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Role of the pharmacist in personalized medicine in community pharmacy

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Objectives

1. Review the basic principles of pharmacogenomics (PGx) and how they can be used to optimize drug therapy.
2. Discuss strategies for implementation of pharmacogenomic services into community pharmacy practice.
3. Explore real-world case examples from one of the nation's first community pharmacy-directed pharmacogenomic clinics.

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IT IS NOT ALL DOOM AND GLOOM

Expanding Pharmacist Scope

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Evolving scope of pharmacy practice

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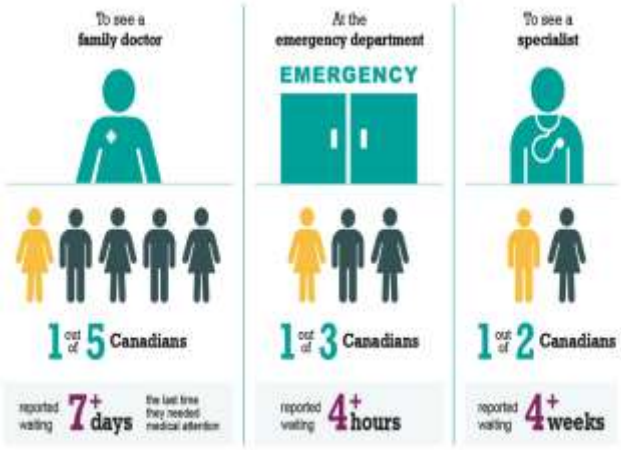
Canadians report the longest wait times



Source: The Commonwealth Fund's 2016 International Health Policy Survey of Adults in 11 Countries.

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Pharmacists are part of the solution

Source: 9000 Points of Care: Improving Access to Affordable Healthcare

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Canadians trust their pharmacists

94%
have a positive impression of pharmacists – more than doctors, teachers, military officers or police officers

94%
believe pharmacists play an essential role in Canada's healthcare system

4 in 5 agree that allowing pharmacists to do more for patients will improve health outcomes and reduce healthcare costs

Source: Survey on perceptions and attitudes towards pharmacists conducted by Abacus Data, as reported by the Canadian Pharmacists Association, 2017

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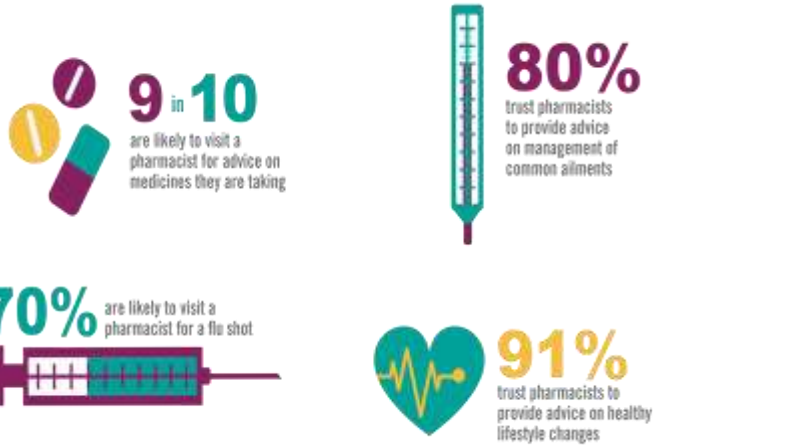
And they trust them to deliver healthcare services



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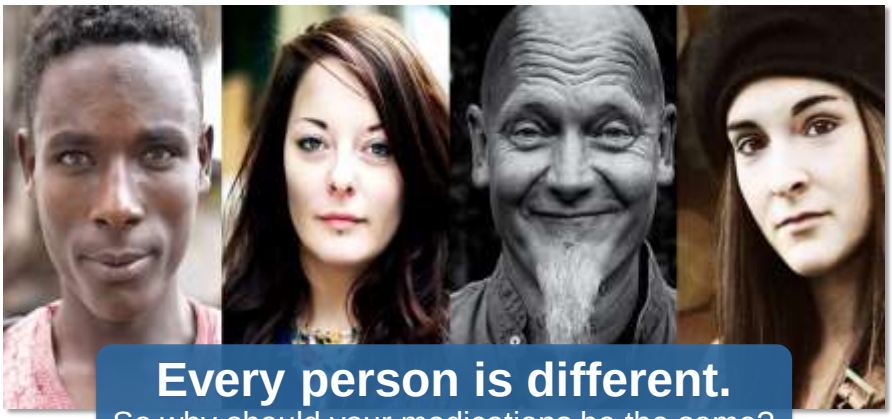

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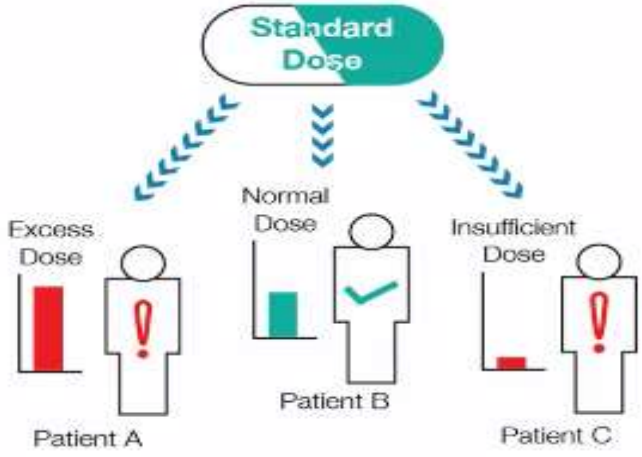
Pharmacogenomics

Study of how an individual's genes can affect their response to drugs.



