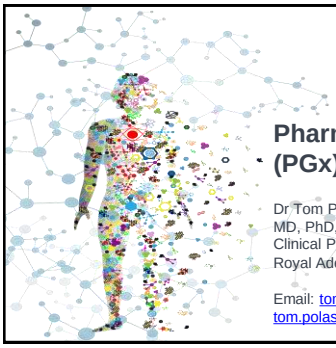

Pharmacogenomics (PGx) and Depression

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Disclosures

- I am employed by SA Health
- I am a clinical pharmacologist in training
- I am paid consultant of Certara and Sonic Genetics

Government of South Australia
SA Health

CERTARA
d3 Medicine

Sonic Genetics

Learning Objectives

The Theory of PGx

1. Understand why between patient variability (BPV) impacts pharmacotherapy
2. Know about the sources of BPV in drug response
3. Understand the scientific basis of PGx and why clinical implementation is hard
4. Know that commercial PGx reports reference clinical PGx guidelines

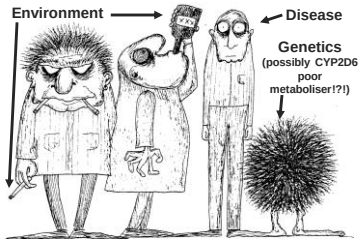
The Practice of PGx for MDD

5. Know the main clinical question that PGx might help with for MDD
6. Know that RCTs on PGx for MDD have been published
7. Identify the antidepressants with the highest quality PGx guidance
8. Describe clinical scenarios where PGx testing may be warranted
9. Know what PGx tests are available and how to order

Pharmacogenomics (PGx) is the study of the role of genetics in drug response

Between Patient Variability in Drug Response

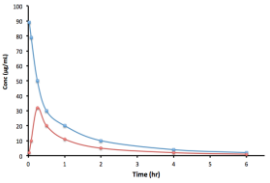
All patients are different!



Slide courtesy of Geoff Tucker, University of Sheffield

Pharmacokinetics (PK)

- "What the body does to the drug"
- Determines the level of drug exposure at its target
- **ABCD**
  - **A**dministration
  - **B**ioavailability
  - **C**learance
  - **D**istribution
- **BCD** processes occur via:
  - Drug metabolising enzymes
    - CYP, UGT, NAT
  - Drug transporters
    - P-gp, SLCO1B1



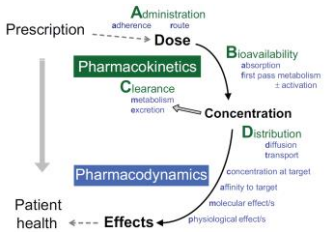
Doogue & Polasek 2013 TADS 4(1):5-7

Pharmacodynamics (PD)

- "What the drug does to the body"
- Determines the level/type of drug response
  - Efficacy and effectiveness
  - Adverse effects
- What we assess and/or measure (biomarkers)
  - Symptoms – mood, pain, sleep quality, memory etc.
  - Signs – BP, temperature, joint swelling,
  - Tests – PSA, tumour size, HIV copies, 6MWT etc.

From Prescription to Patient Health - Dependent on PK/PD

- Many **CO-FACTORS** influence these **STEPS**.
  - Age
  - Weight
  - Kidney function
  - Liver function
  - Environment e.g., smoking
  - Co-medications
  - Time of dose
  - Genetics



Genetics is ONE co-factor that influences PK/PD.

Doogue & Polasek 2013 TADS 4(1):5-7

The Basis of PGx

Genes	Analytical result Genotype (variants or "alleles")	Analytical interpretation Phenotype (enzyme activity)	Clinical interpretation Prescribing guidance for drug
ABCB1 CYP1A2 CYP2C19 CYP2C9 **CYP2D6** CYP3A4 CYP3A5 DPYD HLA-B*1502 HLA-B*5701 HLA-B*5801 OPRM1 SLCO1B1 TPMT UGT1A1 VKORC1	***4/*4** c.12345C>T rs4244285 etc …	**Poor metaboliser** Normal metaboliser Rapid metaboliser etc …	**Choose another drug** Usual care Use with caution Change dose **with strength of evidence for this advice!**

The principles look simple.

Clinical Implementation

Differentiate levels of evidence and clinical utility

CPIC: An international project to assess the evidence for PGx and for prescribing guidance.

Level of Evidence	A: Strong clinical Recommendation	B: Mod. clinical recommendation	C: Optional advice
1 (high)			
2 (modest)			
3 (low)			

https://cpicpgx.org/

Sonic genetics has guidance based on a similar framework using the CPIC evidence.

