CariGenetics

Mental Health Medications:

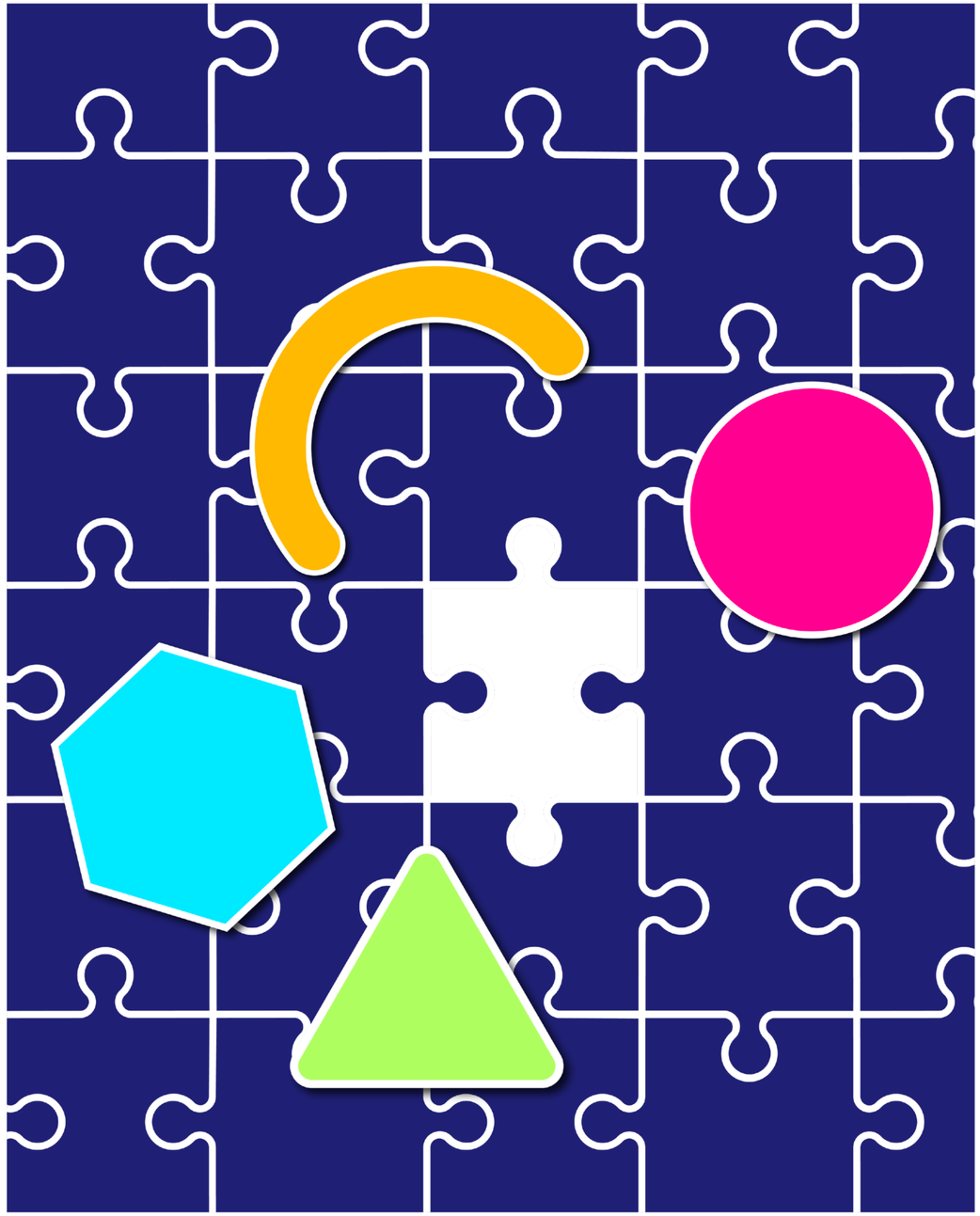
Are they One Size Fits All?
The Role of Pharmacogenetics (PGx)

The Bermuda Mental Health Foundation
Moving Forward Together

Dr Carika Weldon — 27 October 2023

Living longer means more medication

An ageing population means more and more of us are likely to live with long-term health conditions that require medication, means the number of medicines we are taking is increasing.



