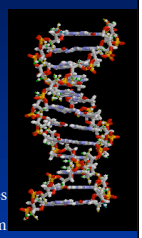
Large Variability in Drug Responses: *Multifactorial*



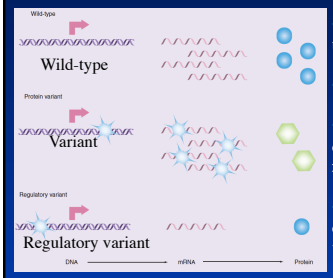
PHARMACOGENOMICS

- The study of variations of DNA and RNA characteristics as related to drug response (ICH E15
- Relates to genotype (often multiple)
  - A,T; C,G
- Gene expression
- Protein expression

- 2 metres DNA/cell
- 3 billion bases
- ~ 5 **million** variants between 2 genomes
- ~23,000 genes for proteins that perform most life functions



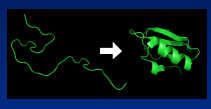
Genetics Snapshot



- Genes encoded by DNA -> transcribed to RNA
- mRNA molecules -> translated to proteins
- 1 protein = 1 function?
- aberrant proteins encoded by mutant gene variants -> aberrant biological activity
- ↑ or ↓ amount normal protein encoded by regulatory gene variant -> ↑ or ↓ biological activity

Bader JP Pharmacogenomics 2008

Gene Mutations



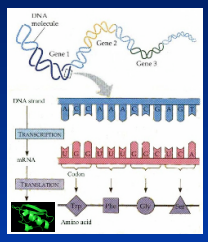
- Changes in base sequence of DNA
  - SNPs [single nucleotide polymorphisms]
  - Insertions/Deletions [called InDels]
  - Gene deletion
- Coding SNPs: Changes in amino acid structure of protein (drug target) -> altered binding to drug
- Transcriptional SNPs: Increased/reduced protein (drug target) expression or degradation
- RNA SNPs: RNA processing is altered -> altered protein folding
- *Loss of function* alleles much more common than gain of function
- Genetic Polymorphisms: frequency of >1% population

Palliative Medicine: Many drugs used

- **Analgesics**
- Antiemetics
- Antidepressants
- Sedatives
- Antipsychotics
- +……..

Candidate Genes, Proteins and Medicines

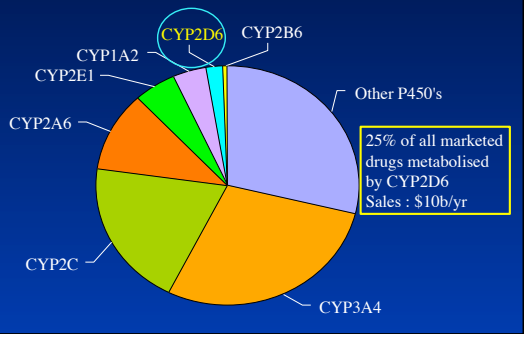
- Drug Metabolising Enzyme
  - CYP2D6: codeine, tramadol, tropisetron
- Drug Transporter
  - P-glycoprotein: morphine, fentanyl
- Drug Target
  - Mu opioid receptor: Morphine



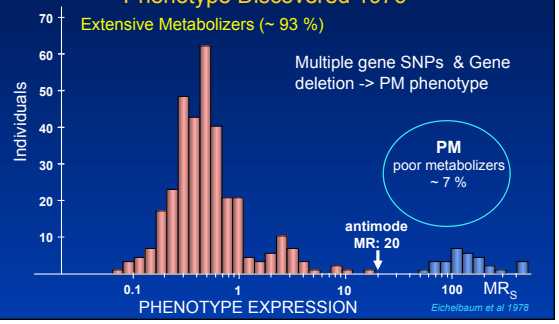
Role of Genomic Factors in Interindividual Variability in Response to Medicines

- Pharmacokinetics
  - Metabolising enzymes
  - Transporters (efflux and uptake)
- Pharmacodynamics
  - Receptors & signalling pathways
- Candidate gene approach