Strength of recommendation	Follow usual advice	Use with caution	Don't use!
Actionable			
Informative			

https://www.pharmgkb.org/

Relling MV, Klein TE. 2009. *Clinical Pharmacology & Therapeutics* 89: 464-7

Categories of PGx

1) **Pharmacokinetic PGx (Exposure PGx)**

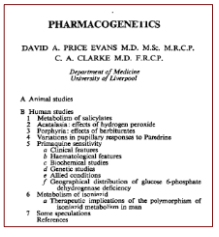
2) **Pharmacodynamic PGx (Response PGx)**

3) **Safety PGx (severe ADR PGx)**

Polasek et al. 2018 Exp Rev Clin Pharmacol 11(8):743-746

Pharmacokinetic PGx

Is my patient at risk of extreme exposure to the drug at a recommended dose?

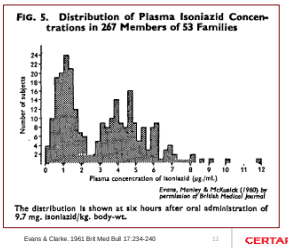


PHARMACOGENETICS

DAVID A. PRICE EVANS M.D. M.Sc. M.R.C.P.
C. A. CLARKE M.D. F.R.C.P.
Department of Medicine, University of Liverpool

A Animal studies

B Human studies
1 Metabolism of salicylates
2 Acatalasia: effects of hydrogen peroxide
3 Porphyria: effects of barbiturates
4 Variations in pupillary responses to Parédrine
5 Primaquine sensitivity
a Clinical features
b Haematological features
c Biochemical studies
d Genetic studies
e Allied conditions
f Geographical distribution of glucose 6-phosphate dehydrogenase deficiency
6 Metabolism of isoniazid
a Therapeutic implications of the polymorphism of isoniazid metabolism in man
7 Some speculations
References



The distribution is shown at six hours after oral administration of 9.7 mg. isoniazid/kg. body-wt.

Evans & Clarke. 1961 Brit Med Bull 17:234-240

Pharmacodynamic PGx

Does my patient have the right molecular target for this drug?

Disease/mechanism	Drug	Indicated subset
Cystic fibrosis/ CFTR potentiator	Ivacaftor	One mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data
Cystic fibrosis/ CFTR potentiator/corrector	Ivacaftor / lumacaftor	Homozygous CFTR F508del mutation
Duchenne muscular dystrophy/ exon skipper	Eteplirsen	Exon 51 skipping amenable mutations
NSCLC/ EGFR inhibitor	Erlotinib Afatinib Gefitinib	EGFR exon 19 deletions or exon 21 L858R substitution*
	Osimertinib	EGFR T790M mutation*
Melanoma/ BRAF inhibitor	Vemurafenib Dabrafenib	BRAF V600E mutation*
Melanoma/ MEK inhibitor	Trametinib	BRAF V600E/K mutations*
Ovarian cancer/ PARP inhibitor	Olaparib	Deleterious or suspected deleterious germline BRCA mutations*
	Rucaparib	Deleterious germline and/or somatic BRCA mutations*
Colorectal cancer/ EGFR inhibitor	Cetuximab	KRAS wild-type* (not RAS mutations)
	Panitumumab	KRAS wild-type (exon 2)* (not RAS mutations)
Solid tumours/anti-PD-L1	Pembrolizumab	Microsatellite instability-high (MSI-H) or mismatch repair deficient
Anticoagulation / VKORC1 Pain / OPRM1	Warfarin Opioids	Some genotypes (e.g., AG, AA) confer greater pharmacodynamics 'sensitivity' AA genotype confers greater pharmacodynamics 'sensitivity'

WARNING – there are association studies showing relationships between genotypes involved in drug action and treatment outcomes in psychiatry e.g., BDNF, HTR1A, HTR2A, HTR2C, GRIK4 etc. The evidence level for the clinical utility of these to inform prescribing is currently LOW.

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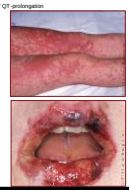
Safety PGx

Is my patient at increased risk of a serious adverse drug reaction at a recommended dose?

