Pharmacogenomics: the future is now !

Maria Luís Cardoso

Departamento de Promoção da Saúde e Prevenção de Doenças não transmissíveis

Porto, 20 de Novembro de 2019

REPÚBLICA PORTUGUESA
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Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P.

Av. Padre Cruz, 1649-016 Lisboa Portugal www.insa.pt info@insa.min-saude.pt
telf. +351 217 519 200 fax: +351 217 526 400

Instituto_Nacional de Saúde
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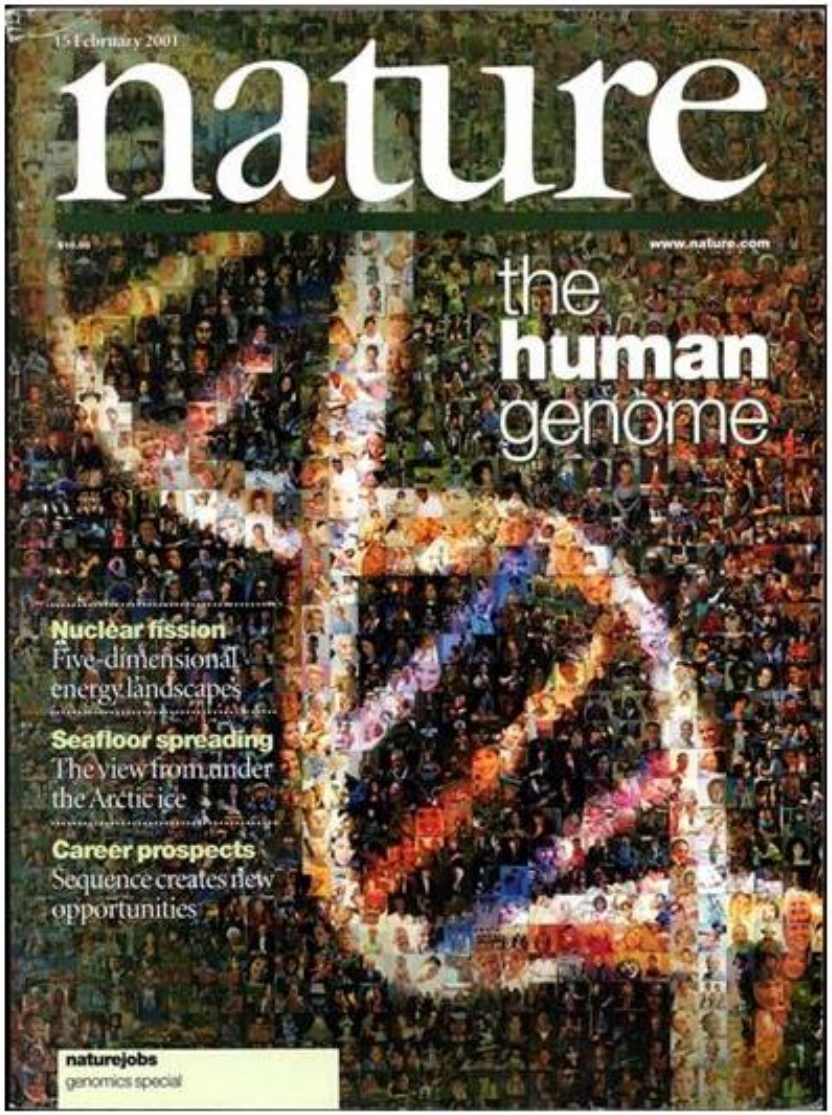
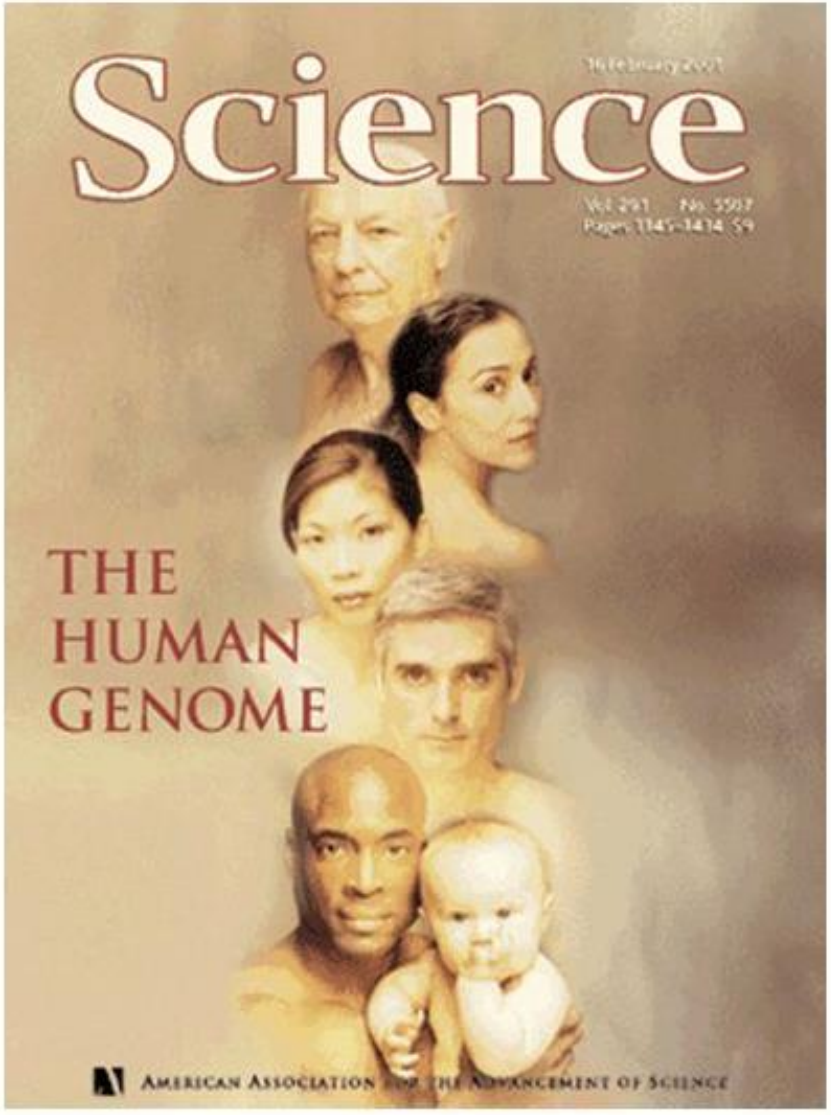
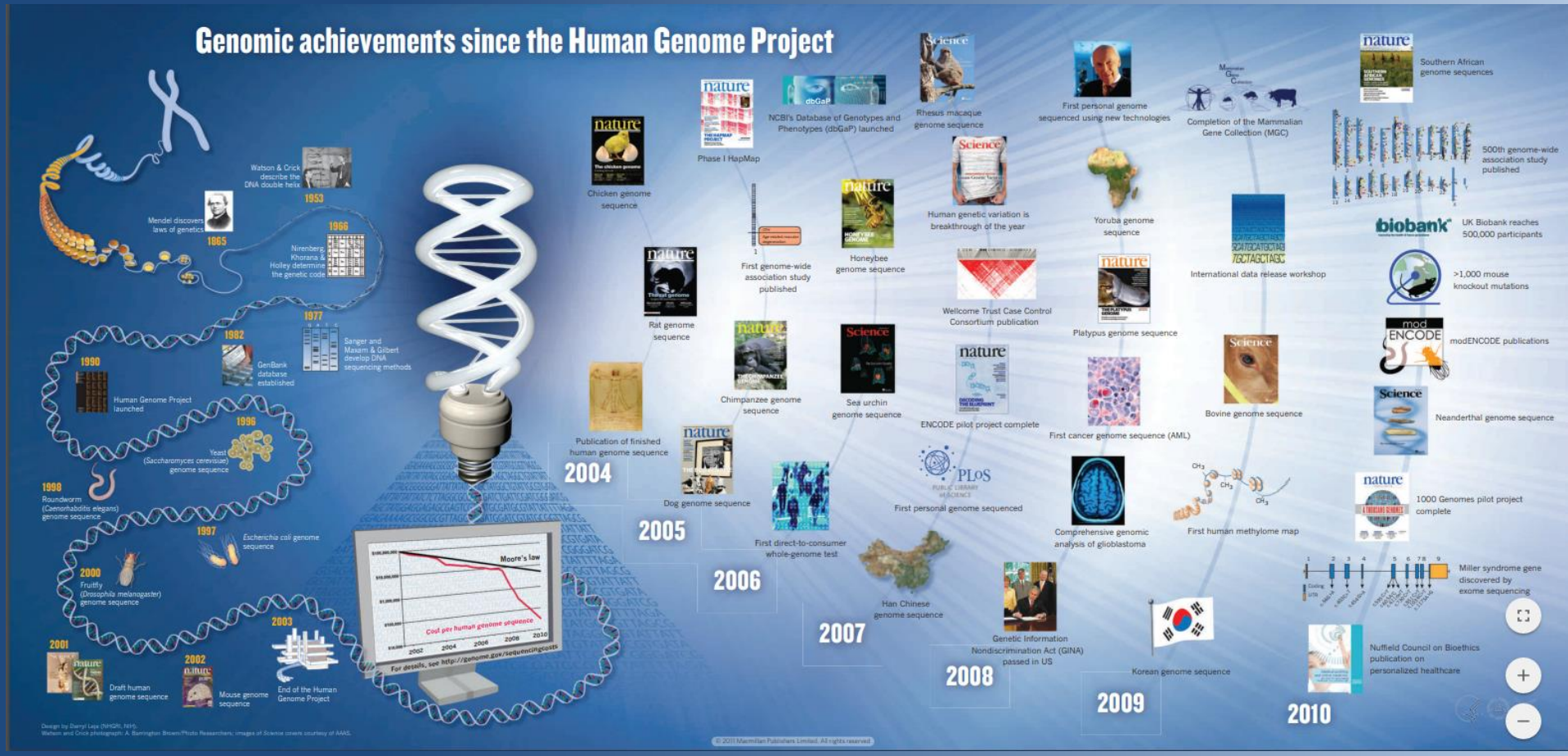
The past ...