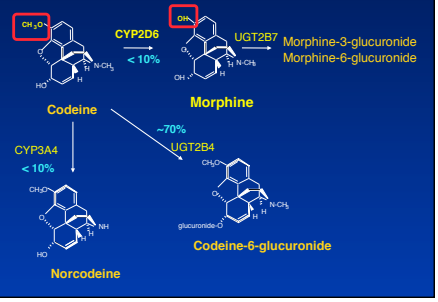
Human Cytochrome P450 Isoforms: Liver Content



CYP2D6: Highly Polymorphic Enzyme- EM/PM Phenotype Discovered 1976



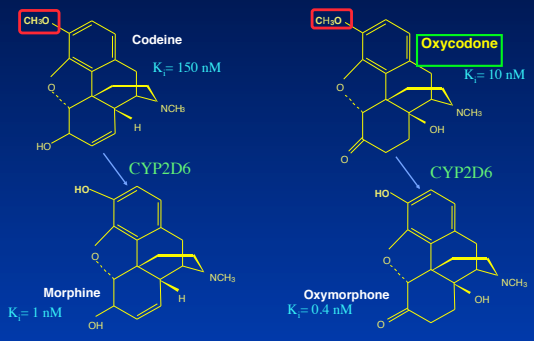
Codeine Metabolic Pathway: Prodrug



CYP2D6 Poor Metabolisers of Codeine: No antinociception in Cold Pressor Test

CYP2D6 Extensive versus Poor Metaboliser

- Poulsen et al 1991: no codeine (75-100 mg) analgesic effect to cold pressor test in PM
- Eckhardt et al 1998: no codeine (170 mg) analgesic effect to cold pressor test in PM
- No clinical pain studies



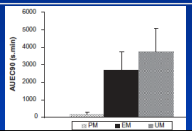
Oxycodone Analgesia and *CYP2D6*

- Attenuation of morphine-induced delirium in palliative care by substitution with infusion with oxycodone (*Maddocks et al. J Pain Symptom Management 12: 182-189, 1996*)
  - 12 EM + 1 PM
  - PM: highest oxycodone dose (250 mg vs 68 (8-180 mg)) + highest number of doses (13 vs 4 (0-9)) of breakthrough analgesic

- No difference in dose required between PMs and EMs for post operative analgesia
- EM 1-16 mg: PM 9-17 mg

(Zwisler et al. Acta Anesthesiol Scand 54, 232, 2010)

↓Cold Pressor Response to Oxycodone in PMs (Samer et al BJP 160, 919, 2010)



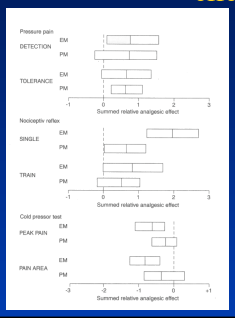
Influences on the pharmacokinetics of oxycodone: a multicentre cross-sectional study in 439 adult cancer patients

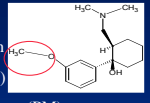
Trine Naalsund Andreassen · Pål Klepstad · Andrew Davies · Kristin Bjordal · Staffan Lundström · Stein Kaasa · Ola Dale

Eur J Clin Pharmacol 67, 493, 2011

- Predictors of plasma oxycodone
  - Sex
  - CYP3A inducers/inhibitors
  - Dose
- CYP2D6 genotype to follow
  - Plasma oxymorphone/oxycodone not normal distribution

CYP2D6 Polymorphism: Tramadol reduced effect in PMs





- Experimental pain
- 15 extensive (EM)
- 12 Poor metabolisers (PM)

Poulsen et al Clin Pharmacol Ther 60, 636, 1996

- Post Operative Surgical Patients PCA
- Responder: sufficient analgesia without rescue analgesia
- 81% PM nonresponders
- 17% EM nonresponders (P=0.001)

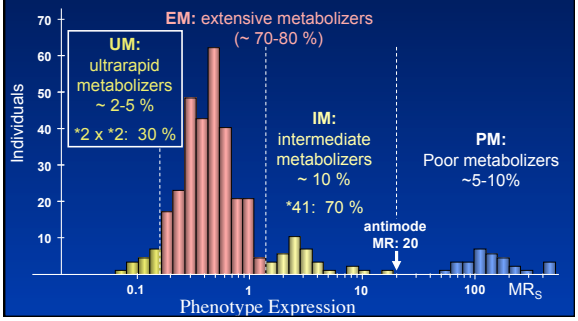
Stamer et al Clin Pharm Ther 82: 41, 2007