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Definitions

- ***Pharmacogenomics*** ("PGx") is the study of how differences in the human genome affect the absorption, distribution, metabolism, elimination, and efficacy of drugs.
- ***PGx testing*** is a *powerful tool* for physicians and pharmacists, which *informs prescribing decisions* and *medication management* by pinpointing differences in a patients' DNA that influence their response to a drug.

CPIC Clinical Pharmacogenetics Implementation Consortium

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Pharmacogenomics: in the news

Pharmacists called to take lead in pharmacogenomics—the bridge to personalized medicine

Your pharmacist's secret weapon: How your DNA can help perfect your medication

ADRIANA BARTON
The Globe and Mail
Published Sunday, Feb. 14, 2016 12:00PM EST
Last updated Wednesday, Feb. 17, 2016 2:14PM

genomeweb

Mayo's Center for Individualized Medicine Explores WGS, Diagnostic Exomes, PGx Analysis, Gene Panels

OneOme to Support Mayo-Baylor Clinical PGx Collaboration

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ASHP Statement on the Pharmacist's Role in Clinical Pharmacogenomics

Position

The American Society of Health-System Pharmacists (ASHP) believes that pharmacogenomic testing can improve medication-related outcomes across the continuum of care in all health system practice settings. These improvements include reduction in suboptimal clinical outcomes, decreased cost of treatment, better medication adherence, more appropriate selection of therapeutic agents, decreased length of treatment, and enhanced patient safety.[1-3] Because of their distinct knowledge, skills, and abilities, pharmacists are uniquely positioned to lead inter-professional efforts to develop processes for ordering pharmacogenomic tests and for reporting and interpreting test results. They are also uniquely qualified to lead efforts to guide optimal drug selection and drug dosing based on those results. Pharmacists therefore have a fundamental responsibility to ensure that pharmacogenomic testing is performed when needed and that the results are used to optimize medication therapy.[3] Pursuant to this leadership role, pharmacists share account-

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Mr. Smith

61y Male

- **Allergies/intolerances:** None
- **Medical conditions & medications:**

(1) Depression/anxiety

- Desipramine 12.5mg po qAM
- Clonazepam 0.25 mg q4h prn

2009-2014

- Sertraline 25mg qhs
- Escitalopram 10mg once daily
- Fluoxetine 10mg once daily

2015

- Bupropion XL 150 mg qAM
- Duloxetine 30mg once daily
- Paroxetine 10mg once daily
- Sertraline 25mg qhs

2016

- Desipramine 50mg qhs x 1 week, then increase to 100mg qhs → decreased to 12.5mg po qAM due to side effects (mostly insomnia)

Note:

- All drugs trialed for >1mo before D/C'd
- Mostly D/C'd due to intolerable side effects
  - **Side effects reported**: Body aches, diarrhea, nausea, headaches (pressure), insomnia, "excited but not present"

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The problem of adherence

50%

Rx non-adherence in Canada after 6 months

...Unchanged for 20+ years

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So what??

1/3

of medication-related

hospital admissions

are related to

poor Rx adherence

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Potential Benefits of PGx

Reduces ADRs & associated costs

Dosing optimization & better treatment outcomes

Improved adherence & confidence

Reduce total healthcare & medication costs

Changing paradigms from reactive to preventative

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Pharmacogenomics 101

An introduction to basic principles

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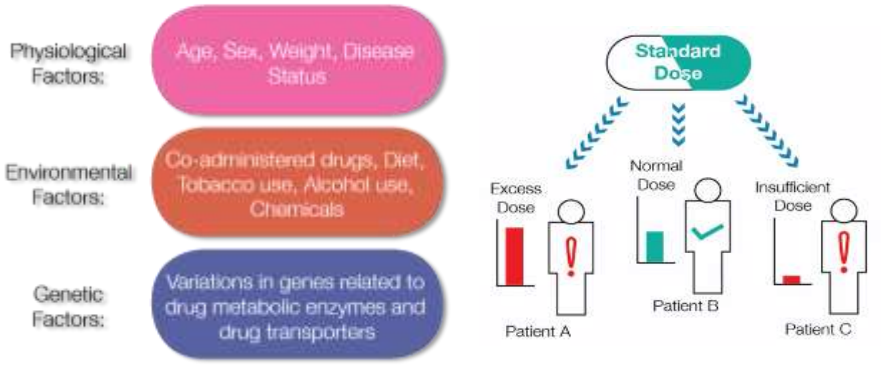
Background

- Drug response depends on several factors:



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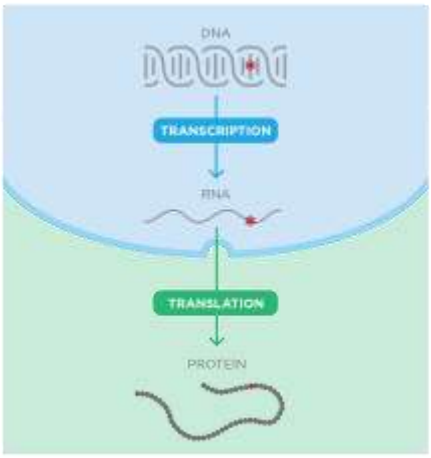
Protein Synthesis