One-Size-Fits-All Does Not Work

We all vary in our responses to medicines

Multiple health conditions

Genomic Variation

Demographic

Drug-drug Interaction

Drug-food Interaction

Environment

Other omics...


We all have unique genetics

Harm can be done

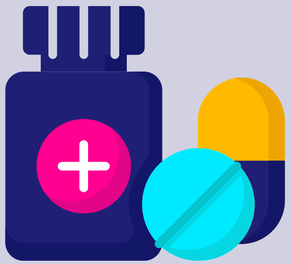
The significant variability in people's responses to drugs can cause harm from adverse drug reactions (ADRs).

Pharmacogenomics (PGx)

The study of how genes affect a person's response to drugs.

Goals of Pharmacogenetics

1

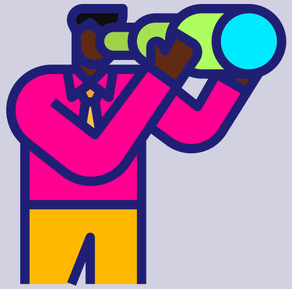


Maximize drug efficacy

2

Minimize drug toxicity

3



Predict patients who will respond to intervention

4

Aid in new drug development

First PGx observation

The first recorded association with PGx dates back to 510 BC when Pythagoras noted that ingestion of fava beans proved fatal in only selected individuals. This was later shown to depend on the deficiency in G6PD, determined by someones genetics

PGx is linked to drug metabolism

90% of drugs are metabolized by six CYP450 enzymes:

- CYP1A2
- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4
- CYP3A45

Different types of metabolizers

The population can be grouped into:

- Poor metabolizers (PMs) with inactive CYP2D6
- Intermediate metabolizers (IMs) with low residual enzyme activity
- Normal metabolizers (NMs) with a normal rate of metabolism
- Ultrarapid metabolizers (UMs) who have multiple copies of CYP2D6 with a very high enzyme activity

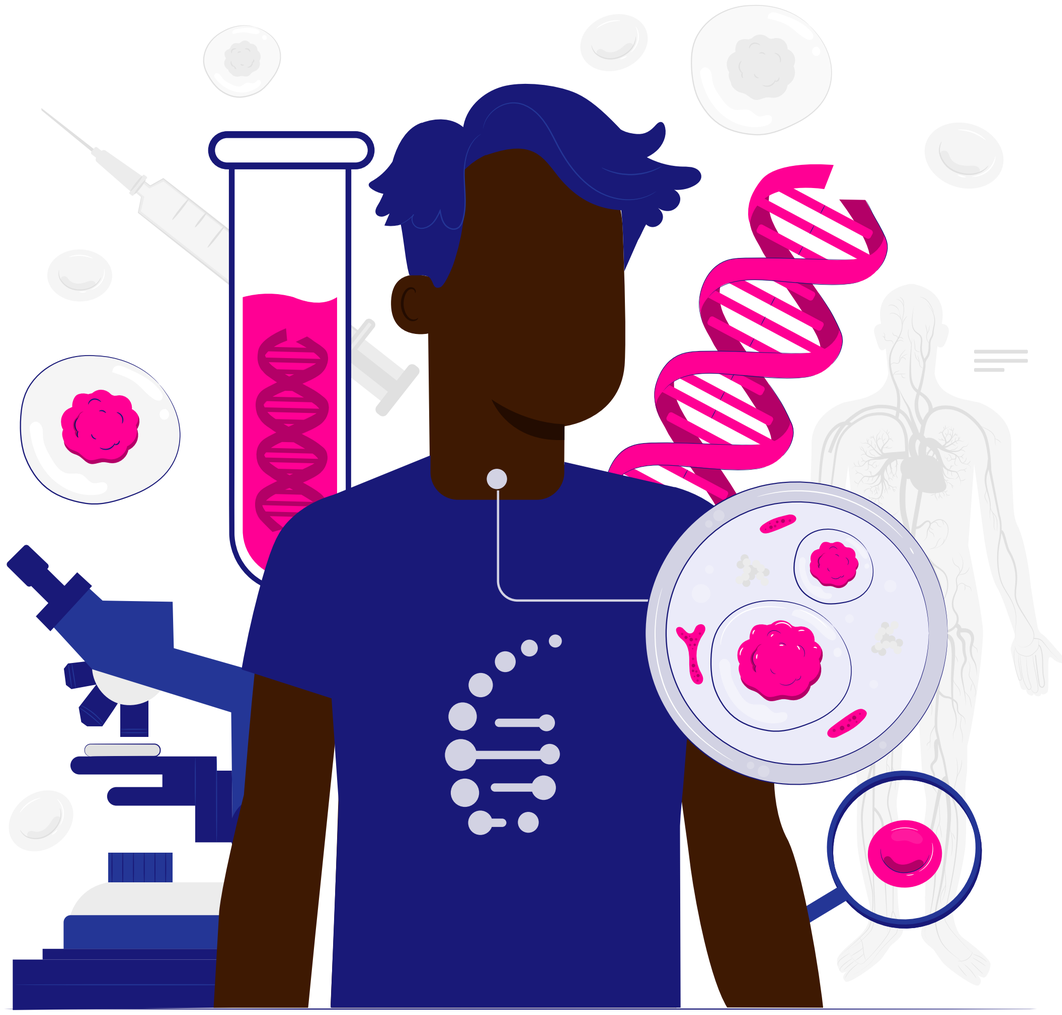
Frequency of different groups varies based on ethnic background