Increased Adverse Effects to Antidepressants in CYP2D6 I/PMs

- 50 psychiatric patients: amitriptyline 150 mg/day
- Side effects: CNS (confusion/agitation), anticholinergic/GI
- Risk of Side effects: related to CYP2D6 allele (P<0.001)
  - 2 functional 2D6 alleles: 12.1%: extensive metaboliser
  - 1 functional 2D6 allele: 76.5%: intermediate metaboliser
- Unlikely in palliative medicine as dose is less but potential interactions with inhibitors
- CYP2D6 Ultrarapid metabolisers: ? Reduced efficacy

Steimer et al Clin Chem 51, 376, 2005

CYP2D6 Polymorphism



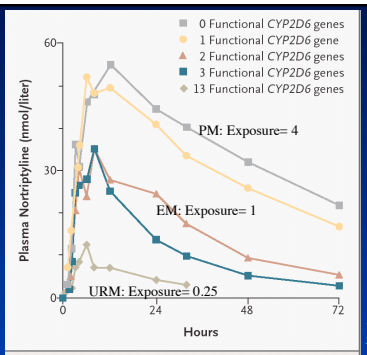


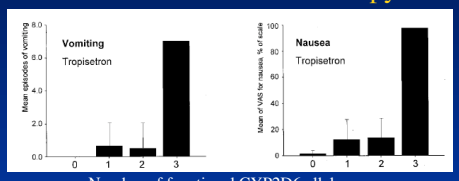
Figure 4. **Pharmacogenetics of Nortriptyline.**

CYP2D6 Genotype and Pharmacokinetics

Failure to respond to antidepressants has been reported in patients with multiple gene copies: gene-dose effect
(Kawanishi et al EJCP 2004)

Weinshilboum et al NEJM 348: 529, 2003

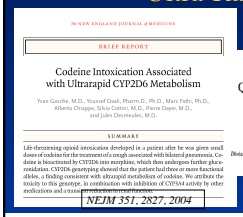
Tropisetron: less effective in CYP2D6 Ultra Rapid Metabolisers with 3 functional alleles 5-24 hr after chemotherapy



- Ondansetron: results not as conclusive as other CYPs involved

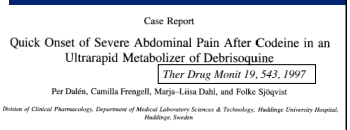
Kaiser et al J Clin Oncol 20, 2805, 2002

Case Reports of Codeine Toxicity in CYP2D6 Ultra-Rapid Metabolisers



Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

NEJM 351; 2827, 2004



Case Report

Quick Onset of Severe Abdominal Pain After Codeine in an Ultrarapid Metabolizer of Debrisoquine

Ther Drug Monit 19, 543, 1997

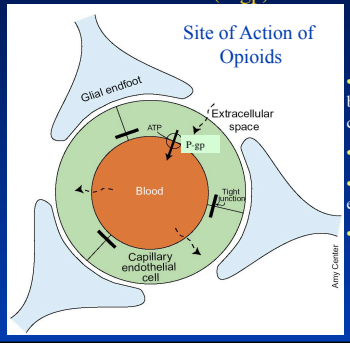
Per Dalén, Camilla Frengell, Marja-Liisa Dahl, and Folke Sjöqvist

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Role of Genetic Factors in Interindividual Variability in Response to Medicines

- Pharmacokinetics
  - Metabolism: CYP2D6
  - Transporter (efflux and uptake)
- Pharmacodynamics
  - Receptor & signalling pathways

P-GLYCOPROTEIN (P-gp): Blood Brain Barrier

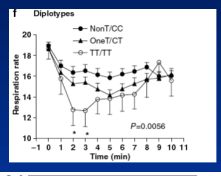


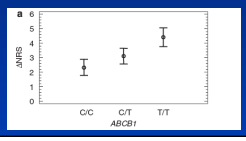
- Apical membranes of brain capillary endothelial cells.
- Basal > apical transport
- Potential to limit CNS exposure
- Encoded by *ABCB1*