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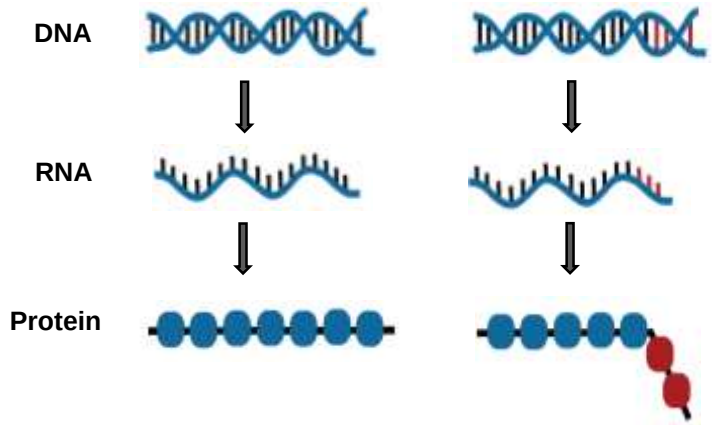
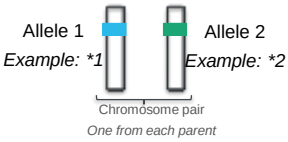
Variations in DNA can alter function of enzymes



Changes in DNA can alter structure and function of proteins

Alleles explain differences between individuals

- We receive two copies of DNA, one from each parent → two *alleles* carrying potentially different information



- The combination of these alleles constitute the **genotype**: *1/*2
  - *"What you are"*
- The **phenotype** is the "visible" result of the genotype
  - *"What you see" (PM, IM, EM, UM)*

Drug Metabolism

Phase I

- Metabolism primarily via CYP450 oxidases in liver
- Six CYP450 enzymes are responsible for metabolizing ~90% of drugs

Phase II:

- Conjugation reactions via transferases

Phase III:

- Elimination reactions via drug transporters

Active drug: Direct effect; inactivated by metabolism

Pro-drug: Must be converted to have clinical effect

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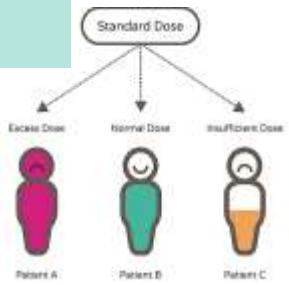
Why do drugs affect people differently?



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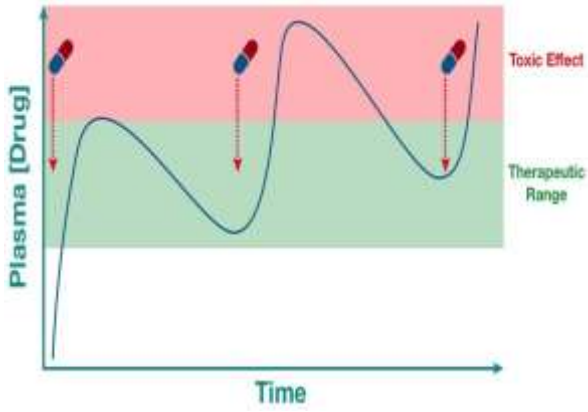
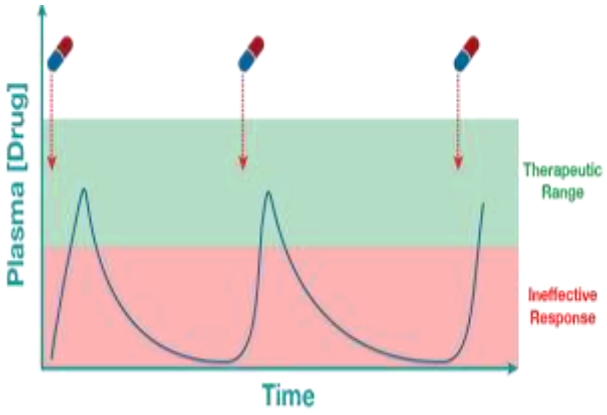
One person could be clearing a medication very slowly……

Poor metabolizer



….leading to a build-up of the drug in the plasma, resulting in side effects

…while another could process the same medication too fast



Rapid metabolizer

…..and the standard dose is not effective

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When drugs are not processed at the expected or 'normal' rate, it leads to adverse side effects or lack of efficacy

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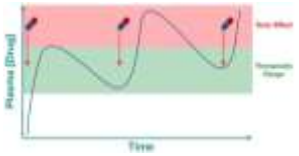
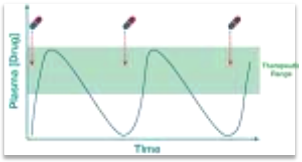
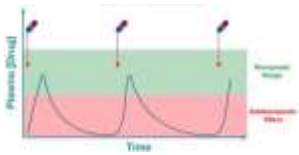
Effects of phenotypic variation

Poor Metabolizer (PM)	**Poor** drug clearance	**Increased Efficacy** High Risk of Adverse Drug Reaction	
Intermediate Metabolizer (IM)	**Reduced** drug clearance	**Increased Efficacy** Intermediate Risk of Adverse Drug Reaction	
Extensive Metabolizer (EM)	**Normal** drug clearance	**Normal Response**	
Ultrafast Metabolizer (UM)	**Rapid** drug clearance	**Decreased Efficacy**	

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How common are variations in drug transporting and processing genes ?

