Pharmacogenomics Based Personalized Medicine

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Presenter Disclosure

- I have no current or past relationships with commercial entities
- I have received an honorarium for this presentation

Commercial Support Disclosure

- This Learning Activity has received no financial or in-kind support from any commercial or other organization

Learning Objectives

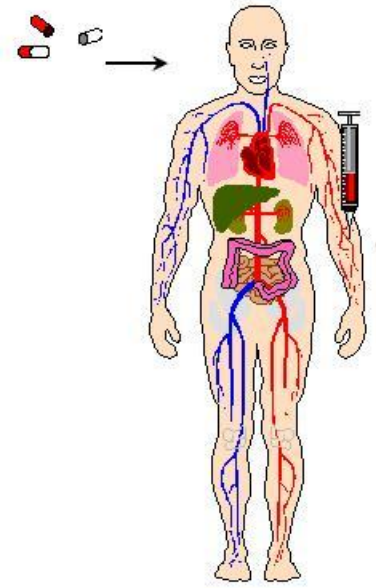
By the end of this presentation, you will be able to:

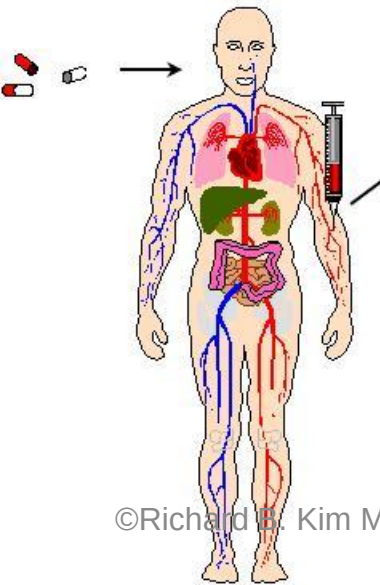
- Define clinically meaningful pharmacogenetic tests of relevance to commonly prescribed medications.

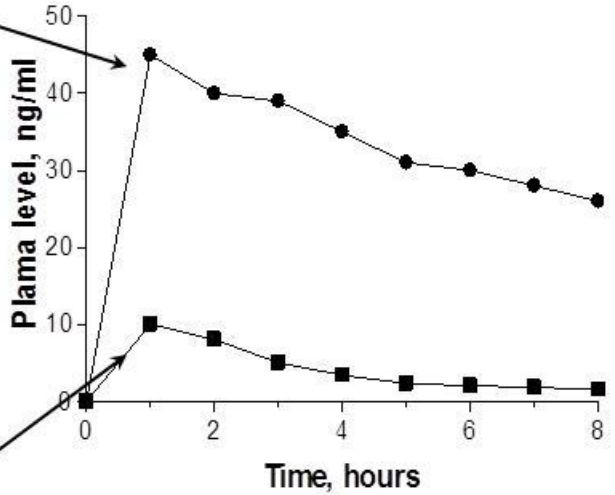
- Describe recent advances in pharmacogenetic testing including those that are likely to become a standard of care prior to start of drug therapy.

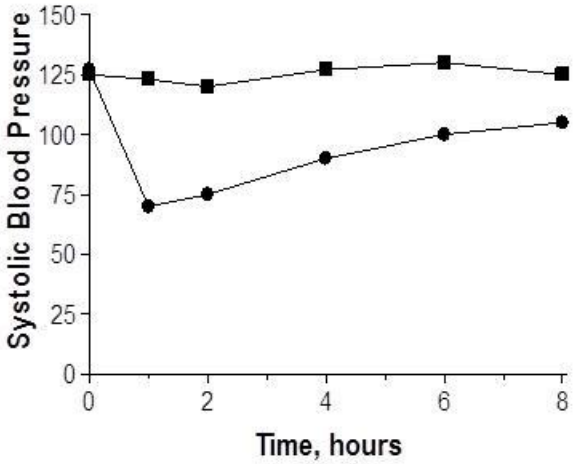
Personalized Medicine: Prescribing the right drug at the right time, may save many lives

Our Focus: Figuring out "Determinants of intersubject variation in drug responsiveness"









Our Approach

Personalized Medicine at LHSC

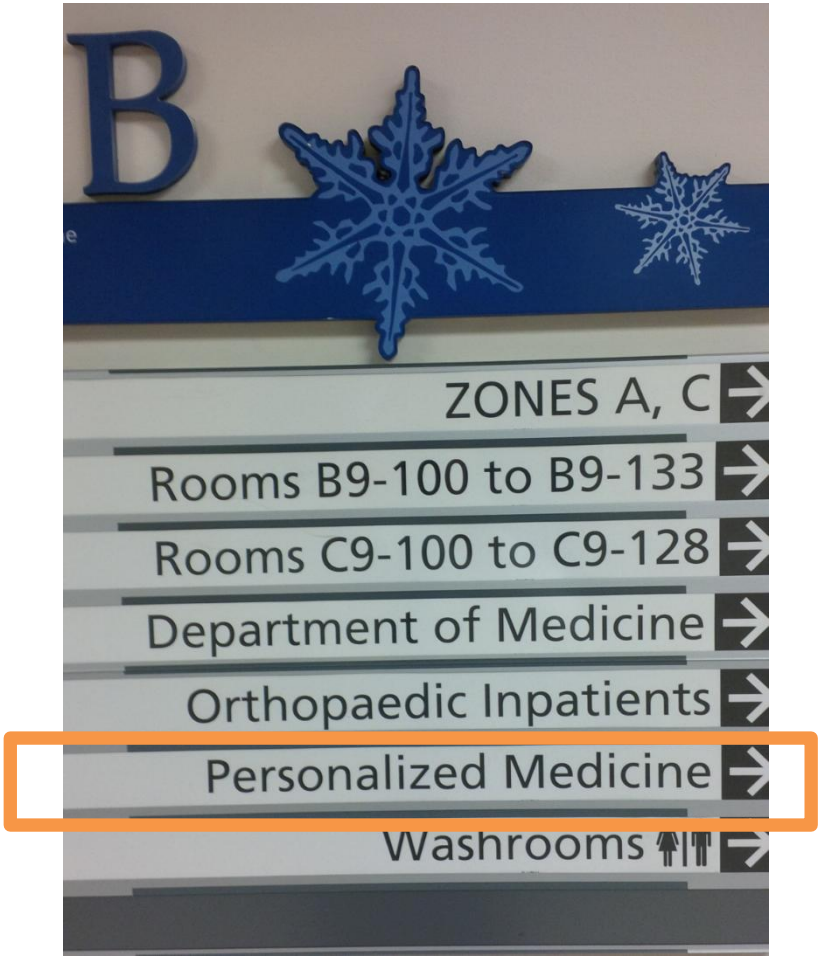
Blood sample

Determine Drug level

Determine Genotype

New insights

Sign of the times: At our Medical Centre, we have been embraced as a part of innovative patient-centred model of care