Genetics of CYP2D6

Genetic Type	CYP2D6 Activity	Ethnic Differences (Approximate)
Poor metabolizers	None	Caucasians 6%-10% Mexican Americans 3%-6% African Americans 2%-5% Asians ~1%
Intermediate metabolizers	Low	Not established
Extensive metabolizers	Normal	Most people are extensive metabolizers
Ultrarapid metabolizers	High	Finns and Danes 1% North Americans (white) 4% Greeks 10% Portuguese 10% Saudis 20% Ethiopians 30%

A one-time test for life

Because your genes hardly change throughout your lifetime, a pharmacogenomic blood test needs to be done once.



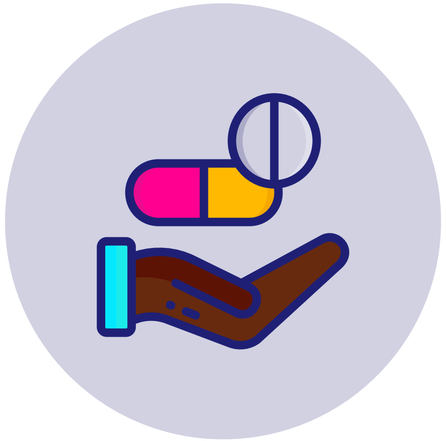

PHARMACY +
“Here’s my sequence…”
This is the hope / hype

Already used for cancer treatment

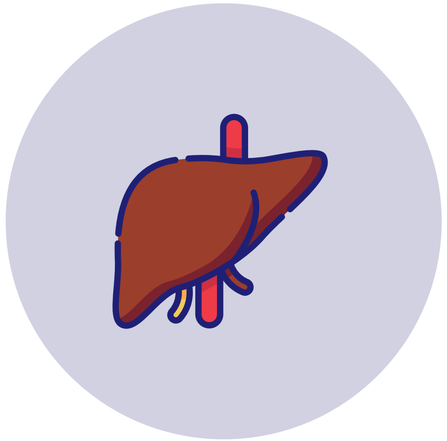
Fluoropyrimidines — DPYD

A 68-year-old man goes to his GP with altered bowel habits and is diagnosed with a left-sided colon adenocarcinoma. The oncologist undertakes DPYD genetic screening which reveals the patient carries a reduced-function DPYD genetic variant. He commences chemotherapy this reduced dose and it is cautiously incremented to 75% of the standard dose dose over subsequent cycles.

Codeine Metabolism



Codeine —
An inactive prodrug



Metabolism —
In hepatocytes

0-15% is metabolised in CYP2D6 to the **active metabolite morphine**

Analgesic —
Effect on pain

Codeine — *CYP2D6*

- There is a body of research evidence collectively reporting that CYP2D6 PMs exibit reduced exposure to morphine after receiving codeine, experience reduced analgesic benefit, and CYP2D6 genotype-guided codeine prescribing results in improved analgesia for IM and PM patients compared with standard prescribing.