By F**ebruary 2001** a working **draft** had been completed and **published**
The **final sequencing mapping** of the **human genome** was concluded on April 14, **2003.**

2001 - 2010



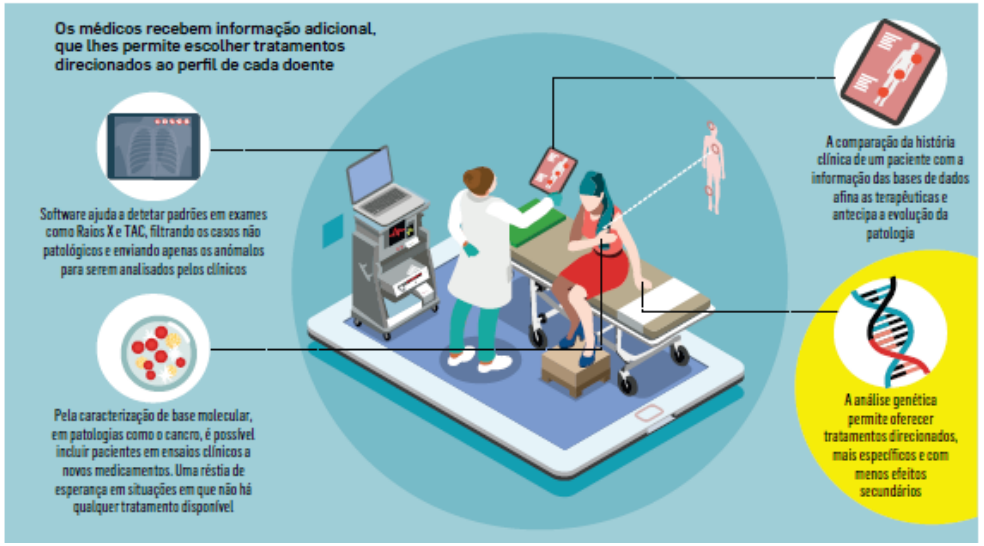
1865 - 2001

Capturing the History of Genomics: A Workshop

https://www.yourgenome.org/facts/timeline-history-of-genomics

The Present continuous ...

A Medicina está a mudar, e rapidamente. Recolher dados e usá-los de forma eficiente pode ajudar a poupar euros e anos de vida



Visão 14-12-2017
+ Minority report

The Future

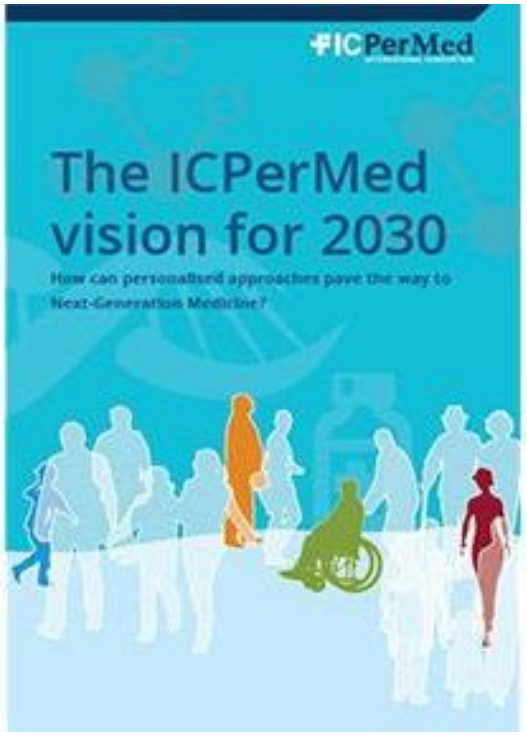
REGIONAL COMMITTEE FOR EUROPE 66TH SESSION

Copenhagen, Denmark, 12–15 September 2016

Towards a roadmap to implement the 2030 Agenda for Sustainable Development in the WHO European Region

Dr Zsuzsanna Jakab
WHO Regional Director for Europe

World Health Organization Europe | Organisation mondiale de la Santé Europe | Weltgesundheitsorganisation Europa | Всемирная организация здравоохранения Европейское региональное бюро



nature OUTLOOK

THE FUTURE OF MEDICINE

8 March 2018 / Vol 555 / Issue No 7695

From the nineteenth-century benches of microbiologists Louis Pasteur and Robert Koch to the sequencing of the human genome in 2003, the past 200 years have seen medicine advance at an extraordinary pace. People are now enjoying longer and healthier lives than their ancestors. But as any medical researcher will attest, ambitions go much further.