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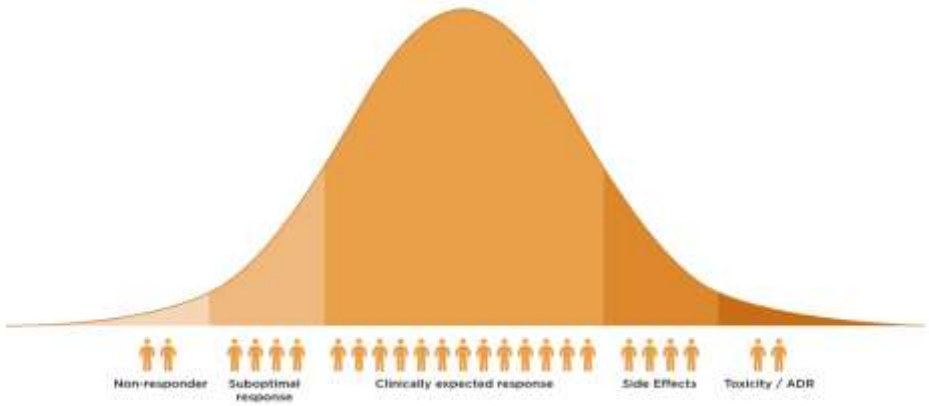
Only 48% of Patients are "Normal Metabolizers"



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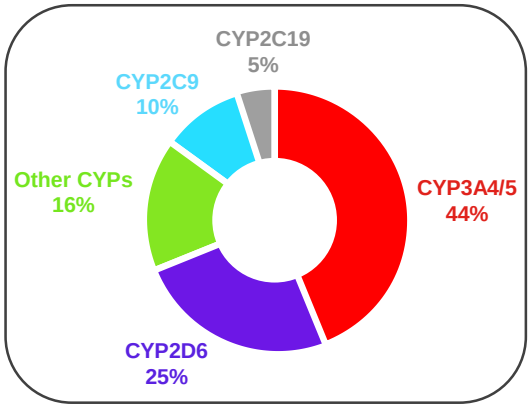

- Estimated that 85% of individuals have at least one variation in their CYP450 enzymes
- Evidence for clinical significance of polymorphisms in several CYP450 enzymes is compelling and growing

Genetic variations impact response to prescribed therapy

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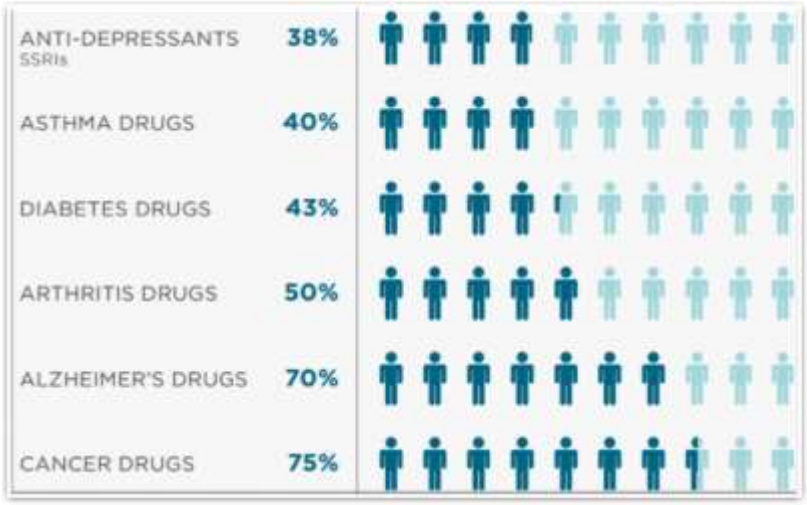
Opportunities in personalized medicine

Percentage of patients of which a particular drug class is ineffective



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Why codeine painkillers don't work for millions - and may even harm your health

- Up to six million Britons do not produce enzyme CYP2D6
- It breaks down codeine into morphine to provide pain relief
- Pain killer codeine is the tenth most prescribed drug in the UK

By JO WATERS
PUBLISHED: 22:00 BST, 30 December 2013 | **UPDATED:** 09:13 BST, 31 December 2013

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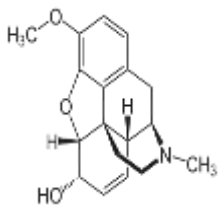
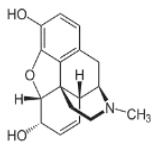
CYP2D6 and codeine metabolism



Codeine

Poor metabolizers



No morphine

Insufficient therapeutic effect:
Pain

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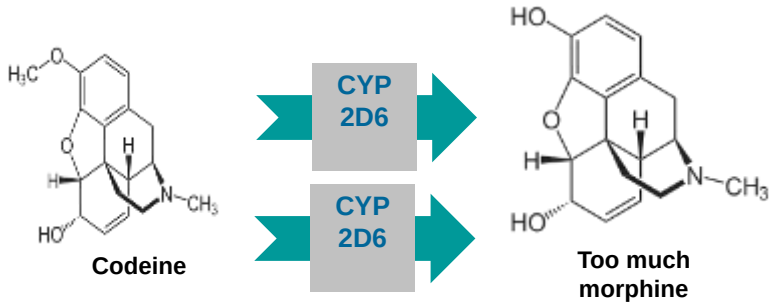
CYP2D6 and codeine metabolism