- On the other hand, morphine exposure is higher after codeine intake in UMs than EMs. UM individuals appear to be at an increased risk of opioid-related adverse events, including life-threatning and fatal toxicity in young children with obstructive sleep apnoea (OSA) receiving codeine after (adeno)tonsillectomy.

- The codeine summary of product characteristics (SmPC) now states that codeine is contraindicated in both paediatric patients undergoing (adeno)tonsillectomy for OSA and in patients known to be CYP2D6 UMs (of any age).

Better care for patients

Patient requiring medication

Standard approach

The patient is **prescribed a medicine** for their health problem often at a set dose — a one-size-fits-all approach

The patient's genes affect how they **respond to the medicine** and whether they have side effects

Pharmacogenomic approach

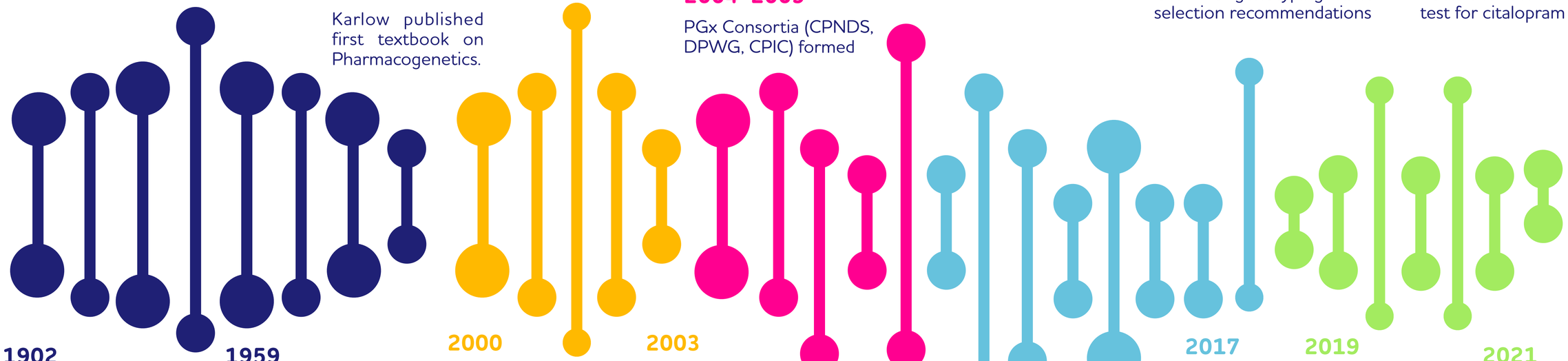
The patient has a **pharmacogenomic test** — a blood test carried out once in a person's lifetime

*The patient is given **the right medicine at the right** dose for them*

Huge savings for healthcare

- Unwanted side effects from prescription drugs cost the NHS £530 million annually in hospital admissions.
- Getting it right the first time could help save the NHS money and resources.
- Can also apply in Bermuda.

History of PGx & links to Psychiatry



1902
Garrod links genetic factors to metabolism

1957
Motulsky published: Drug reactions, enzymes and biochemical genetics.

1959
Vogel coined the term "Pharmacogenetics"

1962
Karlow published first textbook on Pharmacogenetics.

2000
PGRN & PharmGKB established

2002
Human Cytochrome P450 (CYP) Allele Nomeclature Database established

2003
Completion of Human Genome Project

2004-2009
PGx Consortia (CPNDS, DPWG, CPIC) formed

2008-2011
DPWG published guidelines for antidepressants & antipsychotics

2009
FDA starts adding PGx information to product labels

2013-2015
CPIC publishes guidelines for antidepressants & carbamazepine

2017
PharmVar established

2018-2021
AMP publishes CYP2C19 & CYP2D6 genotyping allele selection recommendations