Clinical Consultation Process

Referral

- Initiating a new drug or experienced an ADR
- Fax referral to PM (now automated in chemo orders)

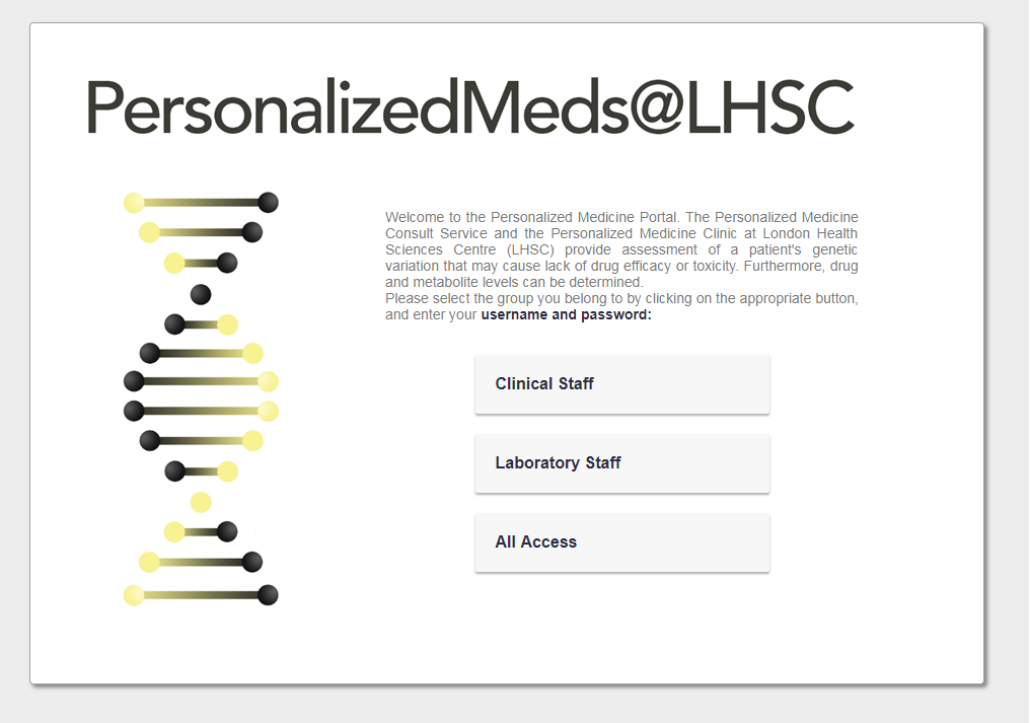
PM Consult

- Patient is seen in our Personalized Medicine Clinic
- Consultation, patient education
- Physicians, Residents and Pharmacists

Research Consent

- Consent is obtained by research coordinator
- Obtain blood sample for genotyping, store DNA for future research
- Research consent obtained
- Patient surveys completed

We have Created Innovative Technologies

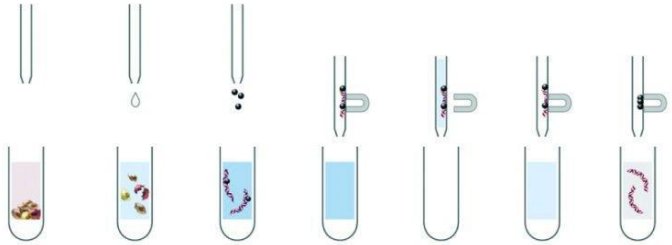


Secure Web application

- Behind the hospital firewall
- Features for clinical and laboratory staff
- Log and track samples
- Upload PGx data
- Generate custom reports

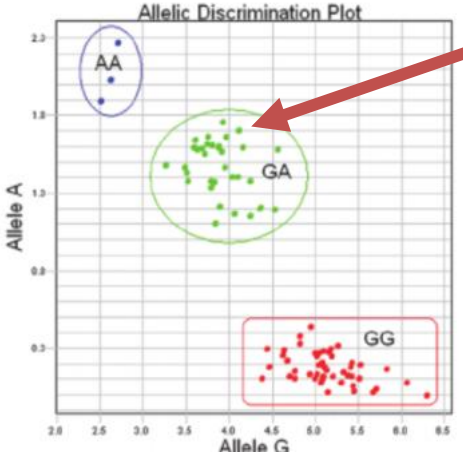
Genotyping requests

1 Genotyping

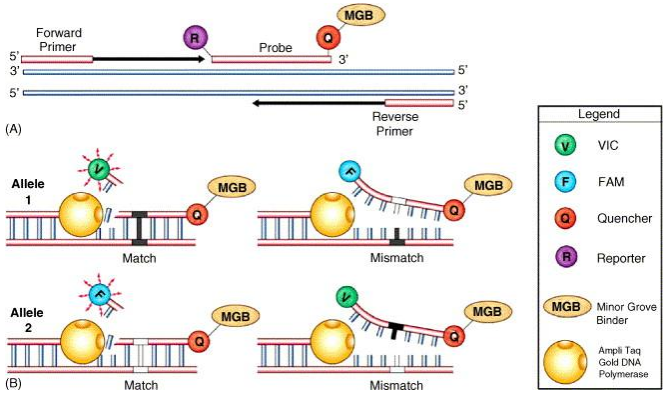


Automated DNA extraction (8 samples in ~30 min)

Real-Time PCR: TaqMan SNP Assays
(~ 40 min)



Mr. M



Over 300 drugs have FDA pharmacogenetic information, yet most clinicians don't know when to request PGEN testing…

Lesson Learned: If you teach pharmacogenetics and are available to see patients, interesting cases often come along

Case

- Inpatient Medicine services asks our team to carry out pharmacogenetic testing for a patient.
- Patient: 87 year old female, on 200 mg twice daily dose of metoprolol for heart rate control in the setting of atrial fibrillation.
- Patient had been admitted to orthopedics inpatient floor after a hip fracture.