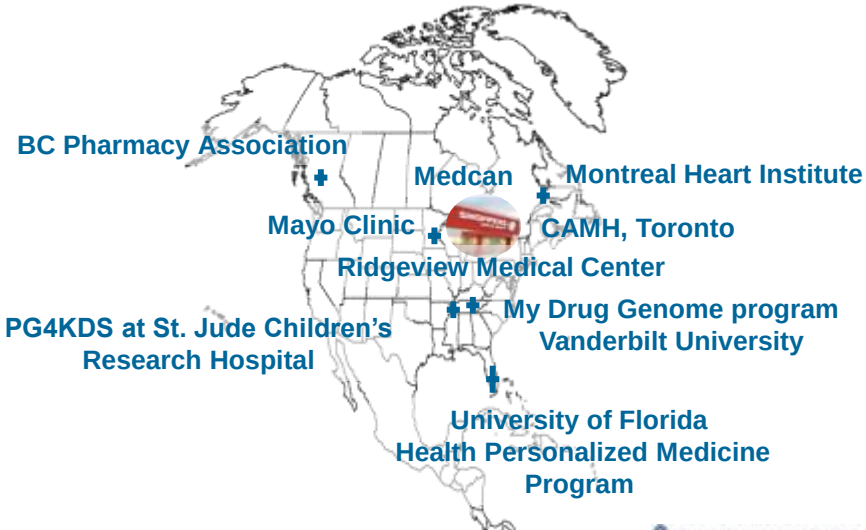
Codeine

Too much morphine

Ultrafast metabolizers

Intoxication:
sedation, respiratory depression

Some successful PGx implementation in North America



Community Pharmacy Experience

ICANPIC study

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Simple Process

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Partnering with a vendor

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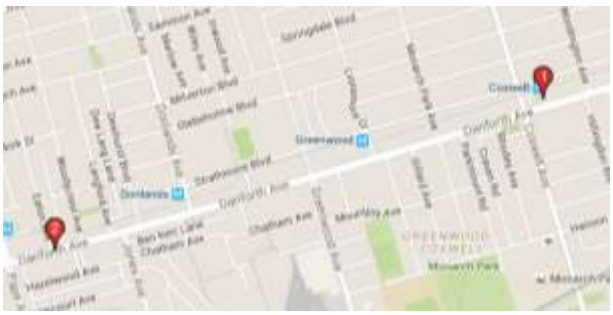
ICANPIC study

Objective:
Determine the effectiveness of community pharmacist-mediated pharmacogenetic testing in identifying drug therapy problems (DTP)

2 pharmacies

100 patients



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Pharmacist training

Introductory classroom course (1 hour)
- Practical aspects of getting started, providing PGx testing services to patients, handling data and interpreting the reports

Online webinars and reference materials
- Module A (5 online webinars, ~1 hour total)
- Module B (~1.5 hours total)

Small group interactive sessions (45 – 60 min, 3 – 4 people each)
- Follow up on personal experience with the PGx test report, interactive/classroom session to encourage team learning

Weekly practical clinic training
(9 sessions, Thursdays 10 a.m. – 4 p.m.)
- One-on-one support from medical geneticists for consulting pharmacists

Methods: PGx testing

Screened patient invited for medication review appointment (MedsCheck)

Swab

Mail

ANALYSIS

CPIC guidelines

Review

Follow-up with patient (identify DTPs)

Send recommendations to MD

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PGx test reports help translate results from genetic laboratory test into clinically actionable prescribing decisions for affected drugs

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Methods: interpreting the report

Potential pros of the medication based on its intended function and potential cons based on the body's altered response

- Gives responsible gene and allele
- Information on the activity of a particular genotype

Patient-specific recommendations based on the results (sourced from FDA labelling)

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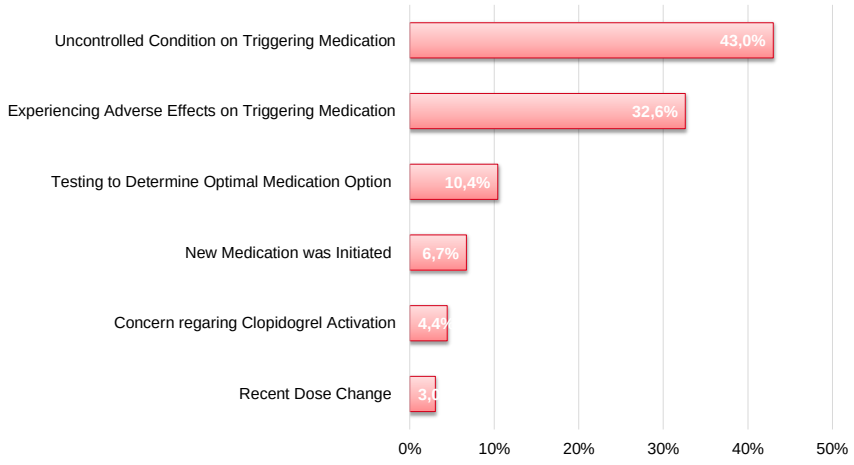
Patient demographics

Total patient enrolment	100
Lost to follow-up	4
Failed test	1

Patient demographics	
Mean age (years)	56.7
Gender (female)	62.0%
Gender (male)	38.0%
Mean number of chronic medications	4.9
Mean number of Pillcheck medications	2.0

Rationale for PGx testing



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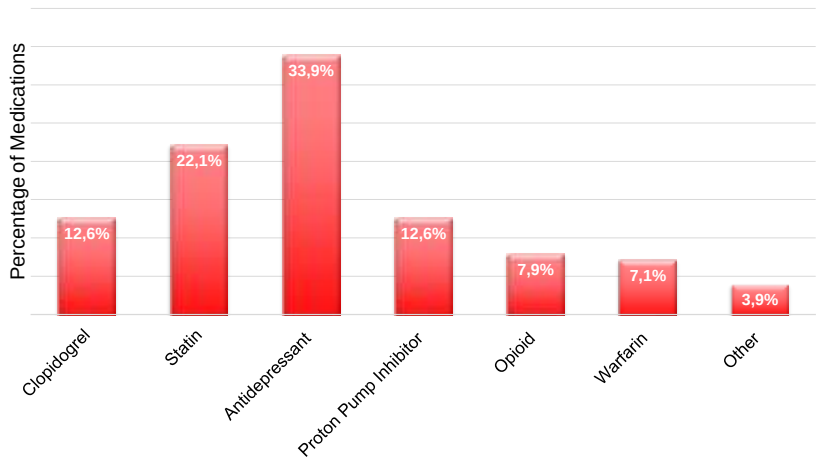
Medications triggering pharmacogenetic testing