Edwards Nature Neuroscience 4, 221, 2001

ABCB1 Variants and Other Opioids

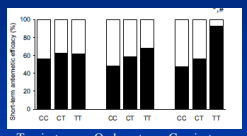
- Fentanyl: increased respiratory depressant effect in *ABCB1* variants (G2677T, C3435T)[n=126]
  (Park et al Clin Pharmacol Ther 81, 539, 2007)
- Morphine: increased analgesic effect in *ABCB1* variant C3435T [n=145]
  (Campa et al Clin Pharmacol Ther 83, 559, 2008)





5HT$_3$ Antagonists: *ABCB1*

- All are substrates and require effective CNS concs
- Polymorphisms in *ABCB1* gene: better response

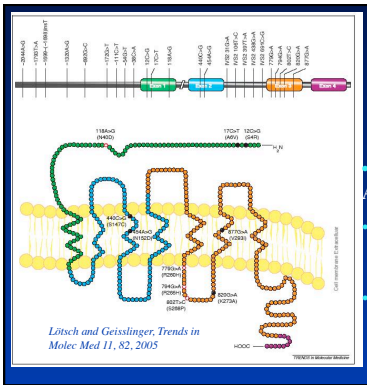


- Granisetron: better response in *ABCB1* 3435 variant
- Tropisetron, Ondansetron: no difference

Babaoglu et al Clin Pharmacol Ther 78, 619-26, 2005

Role of Genetic Factors in Interindividual Variability in Response to Opioids

- Pharmacokinetics
  - Metabolism: CYP2D6
  - Transporter: *ABCB1*- p-glycoprotein
- Pharmacodynamics
  - Receptor

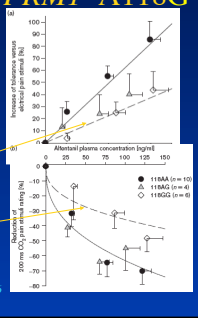


OPRM1: Mu Opioid Receptor Gene

- 30 Mutations: with amino acid changes & variant frequency > 1%
- A118G: best studied Asn40→Asp
- alters mRNA/Protein
  - Loss of function
- G variant allele:
  - 12% Caucasians
  - 40% Asians

Alfentanil Analgesia and Respiratory Depression: *OPRM1* A118G

- Healthy subjects dosed with alfentanil
- G variant allele: reduces
  - analgesia- electrical stimulation (2-4-fold)
  - Respiratory depression (10-12 fold)



Oertel et al Pharmacogenetics & Genomics, 16, 625, 2006

Morphine Analgesia and *OPRM1* A118G Polymorphism (1): Cancer patients on chronic oral morphine

A118G Genotype	Oral Morphine Dose (mg/day)[mean±SD]	
AA (n=78)	97±89	No difference in plasma morphine or M6G concentrations
AG (n=17)	66±50	
GG (n=4)	225±143*	

*P = 0.006

Klepstad et al Acta Anesthesiol Scand 48, 1232, 2004

- low responder to 2 g morphine was A/G *(Hirota et al Drug Metab Dispos 31:677, 2003)*

OPRM1 A118G Variant: Increased Opioid Requirements in Postoperative Pain

- 22%: PCA Morphine- hysterectomy (Chou et al 2006)
- 60%: PCA Morphine- knee arthroplasty (Chou et al 2006)
- 60%: PCA Morphine- caesarian (Sia et al 2008)
- 20%: Epi Morphine/fentanyl- abdominal (Hayashida et al 2008)
- 75%: PCA Morphine- caesarian (Choo et al 2009)
- 0% : PCA fentanyl- cosmetic (Fukuda et al 2009)

IASP PAIN® 146 (2009) 270–275 PAIN®
www.elsevier.com/locate/pain

Meta-analysis of the relevance of the *OPRM1* 118A>G genetic variant for pain treatment

Carmen Walter, Jörn Lötsch *

"…. Despite initially promising results, available evidence of the clinical relevance of the OPRM1 118A>G polymorphism does not withhold a meta-analysis"