Quiz (pick one best answer)

- Which pharmacogenetic testing was requested?
  1. CYP3A4 because it is involved in the metabolism of most medications
  2. CYP2C19 because it affects metoprolol metabolism
  3. CYP2D6 because it affects metoprolol metabolism
  4. CYP2C19 and CYP2D6

Quiz (Correct Answer)

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  3. CYP2D6 because it affects metoprolol metabolism
  4. CYP2C19 and CYP2D6

Case

- Typical dose of metoprolol is 25 to 50 mg twice daily.
- Medicine team tried to lower the dose of metoprolol to 100 mg twice daily.
- Patient experienced significant tachycardia that subsided when the dose of metoprolol was increased back to 200 mg twice daily.
- Medicine team asked us to carry out CYP2D6 genotype testing.

Quiz (pick one best answer)

- Which CYP2D6 genotype would you predict for the patient
  1. Normal metabolizer because that is the most common
  2. Poor metabolizer because those patients always have more problems with medications
  3. This has to be a trick question because predicting the future is really hard
  4. Ultrarapid metabolizer, even though this is rare

Quiz (Answer)

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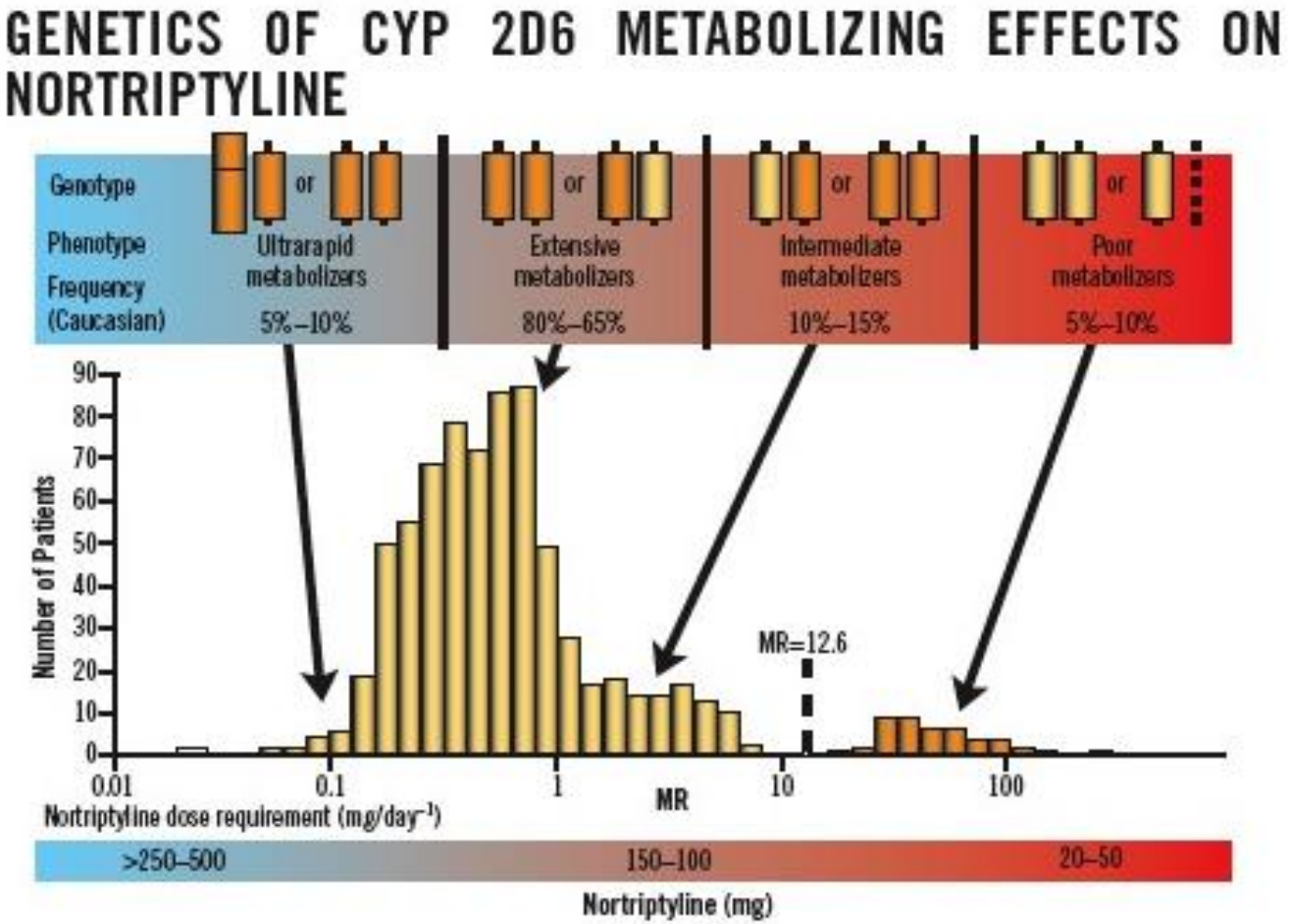
Case

- Patient seen as a consultation and consent obtained to carry out CYP2D6 genotype testing through my research laboratory.
- There is no out-of-pocket cost to any of our patients for PGEN testing carried out through my research laboratory.
- Patient turned out to be a CYP2D6 ultrarapid metabolizer, thus predicted to require very high doses of metoprolol.
- We recommended beta blocker change to bisoprolol (not a CYP2D6 substrate).

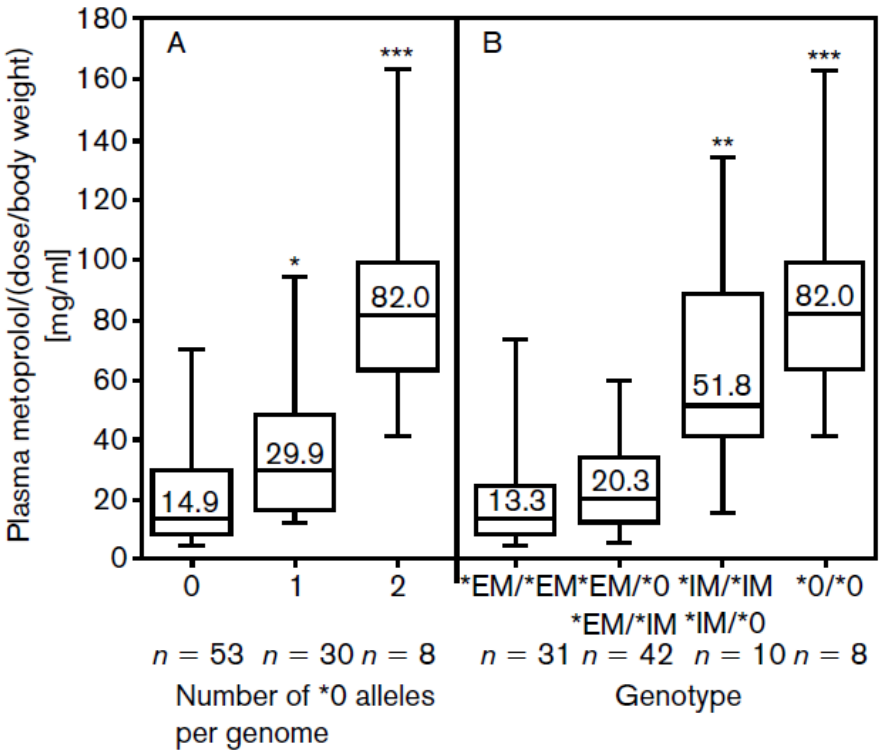
CYP2D6 Activity



CYP=cytochrome P450; MR=metabolic ratio of parent debrisoquine ÷ metabolic OH-debrisoquine.