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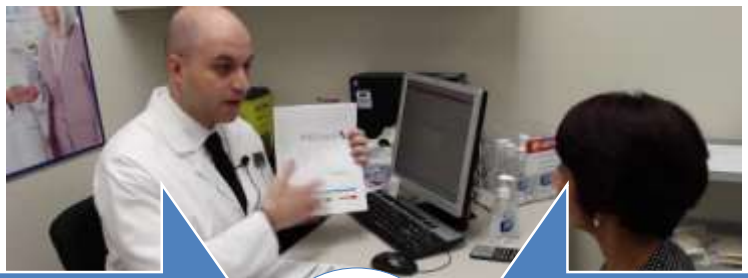
Pharmacist Interventions



Pharmacogenomic recommendations:
119 DTPs identified
(1.3/patient)

175
DTPs

Pharmacist recommendations:
56 DTPs identified
(0.60/patient)

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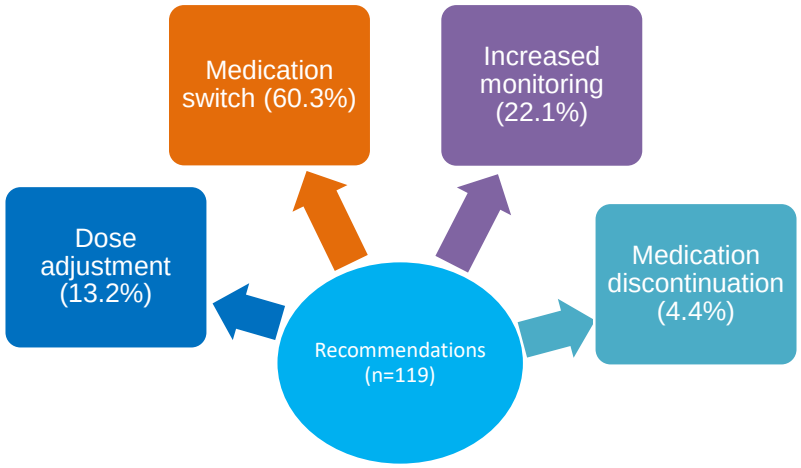
Actionable Results



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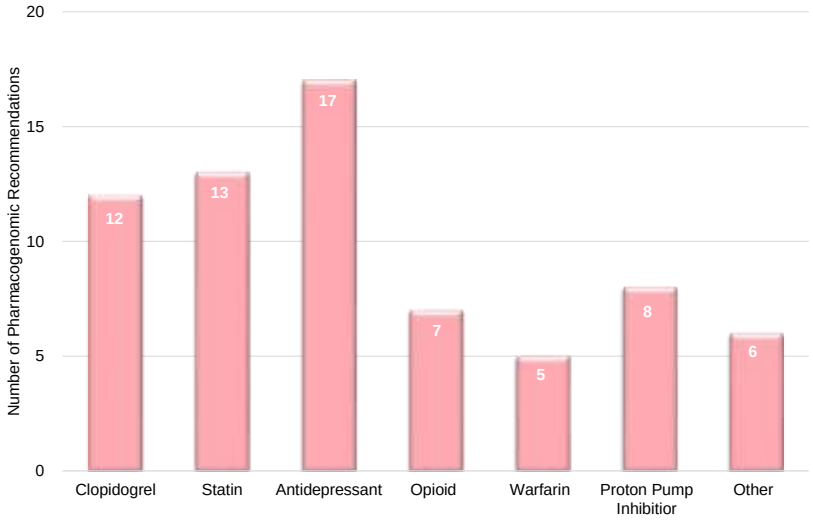
55

PGx recommendations based on drug class



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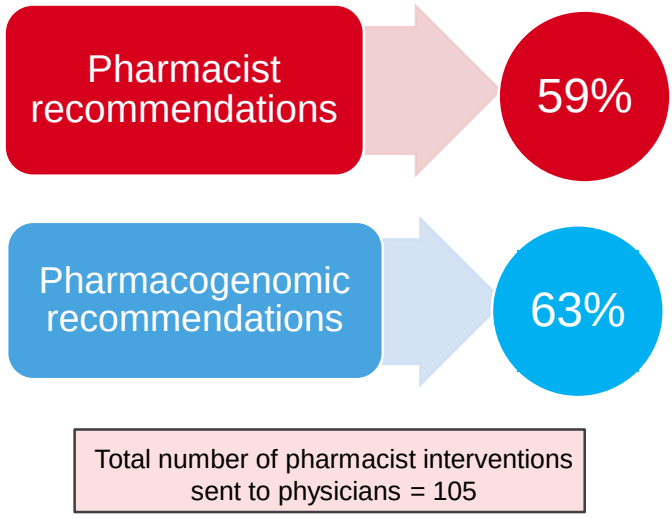
MD approval



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Patient comments

"I feel I have better control over what medications to take - better effectiveness"

"... I think that OHIP should cover the cost since it promotes effective health care…

"The information provided through the study and consultation with Peter was extremely valuable"

"Based on the finding and recommendation I will be scheduling an appointment with my family physician"