Drug	Details
Valproate	Contraindication in children with mitochondrial disorders resulting from POLG mutations based on risk of fatal hepatic failure
Codeine	Contraindication in children under 12 years of age based on risk of respiratory depression and death in CYP2D6 ultra-rapid metabolisers
Citalopram	Specifies a maximum recommended dose in CYP2C19 poor metabolisers is 20mg based on risk of QT-prolongation
Phenytoin	Warning regarding HLA-B*15:02 and risk of cutaneous reactions
Carbamazepine	Information regarding HLA-B*15:02 and HLA-A*31:01 and risk of cutaneous reactions
Allopurinol	Warning regarding HLA-B*5801 and risk of cutaneous reactions
Abacavir	Contraindicated in patients with HLA-B*5701 allele due to severe hypersensitivity reactions



Idiosyncratic reaction to carbamazepine
(usually within 8 weeks)
- **rash**
- **… fever, eosinophilia, hepatitis/nephritis**
- **… … severe mucosal ulceration**

Test for potential sensitivity before prescribing.

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PGx for Major Depressive Disorder

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The Challenge in Managing Depression

Major depressive disorder is common

- prevalence 6-12%
- significant clinical, social, and financial impact
- with poor response rate (~50%) to initial medication
- prolonged "trial and error" approach to drug choice and dose
- <50% achieve remission by 12 months

Changes to medication are common, drawn out, and complicated.

Prescribing in depression is tough.

Aust Prescr 2016 39:76-83

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Case Study – Failed SSRI Treatment

- 55 year-old women with a history of **anxiety and depression** under care of a psychologist.
- Patient lost her job, her mood deteriorated, she spent most days in bed, and motivation for finding new work was poor.
- Her GP prescribed **sertraline**, and titrated to 200 mg daily.
- No improvement after several months. Swapped to **citalopram**.

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Case Study – Failed SSRI Treatment cont.

- Symptoms worsened on citalopram, requiring psychiatric admission about 6 months after her initial clinical decline.
- Just prior to hospitalisation, pharmacogenomic test showed that she had **high CYP2C19 activity** (CYP2C19*17/*17) leading to rapid metabolism (i.e. probable low exposure) to sertraline and citalopram.
- On admission, she was changed to **venlafaxine** which is metabolised primarily by **CYP2D6** (for which she had normal activity).
- The patient recovered and came off medication 12 months later.

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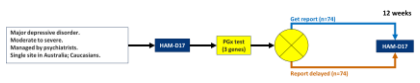
CNSDose Trial: Clinical Utility



Results

	Sertraline Escitalopram	Clomipramine Nortriptyline Amitriptyline
Mean HAM-D17 score	24 24	
% patients with normal HAM-D17 at 12 weeks	72% 28%	RR 2.52, p<0.0001
% patients tolerating Medications at 12 weeks	96% 85%	RR 1.13, p=0.027
% patients taking sick leave over 12 weeks	4% 15%	RR 1.13, p=0.027
Average number of sick days taken over 12 weeks	4.3 7.3	p=0.01

Singh. 2015 Clin Psychopharmacol Neurosci 13:150-156

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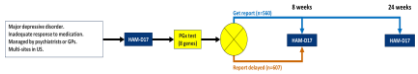
GUIDED Trail of Genesight®: Clinical Utility



Results

	Sertraline Citalopram Escitalopram Fluoxetine	Bupropion Trazodone Mirtazapine
Mean HAM-D17 score	21 21	
% decrease in mean HAM-D17 score at 8 weeks	27% 24% n.s.	42%
% patients with 50% drop in HAM-D17 score at 8 weeks	26% 20% RR 1.31, p=0.01	44%
% patients with normal HAM-D17 at 8 weeks	15% 10% RR 1.53, p=0.007	31%

Doxepin Imipramine | Chlorpromazine

Greden et al. 2019 J Psychiatr Res 111:59-67

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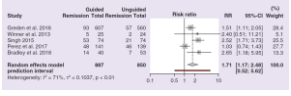
Meta-Analysis of PGx RCTs in MDD

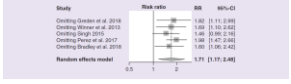
5 trials (US, Australia, Spain)

Remission as defined by HAM-D17 (score reverts to normal).

Heterogeneity in effect size

Pooled RR 1.71, p= 0.005





Bousman et al. 2019 Pharmacogenomics 20:37-47

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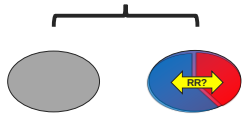
Potential of 'PGx Enriched' RCTs

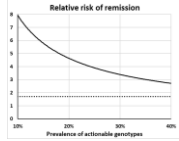
RR between cohorts = 1.71



no PGx | with PGx

PGx-informed prescribing can only benefit the minority of patients i.e. **those with actionable variants**

Estimating the potential benefit of PGx-informed prescribing within the test cohort from benefit between the cohorts and variant frequency.



If RR of remission between cohorts is 1.71, and 30% of patients have actionable PGx result then

the RR for remission in those with an actionable result is ~3.4.