Preskorn SH, Flockhart D. *Primary Psychiatry.* Vol 16, No 12. 2009.

Metoprolol and CYP2D6



- Mean Age: 62.5 +/- 13.3
- Median Dose: 47.5mg/day
- HTN: 84%
- CAD: 66%
- Past MI: 43%
- Other Drugs; ACE-I and/or diuretics: 86%

PMs had 6-fold higher metoprolol level compared to EMs
IMs had 4-fold higher metoprolol level compared to EMs

Rao et al Pharmacogenetics 12:465, 2002

Quiz (pick one best answer)

- She is in pain from her hip fracture. Your colleague suggests acetaminophen/caffeine/codeine. What will you do?
  1. You will start her on higher than normal dose acetaminophen/caffeine/codeine because she is an ultrarapid metabolizer for CYP2D6
  2. You will start her on normal dose of acetaminophen/caffeine/codeine because you want to be careful, even though she is an ultrarapid metabolizer
  3. Don't bother with acetaminophen/caffeine/codeine as it won't work so use tramadol instead
  4. Do not start her on acetaminophen/caffeine/codeine or tramadol

Quiz (Answer)

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  3. Don't bother with acetaminophen/caffeine/codeine as it won't work so use tramadol instead
  4. Do not start her on acetaminophen/caffeine/codeine or tramadol

Codeine is not an analgesic: Requires bioactivation by CYP2D6 to morphine

UMs

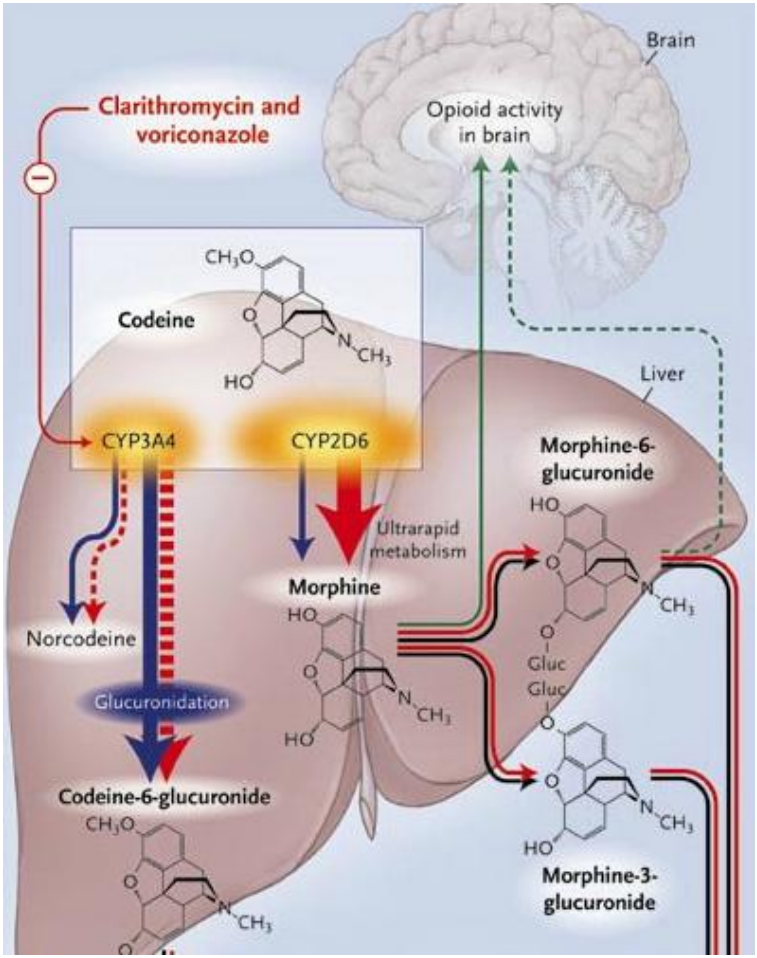
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism

Yvan Gasche, M.D., Youssef Daali, Pharm.D., Ph.D., Marc Fathi, Ph.D., Alberto Chiappe, Silvia Cottini, M.D., Pierre Dayer, M.D., and Jules Desmeules, M.D.

N Engl J Med 2004;351:2827-31.



Codeine and tramadol

- Analgesic effect due to conversion of codeine to morphine and tramadol to its active metabolite by CYP2D6
- There can be excessive opioid response among CYP2D6 ultrarapid metabolizers when prescribed codeine or tramadol containing analgesics.

Many SSRIs are inhibitors of CYP2D6

- Potent interacting antidepressants
  - Paroxetine
  - Bupropion
  - Fluoxetine

- Modest/minimally interacting
  - Citalopram, escitalopram, venlafaxine, desvenlafaxine, vortioxetine

Why understanding CYP2D6 is helpful

- Most of the tricyclic antidepressants are substrates of CYP2D6
- Many SSRI are substrates, and some are potent inhibitors of CYP2D6
- Some opioids are metabolized by CYP2D6
- Commonly prescribed beta blockers such as metoprolol are highly affected by CYP2D6 genotype.
- Antiemetic ondansetron is also affected by CYP2D6
- Breast cancer drug tamoxifen is affected by CYP2D6

New Oral Anticoagulants: Now we have much more to choose from, when warfarin is not optimal