2019
CPIC publishes guideline for atomoxetine

2020
FDA clearance of 23andMe *CYP2C19* test for citalopram

2021
ISPG consesus statement on PGx in psychiatry published

Different psychotropics affected by different enzymes

	Antipsychotic	CYP2D6	CYP3A4	CYP1A2
Second Generation	Aripiprazole	●	○	
	Asenapine			○
	Clozapine	○	○	●
	Iloperidone	●	○	
	Lurasidone		●	
	Olanzapine	○		●
	Paliperidone	●	○	
	Quetiapine		●	
	Risperidone	●	○	
	Ziprasidone		○	
First Generation	Chlorpromazine	●		●
	Fluphenazine	●		
	Haloperidol	●	●	
	Loxapine	●	●	●
	Perphenazine	●		●
	Thioridazine	●		●
	Zuclophenthixol	●		

● Primary metabolism ○ Secondary metabolism

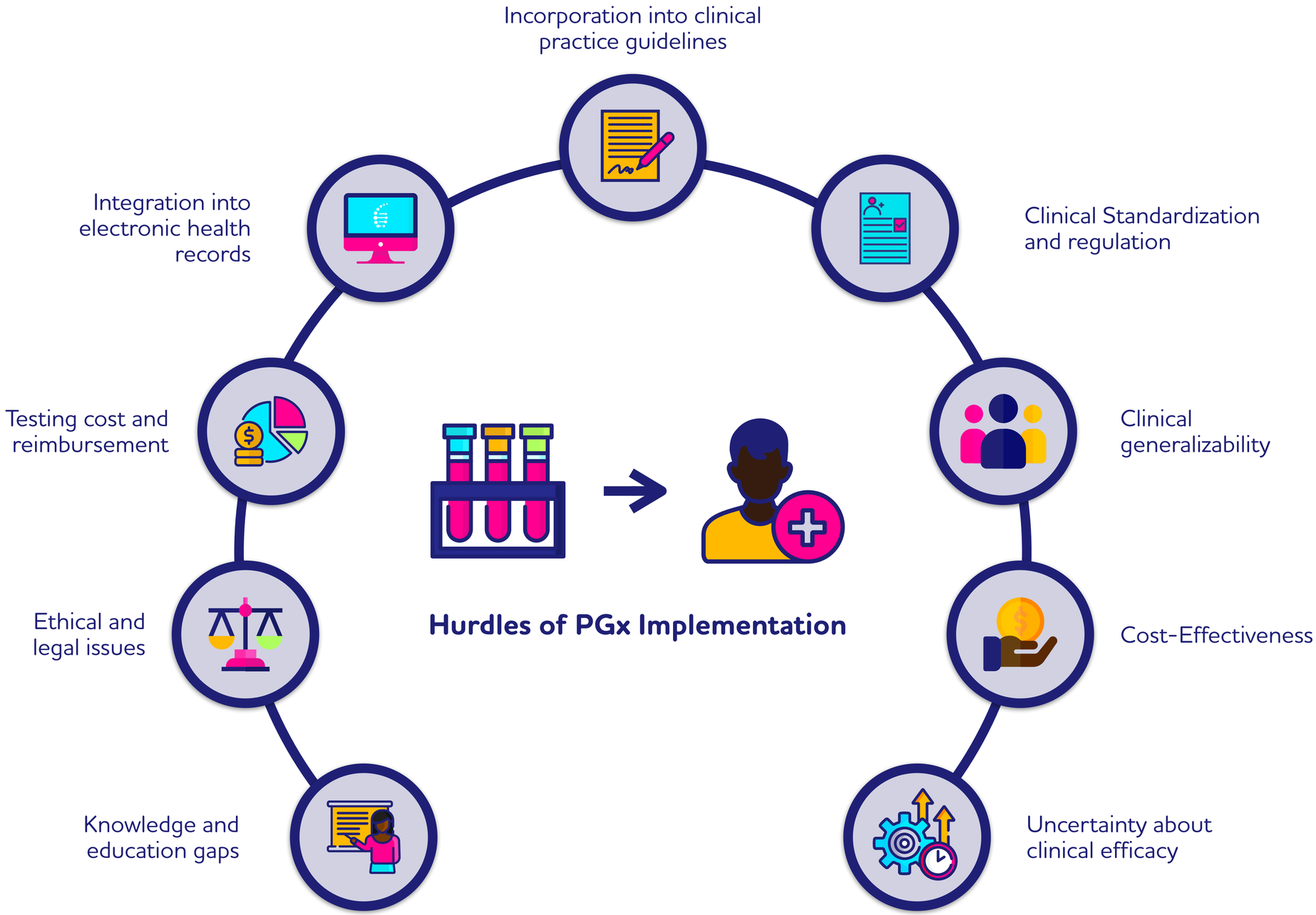
Clear guidance for prescribing

Class	Drug(s)	Gene(s)	Genotype-predicted phenotype(s)	Recommendation summary
Antidepressants	Citalopram	CYP2C19	UM or PM	Select alternative drug
	Escitalopram	CYP2C19	UM or PM	Select alternative drug
	Fluvoxamine	CYP2D6	PM	25-50% lower starting dose, slower titration
	Paroxetine	CYP2D6	UM	Select alternative drug
			IM	Lower starting dose, slower titration
			PM	50% lower starting and maintainenance dose or select alternative drug
	Sertraline	CYP2C19 - CYP2B6	UM - UM; UM - RM; RM - UM	High maintenance dose or select alternatve drug
			NM - IM; IM - NM; IM - PM	Slower titration and lower maintenance dose
			NM - PM	Lower starting dose, slower titration, 25% lower maintenance dose
			PM - UM; PM - NM; PM - IM	Lower starting dose, slower titration, 50% lower maintenance dose
			PM - PM	Select alternative drug

PGx and antidepressants in children

Antidepressants: Pharmacogenetic guidelines and metabolizing enzymes

Medication	Metabolizing enzyme(s)
Tricyclic antidepressants	
Amitriptyline	CYP2D6 and CYP2C19
Clomipramine	CYP2D6 and CYP2C19
Desipramine	CYP2D6
Doxepin	CYP2D6 and CYP2C19
Imipramine	CYP2D6 and CYP2C19
Nortriptyline	CYP2D6
Trimipramine	CYP2D6 and CYP2C19
Atypical antidepressant	
Vortioxetine	CYP2D6
Selective serotonin reuptake inhibitors	