- Many Pain Types: Experimental, Cancer, Postoperative, Disease, Childbirth
- Many Opioids: morphine, M6G, fentanyl, alfentanil, methadone
- Low patient numbers: 8/24 studies > 100 subjects

Summary: Impact of Pharmacogenomics on Drugs

- Efficacy & side effects of medicines:
  - Metabolism: *CYP2D6* → ↓↑ effect PMs ; ↓↑effect URMs
    - Active metabolites: tramadol, codeine, oxycodone (?)
    - Active Drug: nortriptyline, amitriptyline, tropisetron
  - Transporters: *ABCB1 variant* → ↑effect
    - fentanyl, morphine, granisetron
  - Target Sites: *OPRM1 variant* → ↓↔ effect
    - morphine, alfentanil
- *Examples of Candidate Gene Approach*

Genes Associated with Altered Pain Perception & Processing

- Opioid receptors
- **Catechol-O-Methyltransferase**
- Transient Receptor Potential Cation Channels
- Fatty Acid Amino Hydrolase
- GTP Cyclohydrolase
- **Interleukin-1 related (cytokines)**

Other Pain Targets (1) Morphine & COMT Polymorphism: G474A

Cancer patients on chronic oral morphine

COMT Genotype	Oral Morphine Dose (mg/day)[mean±SD]	
Val/Val (n=44) HW	155±160	No difference in plasma morphine or M6G concentrations
Val/Met (n=96) HetV	117±100	
Met/Met (n=67) HV	95±99*	

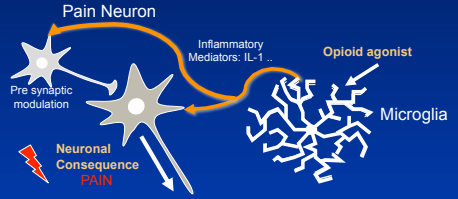
*P = 0.025 Jonkcheere-Terpstra

Rakvåg et al Pain 116, 73, 2005

COMT(Catechol-O-methyltransferase): metabolises noradrenaline, adrenaline, dopamine

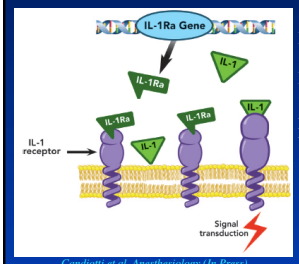
Opioids – Glia – Cytokines – Pain

- Glia are activated by opioids
- Proinflammatory response
- Enhanced Pain - decreased analgesia
- Increased tolerance, dependence, reward, etc



Dorsal horn glial activation from any source → enhanced pain

(IL)-1β – Receptor Antagonist (Ra) – Receptor



- IL-1β (pro-inflammatory) acts on IL-1 receptor-> signal transduction
- IL-1Ra gene regulates IL-1β & IL-1Ra release
- IL-1Ra binds to IL-1 receptor, prevents IL-1β binding & signal transduction
- IL-1Ra gene = *IL-1RN*
- *IL-1RN* tandem repeats 86 bp
  - *IL-1RN*1* -> 4 repeats
  - *IL-1RN*2* -> 2 repeats
  - *IL-1RN*3* -> 5 repeats

loss of function

Candiotti et al Anesthesiology (In Press)

Cytokine Genetics and Post-Operative Analgesia (1)

Postoperative pain, morphine consumption, and genetic polymorphism of IL-1β and IL-1 receptor antagonist

Neurosci Lett 404, 154, 2006

H. Bessler[a,*], Y. Shavit[c], E. Mayburd[b], G. Smirnov[b], B. Beilin[b]

- 76 transabdominal hysterectomy patients
- PCA Morphine 24 hr: High (> 38 mg), Medium (28-38), Low (< 28 mg/day)
- Genotype: IL-1β & IL-1Ra(*IL-1RN*1, *2*)
- No effect of genotype on morphine consumption
- *IL-1RN*1/*2* genotype differences between morphine groups:
  - Low 0.42
  - Medium 0.16 (P<0.022)
  - High 0.46