DOACs: When to prescribe.... PK and DDI considerations

ELSEVIER

Canadian Journal of Cardiology 29 (2013) S24–S33

Review

Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban

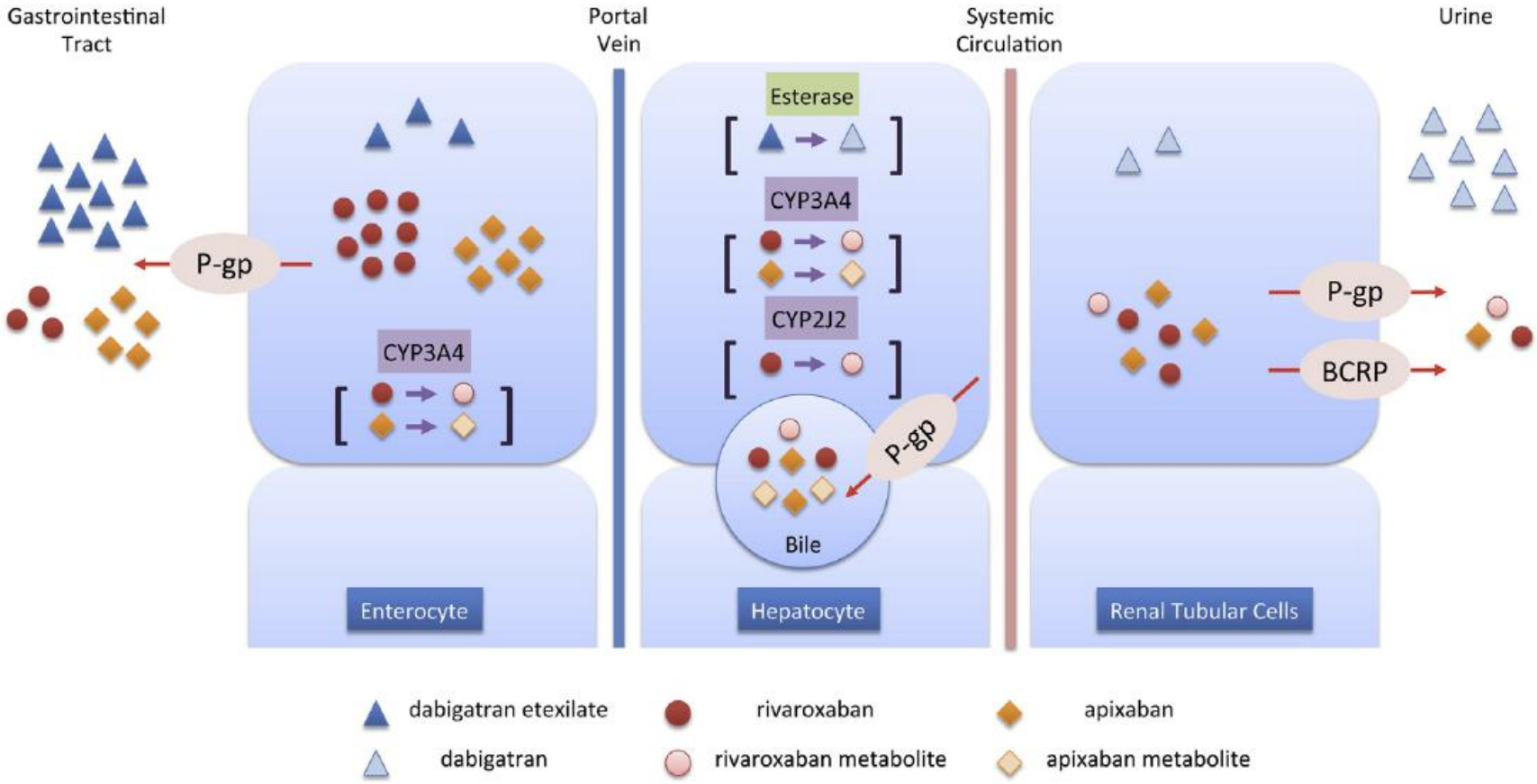
Inna Y. Gong, BMSc,[a,b] and Richard B. Kim, MD[a,b]

[a] *Division of Clinical Pharmacology, Department of Medicine, University of Western Ontario, London, Ontario, Canada*

[b] *Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada*

This review covers the key issues in terms of metabolism and clearance of DOACs

DOAC metabolism and clearance



Do DOAC Patients Bleed more if DOAC Level is Elevated?

Yes

High DOAC concentration increases bleeding risk with little additional benefit to stroke reduction: Edoxaban data from ENGAGE-TIMI

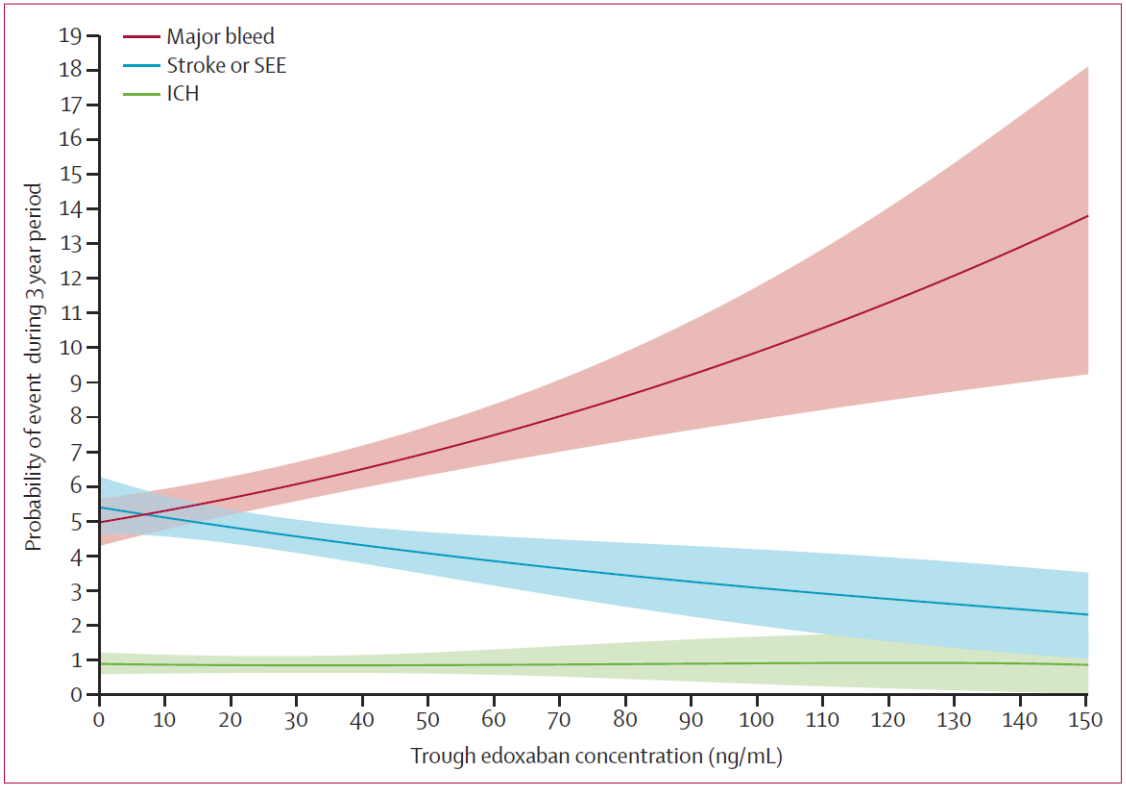


Figure 2: **Probability of clinical outcomes versus edoxaban concentration**
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