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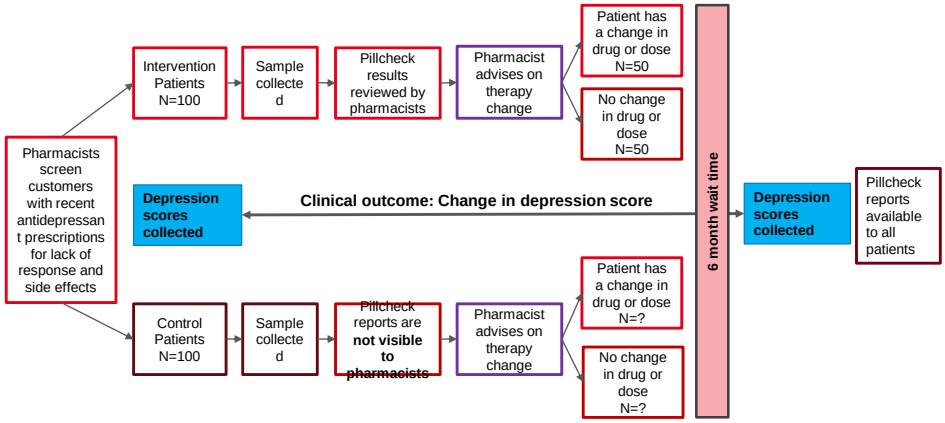
What's Next?



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ESCP European Society of Clinical Pharmacy

PUTTING IT ALL TOGETHER

Revisit Mr. Smith

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Mr. Smith
61y Male

- **Allergies/intolerances:** None

- **Medical conditions & medications:**

(1) Depression/anxiety
- Desipramine 12.5mg po qAM
- Clonazepam 0.25 mg q4h prn

2009-2014
- Sertraline 25mg qhs
- Escitalopram 10mg once daily
- Fluoxetine 10mg once daily

2015
- Bupropion XL 150 mg qAM
- Duloxetine 30mg once daily
- Paroxetine 10mg once daily
- Sertraline 25mg qhs

2016
- Desipramine 50mg qhs x 1 week, then increase to 100mg qhs → decreased to 12.5mg po qAM due to side effects (mostly insomnia)

Note:
- All drugs trialed for >1mo before D/C'd
- Mostly D/C'd due to intolerable side effects
  - **Side effects reported**: Body aches, diarrhea, nausea, headaches (pressure), insomnia, "excited but not present"

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Mr. Smith PGx Results

Medicine	Use with caution / consider alternatives	Use with increased caution and more frequent monitoring	Standard precaution / use as directed
Psychiatry	Amitriptyline Aripiprazole Atomoxetine Clomipramine Clozapine Desipramine Doxepin Fluoxetine Fluoxetine and olanzapine Fluvoxamine Imipramine Modafinil Nefazodone Nortriptyline Paroxetine Pimozide Risperidone Trimipramine Venlafaxine	Citalopram Diazepam Sertraline	

As many antidepressants are metabolized by CYP2D6, this would explain why he has had to discontinue therapies due to intolerable side effects.

Enhanced CYP450 Genotype Report

Marker:	CYP2C9	CYP2D6	CYP2D6CNV	VKORC1	SLCO1B1	OPRM1	CYP2C19	CYP3A4
Value:	*1/*1	*4/*4	2N	GG	*1/*1	AA	*1/*17	*1/*1
Interpretation:	Extensive	Poor	§	§	Normal	§	Ultrafast	Extensive

Mr. Smith PGx Results: desipramine (current therapy)

Mr. Smith PGx Results: citalopram & sertraline

- **Citalopram** and **Sertraline** are metabolized by **CYP2C19**
- As an UM of CYP2C19, Mr. KS would require a higher dose of citalopram and sertraline to experience benefit.

Mr. Smith Recommendations

Pharmacist recommended to MD:

1) D/C Desipramine
2) Start Citalopram (or Escitalopram) or Sertraline at recommended starting dose and titrate up as tolerated until patient experiences benefit

– MD agreed, started on Escitalopram 10mg once daily with f/u appointment in 3 weeks to assess increase in therapy.

Patient feedback from experience:

- PGx test validated his concerns with previous medications – "It wasn't all in my head".

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Ms. Roy

67y Female

- **Allergies/intolerances:** Penicillin (hives/rash)

- **Medical conditions & medications:**
- **(1) Dyslipidemia:** Rosuvastatin 5mg once daily
- **(2) Peptic ulcer** due to *H. pylori* infection*:* Pantoprazole 40 mg daily

Past medical history:

- Ms. RC is suffering from a "chronic" *H. pylori* infection
- She has tried numerous courses of standard "triple therapy" (clarithromycin + amoxicillin + PPI)
- Her current prescription of pantoprazole 40 mg once daily is not helping her symptoms associated with her recurrent *H. pylori* infection

Pharmacist recommended PGx testing

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Ms. Roy PGx Results

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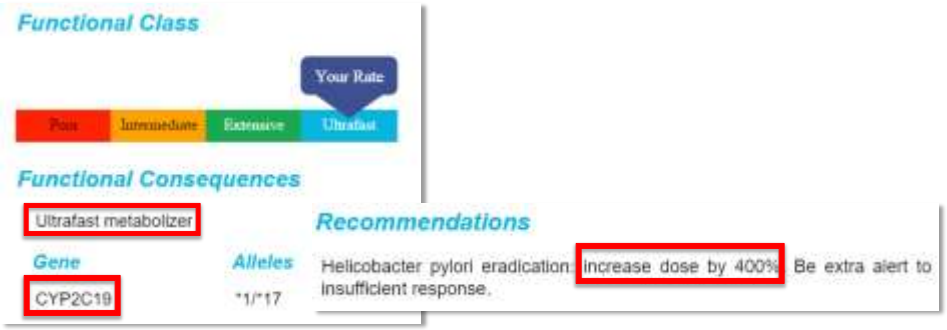
Ms. RC PGx Results