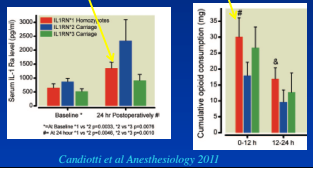
Why no direct genotype –morphine consumption is unclear

Cytokine Genetics and Post-Operative Analgesia (2)

- 96 patients- nephrectomy
- *IL-1RN*1, *2, *3*
- Serum IL-1Ra: 0 & 24 hr
- PCA: morphine

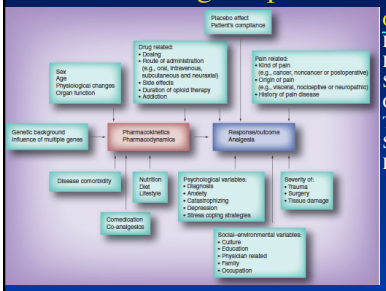
Results

- *IL-1RN*1/*1*:
  - lower conc IL-1Ra
  - higher morphine dose



Candiotti et al Anesthesiology 2011

Genetic & Non-genetic Factors Influencing Response to Analgesics



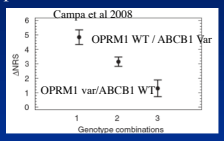
Genetic Research Pitfalls

Pain: difficult phenotype
Population stratification
Sample size- small
Genes & SNPs: which?
Type 1/2 errors
Statistical Analysis
Publication bias

Applicable to many drugs & drug classes

Pharmacogenomics & Opioids

- Role becoming clearer - Large prospective studies needed
- Haplotype analysis is important
- Epistasis: gene-gene interactions
  - Metabolic enzymes
  - Transporters
  - Receptors
  - Cytokines
- important genetic factors that contribute to interpatient variability in pain relief to opioids
- Large prospective studies needed: Current NHMRC Project Grant with EPOS



No Effect of 25 Gene Polymorphisms on Opioid Dose

Influence from genetic variability on opioid use for cancer pain: A European genetic association study of 2294 cancer pain patients

Pain 152, 1139, 2011

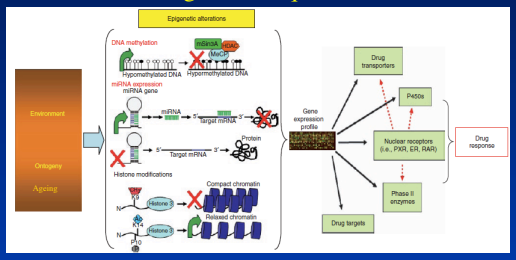
P. Klepstad[a,n,*], T. Fladvad[a], F. Skorpen[a], K. Bjordal[b], A. Caraceni[c], O. Dale[a,n], A. Davies[d], M. Kloke[e], S. Lundström[f,g], M. Maltoni[h], L. Radbruch[i], R. Sabatowski[j], V. Sigurdardottir[k], F. Strasser[l], P.M. Fayers[a,m], S. Kaasa[a,n], On behalf of the European Palliative Care Research Collaborative (EPCRC) and the European Association for Palliative Care Research Network

- 2294 patients: 17 Centres, 11 European Countries (EPOS)
- morphine (830), oxycodone (446), fentanyl (619) +… : Oral, SC, IV, TD
- Oral opioid morphine equivalents
- *OPRM1, OPRD1, OPRK1, ARRB2, GNAZ, HINT1, Stat 6, ABCB1, COMT, HRH1, ADRA2A, MC1R, TACR1, GCH1, DRD2, DRD3, HTR3A, HTR3B, HTR2A, HTR3C, HTR3C, HTR3D, HTR3E, HTR1, CNR1*
- Opioid: receptors, signalling, expression, transporters, modifiers (adrenergic, melanocortin, neurokinin, dopamine, serotonin, histamine, cannabinoid receptors; enzymes: COMT, cyclohydrolase)

Currently: No rationale for PGx Testing in Palliative Medicine to Guide Therapy

- Might help to explain:
  - Abnormal dosing requirements
  - Severe adverse effects
- It is possible to do good science in Palliative Medicine
  - 1 blood sample at any time allows
    - Pharmacokinetics
    - Pharmacogenomics

Epigenetic Phenomena: phenotypic changes not involving DNA sequence alterations



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