Lancet 2015; 385: 2288–95

We measure DOAC concentration using LC-MS/MS

LA PRESSE+ DISCOVER LA PRESSE + WHAT YOU NEED INSTALLATION STEPS USER GUIDE WHAT'S NEW

THIS SCREEN HAS BEEN SHARED FROM LA PRESSE +

Edition of September 8, 2015, section NEWS , screen 2

CHEMOTHERAPY

"HOW MANY DEATHS WILL IT TAKE? "

MARIE-CLAUDE MALBOEUF
THE PRESS

La Presse Sept 8, 2015

MARIE-CLAUDE MALBOEUF
THE PRESS

On his funeral picture, Paul Allard smiles. But his family will never forget his nightmare face of the last days.

After having had a colon tumor removed, Sherbrooke's grandfather was bursting with energy. A music lover, whimsical inventor and cabinet maker, the 69-year-old was already back on the slopes and the tennis courts. A great traveler, he planned a trip to the Alps or to Corsica.

No trace of metastases. Ganglia intact. Three out of four chances of ending cancer. All hopes were allowed ...

To further reduce - very slightly - the risk of recurrence (by 5%), Paul Allard has even agreed to undergo oral chemotherapy. From February 3 to 5, 2011, he swallowed five tablets of capecitabine the equivalent of 5-fluorouracil (or 5-FU), used for decades by intravenous.

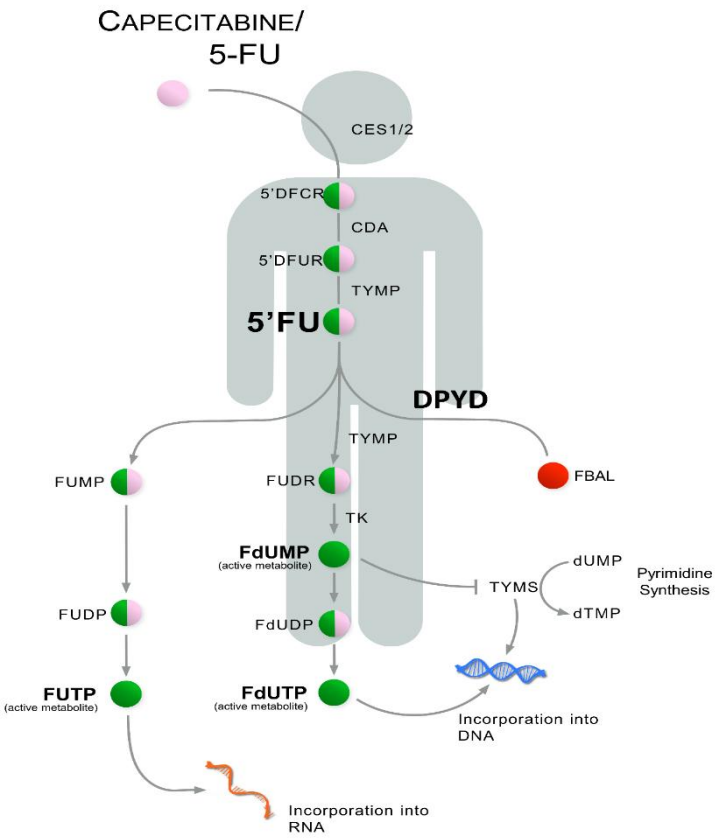
"The oncologist said his chemo was light, not to worry, that Paul could stop when he wanted," said his widow Colette Bibeau.

Two weeks later, Paul Allard was dying in intensive care.

La Presse Sept 8, 2015

DPYD genotype testing: Why it is so important

- Approximately 1 in 15-30 individuals have mutations that result in significantly reduced DPD function
  - leads to severe toxicity and usually leads to hospitalization
- Approximately 1 in 1000-2000 have mutations that result in no activity of DPD
  - Usually fatal toxicity after a single dose
- Currently, we carry out DPYD testing for **all** colon cancer patients prior to capecitabine or 5-FU therapy at our medical centre (LHSC)



When you see a lot of patients, eventually, you do find the 1 in 1000

Case

- 87 year old male
- Presented with profound anemia (Hgb 40) that required transfusion Nov 2018
- May 2019 rectal cancer with liver mets identified
- Seen in our PM clinic Aug 22, 2019
- Patient was being planned for chemoradiation, and for chemo, capecitabine.

Case

- Aug 23, 2019:
- DPYD genotype: DPYD IVS14+1 **G/A**; DPYD 2846 A/A; DPYD 1679 T/T; DPYD 1236 **G/A**
- **Interpretation:**
  The genotype of this patient suggests **deficient enzymatic activity**

Recommended dosing of 5-FU/capecitabine by genotype:
Select an alternative drug. If alternative agents are not considered a suitable therapeutic option, 5-FU or capecitabine should be administered at a strongly reduced dose.

Case

- Referring oncologist notified
- Patient notified
- Preordered capecitabine in EMR removed.
- Oncologist proceeded with a second line agent: Raltitrexed.
- Patient would have had a lethal event had he received even a few doses of capecitabine.