Citalopram	CYP2C19
Escitalopram	CYP2C19
Fluoxetine	CYP2D6
Fluvoxamine	CYP2D6
Paroxetine	CYP2D6
Sertraline	CYP2C19
Vilazodone	
Serotonin-norepinephrine reuptake inhibitors	
Atomoxetine	CYP2D6
Desvenlafaxine	
Duloxetine	
Levomilnacipran	
Venlafaxine	CYP2D6


Incorporation into clinical practice guidelines
Integration into electronic health records
Clinical Standardization and regulation
Testing cost and reimbursement
Clinical generalizability
Ethical and legal issues
Cost-Effectiveness
Knowledge and education gaps
Uncertainty about clinical efficacy
Hurdles of PGx Implementation

CariGenetics™

The 1st Caribbean-based genomics company focused on understanding non-European genomes to improve global human health.

Bermuda PGx Project
Phase 1 - Pilot
Scorecard

4 Samples Needed

Collection of blood samples	100%
DNA extraction for WGS*	100%
Training of targeted library preparation for new platform	100%
Data generation by WGS*	100%
New data analysis pipeline	60%

As of October 25, 2023

*WGS - whole genome sequencing

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Lack of diversity in PGx studies

The PREPARE study was a cluster-randomized, crossover implementation study conducted in **Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the U.K**. It evaluated the clinical utility of a pre-emptive genotyping strategy.

Between March 7, 2017, and June 30, 2020, 41,696 patients were assessed for eligibility and 6,944 (51.4% female, 48.6% male; **97.7% self-reported European Mediterranean, or Middle Eastern ethnicity**) were enrolled and assigned to receive genotype-guided drug treatment (n=3342) or standard care (n=3602).

Our Future Plans

2024:

- Offer to direct-to-consumer PGx testing
- Offer official clinical PGx test in Bermuda
- Offer both tests throughout Caribbean

2025 & beyond:

- Start studies on PGx in the Caribbean

CariGenetics™

Transforming Healthcare in the Caribbean through Genomics

carika@carigenetics.com

+1 (441) 621 - 6309

www.carigenetics.com