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Antidepressants with PGx Guidance

CPIC Level 1 Evidence, Strong or Moderate Recommendation

SSRIs
- Sertraline
- Citalopram
- Escitalopram
- Paroxetine
- Fluvoxamine

TCAs
- Amitriptyline
- Doxepin

Clinical guidance related to EXPOSURE based on CYP2C19 and CYP2D6 genotypes

ALL other antidepressants have either:
1) LOWER levels of evidence (including NO evidence!) not actionable
2) Evidence NOT yet assessed by experts and/or decision published e.g., CPIC

Hicks et al. 2015 Clin Pharmacol Ther 98:127-134
Hicks et al. 2016 Clin Pharmacol Ther 102:37-44

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Case Study – SSRI Intolerance

- 44 year-old women presents to her usual GP 2 weeks after an admission to a public hospital for a **major depressive episode**.
- Follow-up OPD appointment with psychiatrist in 2 weeks but "can't wait".
- Started on **fluvoxamine** in hospital and titrated to 200 mg nocte.
- Previous intolerances to multiple antidepressants (medication history unknown – "felt sick in guts all the time").
- Mental state - mood improved, denied suicidal ideation, sleeping well, back at part-time work as hairdresser.

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Case Study – SSRI Intolerance cont.

- Complaining of constant nausea interfering in daily life, reduced appetite and non-intentional weight-loss since discharge.
- Took PGx test at local pharmacy after discharge, **CYP2D6 Intermediate Metaboliser** (***CYP2D6*4/*41***).
- Fluvoxamine is partly metabolised by CYP2D6, and this phenotype puts her at increased risk of AEs probably due to high exposure.
- PGx report advises to consider lower fluvoxamine dose.
- The dose was reduced to 100 mg at night and the GIT symptoms resolved without a deterioration in mental state.

PGx Tests from Sonic Genetics

Sonic PGx panel

ABCB1
CYP1A2
CYP2C19
CYP2C9
CYP2D6
CYP3A4
CYP3A5
OPRM1
SLCO1B1
VKORC1

1. Report and guidance for the query provided by requestor
2. Analytical result of gene variants
3. Summary table of potential drug/gene combinations across 26 categories of significance for this patient
4. Detailed prescribing advice for each recommendation of **avoid** or **caution**.

This is a big report.

Cost $197

Sonic PGx single gene tests

For hypersensitivity/toxicity
- DPYD **fluoropyrimidines**
- HLA-B*1502 **carbamazepine**
- HLA-B*5701 **abacavir** [MBS]
- HLA-B*5801 **allopurinol**
- TPMT **thiopurines** [MBS]
- UGT1A1 **irinotecan**

Cost $80-$200
or MBS rebate

- 2 week TAT, electronic reporting
- Establish testing through your local lab
- Medically-led service, not direct to consumer
- Pathologists & medical pharmacologist backup

Learning Points – The Theory of PGx

1. Understand why between patient variability (BPV) impacts pharmacotherapy
   - **BPV explains why different patients respond to drugs differently, including antidepressants**
2. Know about the sources of BPV in drug response
   - **Pharmacokinetic and pharmacodynamic, including genetics**
3. Understand the scientific basis of PGx and why clinical implementation is hard
   - **Genotype → phenotype, guidelines try to translate these into prescribing advice (PGx-informed prescribing)**
4. Know that commercial PGx reports reference clinical PGx guidelines
   - **Most use the CPIC guidelines (https://cpicpgx.org/)**

Learning Points – The Practice of PGx for MDD

5. Know the main clinical question that PGx might help with for MDD
   - **Is my patient at risk of extreme high or low exposure?**
6. Know that RCTs on PGx for MDD have been published
   - **RR of remission ~ 1.7 with PGx-informed prescribing but these studies have limitations!**
7. Identify the antidepressants with the highest quality PGx guidance
   - **SSRIs (sertraline, citalopram, escitalopram, paroxetine, fluvoxamine) and TCAs (amitriptyline, doxepin)**

Learning Points – The Practice of PGx for MDD

8. Identify clinical scenarios where PGx testing may be indicated
   - **Failed SSRI treatment, treatment resistant MDD**
   - **SSRI intolerance/AEs/toxicities**
9. Know what PGx tests are available and how to order
   - **Sonic PGx panel (10 genes) includes the EXPOSURE PK genes relevant for MDD**
   - **Single gene tests e.g., HLA-B status**
   - **Sonic PGx request form OR any pathology form**

Further Reading


Genomic testing as a tool to optimise drug therapy


Pharmacogenomics in general practice

Thank-you for listening
?Question? – please email me

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