Translation to patient care: We had requested that DPYD testing become a standard of care in Ontario

EVIDENCE TO IMPROVE CARE

BACK TO SEARCH (/EVIDENCE-TO-IMPROVE-CARE/HEALTH-TECHNOLOGY-ASSESSMENT/REVIEWS-AND-RECOMMENDATIONS)

DPYD Genotyping in Patients Who Have Planned Cancer Treatment With Fluoropyrimidines

Publication date: August 2021 Status: Final recommendation

Final Recommendation

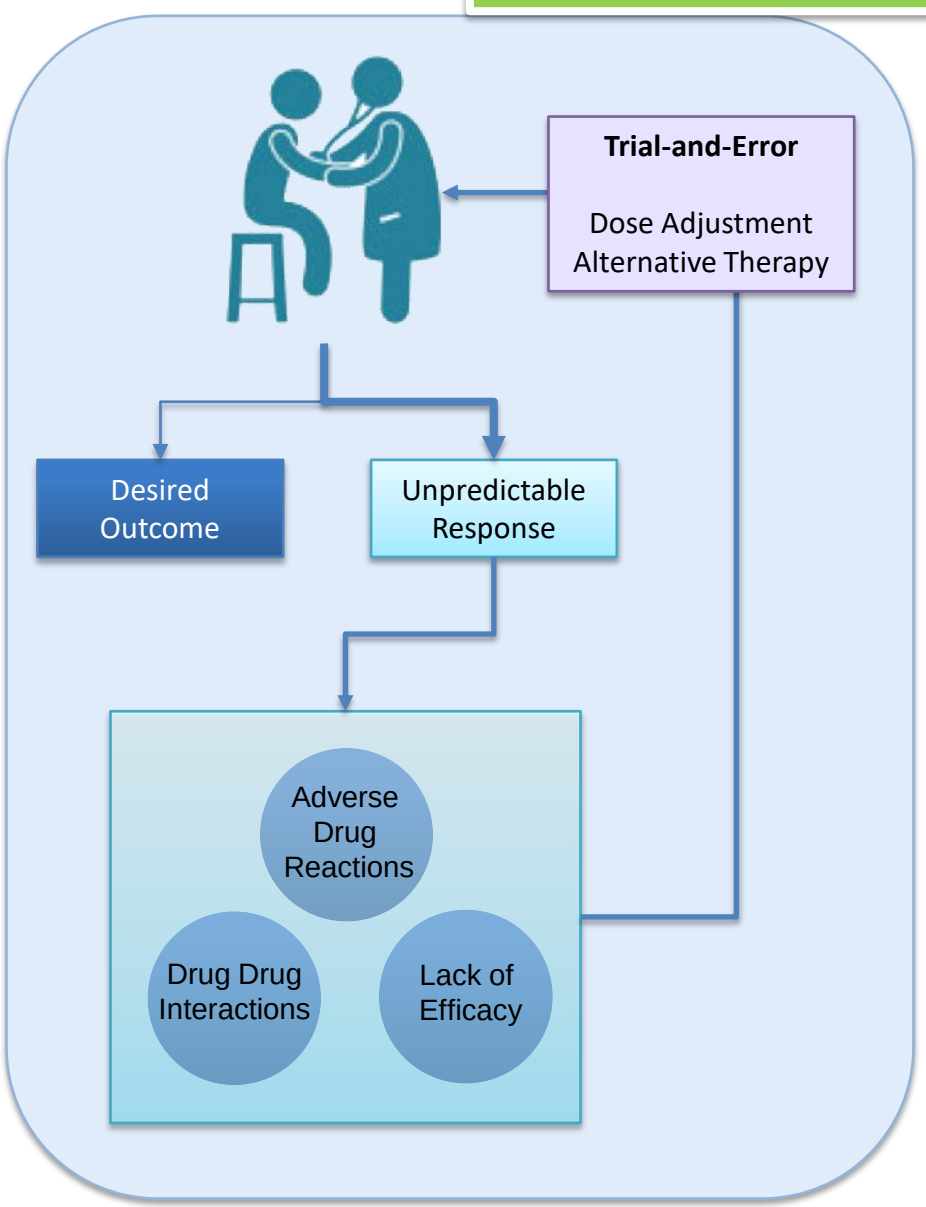
- Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding *DPYD* genotyping for the following variants in patients who have planned cancer treatment with fluoropyrimidines (5-fluorouracil or capecitabine):
  - c.1905+1G>A (*DPYD**2A; IVS14+1G>A; rs3918290)
  - c.1679T>G (*DPYD**13; I560S; rs55886062)
  - c.2846A>T (D949V; rs67376798)
  - c.[1236G>A; 1129-5923C>G]

Read the final recommendation report (/Portals/0/documents/evidence/reports/recommendation-dpyd-genotyping-in-patients-who-have-planned-cancer-treatment-with-fluoropyrimidines-en.pdf)

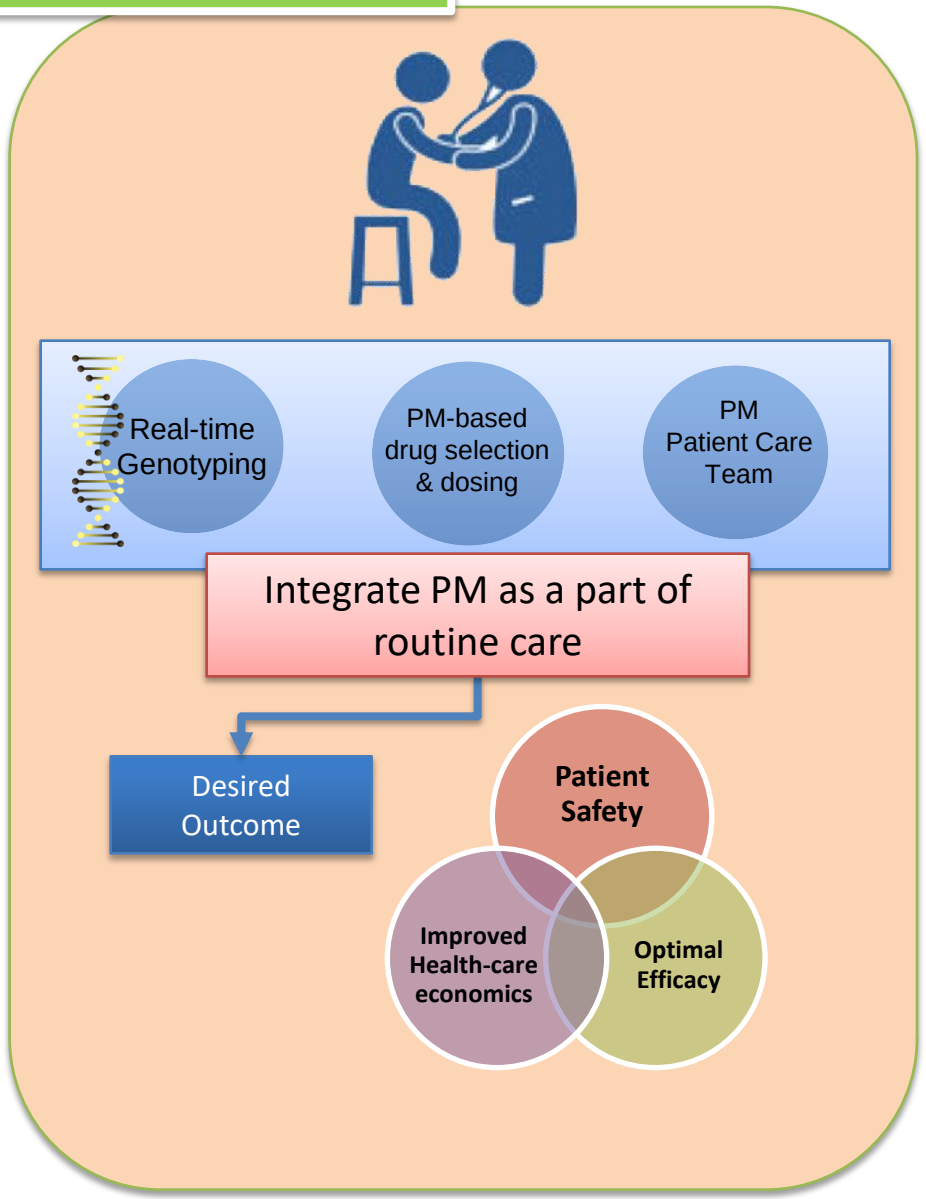
In **August 2021**, Ontario Health Technology Advisory Committee has recommended public funding for DPYD genotype testing