Ms. RC's "chronic" *H. pylori* infection is likely due to enhanced metabolism of pantoprazole resulting in ~25% the serum levels of a patient with normal metabolism

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Ms. Roy Recommendations

- Pharmacist recommendation to MD
  - ~~– Increase pantoprazole dose by 400%~~
    OR
  - – Stop pantoprazole and start ranitidine 150mg BID
    OR
  - – "Quadruple Therapy" using an H_2RA
    - Ranitidine 150 mg BID
    - Bismuth subsalicylate 2 tabs QID
    - Metronidazole 250 mg QID
    - Tetracycline 500 mg QID
    - **Duration 10-14 days**

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Ms. So

56y Female

- **Allergies/intolerances:**
  None

- **Medical conditions & medications:**
- **(1) Atrial fibrilation:**
  - Warfarin 8mg & 9mg alternating days
- **(2) Dyslipidemia**
  - Rosuvastatin 10mg once daily

Past medical history/current issues:

- Diagnosed with atrial fibrillation ~2 months ago
- Two weeks after starting warfarin, RT was admitted to hospital for GI bleed.
- Since then, dose has been changed several times over last month due to **fluctuating INR**
- Discussed drug/food interactions with patient – no clear link + patient feeling frustrated with frequent blood tests.

2 weeks : 4.4 → Last week: 1.8 → This week: 2.9

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Warfarin (Coumadin)

- **Warfarin dosing is complex**
  – many factors can affect INR

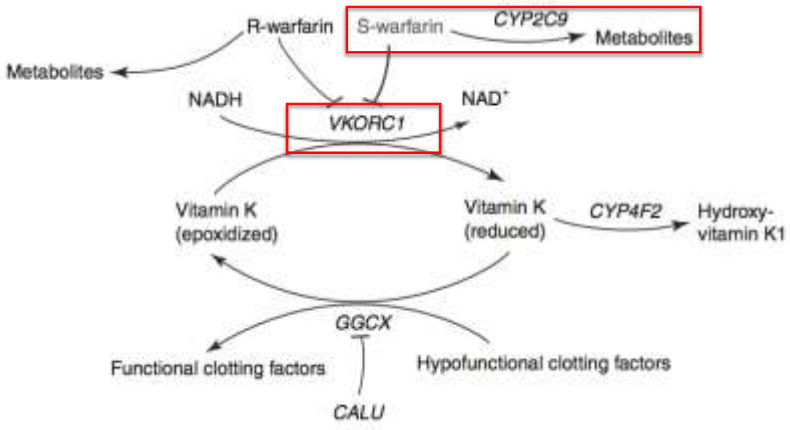
- **Narrow therapeutic range:** Inappropriate doses of warfarin can lead to thromboembolism or bleeding

- **Metabolism**:
  – **CYP2C9** codes for warfarin metabolizing enzyme
  – **VKORC1** codes for molecular target of warfarin

- **40- 60% of the variability** in warfarin response is attributed to polymorphisms in VKORC1 and CYP2C9 genes
  – Non-genetic factors account for ~50% of warfarin dose variability

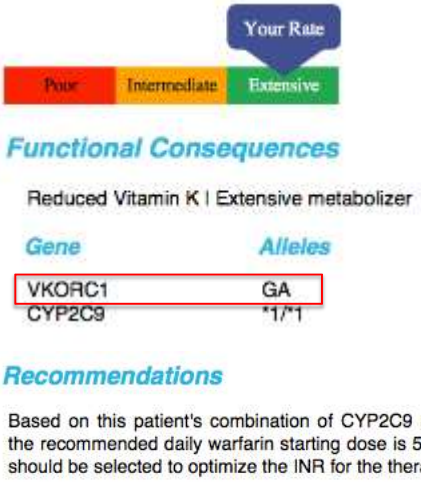
Yin T and Miyata T. *Thrombosis Research* (2007)
Johnson J. et al., *Clinical Pharmacology & Therapeutics* (2011)

Mechanism



Johnson J. et al., *Clinical Pharmacology & Therapeutics* (2011)

Ms. So PGx Results: Warfarin



- **CYP2C9**: extensive
- **VKORC1**: carriers of *VKORC1 A* are at increased risk of out of range INRs (retrospective studies)

Pharmacist recommendations to MD:

- Stop Warfarin and start a direct oral anticoagulant (DOAC)

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Common barriers to implementation

Lack of time *(perceived)* and resources

Lack of pharmacist confidence or knowledge of new devices

Patient hesitancy of adopting new technology

Lack of patient awareness or interest

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Incorporating PGx into Practice

- Challenges of PGx testing
  - Testing genetics is easy, patients are complex
  - Time constraints
- Communicating with physicians
  - Explain the test, results, and accuracy
  - Let them know what information you are sending and inquire about their preferred method for receiving the information
- Feedback from patients & physicians

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PGx Controversies

1. It's not just the test – it's the interpretation of the results
2. Are pharmacies promising more than they can deliver?
3. A business case to sell testing is not the same as a medical reason to offer testing
4. Does genomic testing represent good value for the cost?
5. Not yet a revolution in medicine

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Conclusion

- Pharmacists are ideally suited to offer pharmacogenomic screening
- Comprehensive training is essential
- Early experience is promising
- Anectodal feedback from patients is positive
- Interprofessional collaboration is instrumental for clinics to be successful

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The End

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