Personalized Medicine at London Health Sciences Centre (London ON)

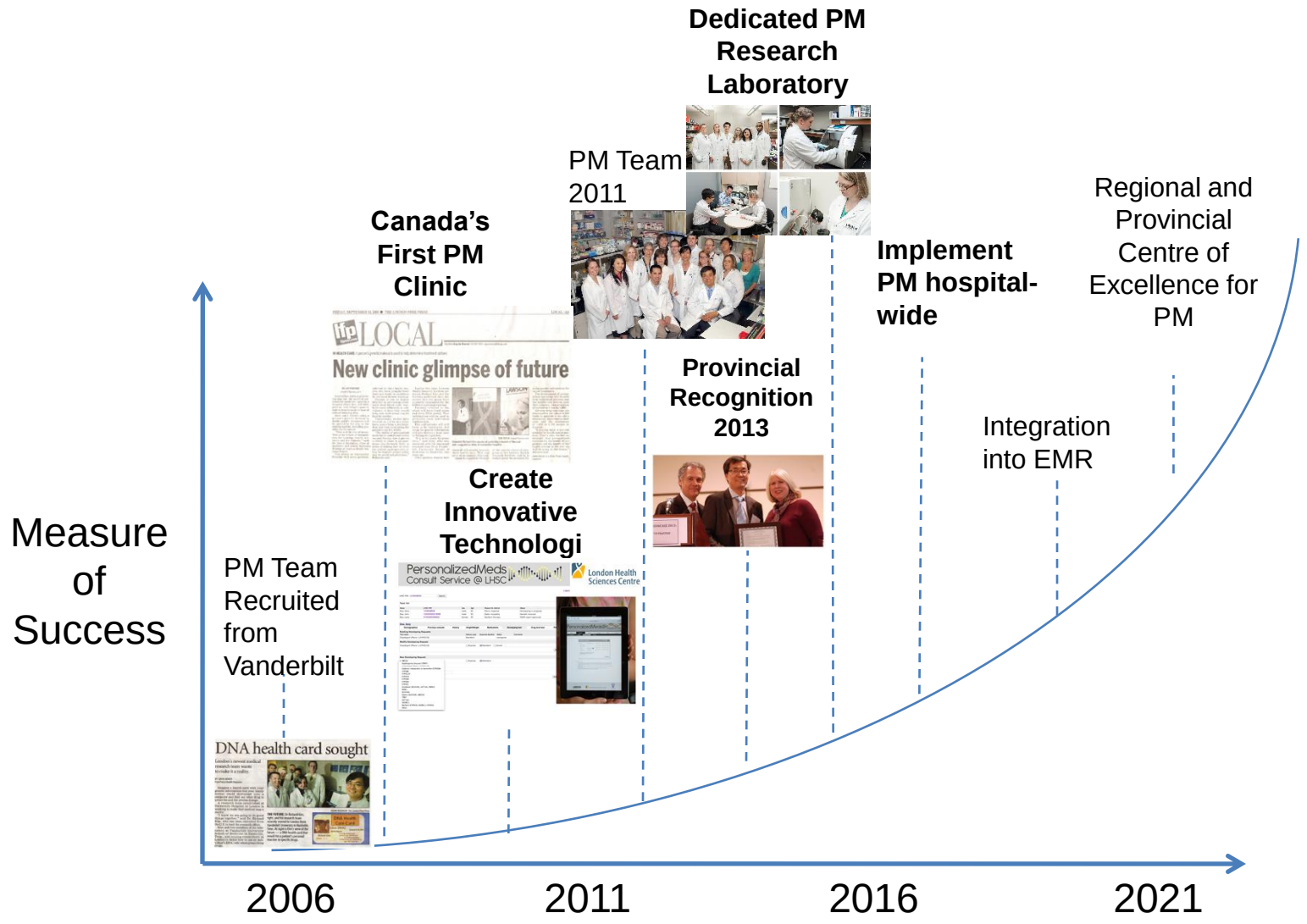
2006



2021



Our Personalized Medicine Program



Funding for our PM Program: Made feasible by donors and research grants

LHSC Auxiliary Donation

CRAIG GLOVER/THE LONDON FREE PRESS

Dr. Richard Kim, who leads London Health Sciences Centre's Personalized Medicine Program, middle, is flanked by London Health Sciences Foundation vice-chairperson Tod Warner, left, and LHSC chief clinical officer Laurie Gould as the foundation unveils a $2.24-million gift to Kim's program.

Something nice from gift shop

Auxiliary's $2.24-million donation to help doctors better predict patients' response to medications

DAN BROWN

ning the five gift shops in facilities like Victoria Hospital.

"Maybe this is the next wave of what modern medicine should be," Kim said.

The funding will allow Kim and his team to implement, in real time, a system that helps doctors better

> *"You get to go home quicker with more confidence."*
> Dr. Richard Kim

three gift shops, which sell greeting cards, purses, toys and other items to patients and hospital visitors.

"Patients are being treated right now, right down to the molecular level," Gould said about how genetics will help doctors determine how patients will react to treatment.

Ontario

Ontario Research Fund: Research Excellence

Wolfe Medical Research Chair in Pharmacogenomics

Canadian Institutes of Health Research (CIHR)