The stories in this Outlook, chosen in consultation with editors from the Nature Research journals, represent some of the biggest opportunities we have to improve our future health. Our selection is not exhaustive, nor can we be certain that all research we report will come to fruition. But if only a fraction does, humanity can look forward to a healthier future.

To avoid antibiotic resistance undoing a century's worth of progress, researchers are racing to restock the antibacterial armoury (see page S5). Others are exploiting the data generated by ubiquitous computers and smartphones to better anticipate outbreaks of infectious disease (S2).

With the potential for gain so great, the prevention of illness is playing an ever-larger part in medicine (S20). Intervention to protect people from long-term disease could begin in the first moments after birth (S18). And although a decline in health in later life might seem normal, there is ongoing debate about where healthy ageing ends and disease begins (S15).

Work to exert greater control over rogue immune systems (S8), as well as to develop technological solutions to paralysis (S12), is showing initial promise. The advent of CRISPR–Cas genome editing has raised hopes for widespread use of gene therapy (S23); meanwhile, this technology is also aiding the search for new drugs (S10). As long as barriers to accessing the best treatments available can be negotiated away (S26), the future of medicine could be very bright indeed.

We are pleased to acknowledge the financial support of Merck in producing this Outlook. As always, *Nature* has sole responsibility for all editorial content.

Richard Hodson
Supplements editor

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CITING THE OUTLOOK
Cite as a supplement to *Nature*, for example, *Nature* **Vol. XXX**, No. XXXX Suppl., S1–S32 (2018).

VISIT THE OUTLOOK ONLINE
The *Nature Outlook The future of medicine* supplement can be found at www.nature.com/collections/future-of-medicine-outlook. It features all newly commissioned content as well as a selection of relevant previously published material that is made freely available for 6 months.

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Cálculo do Risco
Os testes genéticos permitem detetar a predisposição para determinadas doenças (Ex Risco para cancro da mama)

Prevenção
Adopção de comportamentos, estilos de vida e tratamentos
Ex Não fumar diminui o risco de cancro de pulmão e de bexiga. As cirurgias da Angelina Jolie

Diagnóstico precoce
Deteção precoce / pré-sintomática da patologia ao nível molecular
(Ex Intolerância à frutose, argininemia)

Diagnóstico
O diagnóstico das causas permite adoptar uma estratégia de tratamento personalizada (Ex Fibrose quistica, cancro, FH)

Tratamento
Melhoria da saúde através da adopção de terapias direcionadas e redução dos efeitos laterais
(Ex Imunoterapia, Abacavir).

Gestão
Monitorização ativa da resposta ao tratamento e progressão da doença.
(Biópsia liquida aplicada à monitorização do cancro e do transplantes)

Medicina Genómica

Medicina Genómica - É uma área médica emergente que envolve a **utilização da informação genética** de um indivíduo como parte do seu processo clínico para:

1. **diagnóstico,**
2. **cálculo de risco (prevenção)**
3. **prognóstico e**
4. **tratamento farmacológico adaptado.**

Farmacogenética - É uma área da farmacologia que relaciona a **presença de variantes num gene com a diferença na resposta terapêutica** a um determinado fármaco.

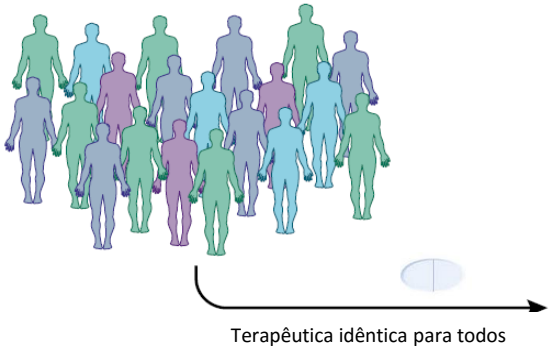
Ex: Deleções no gene CYP2D6 condicionam a conversão do tamoxifeno na forma ativa endoxifeno.

Farmacogenómica - Refere-se à forma como os **genes no seu conjunto** influenciam a resposta aos medicamentos (efeito terapêutico, neutro, adverso).

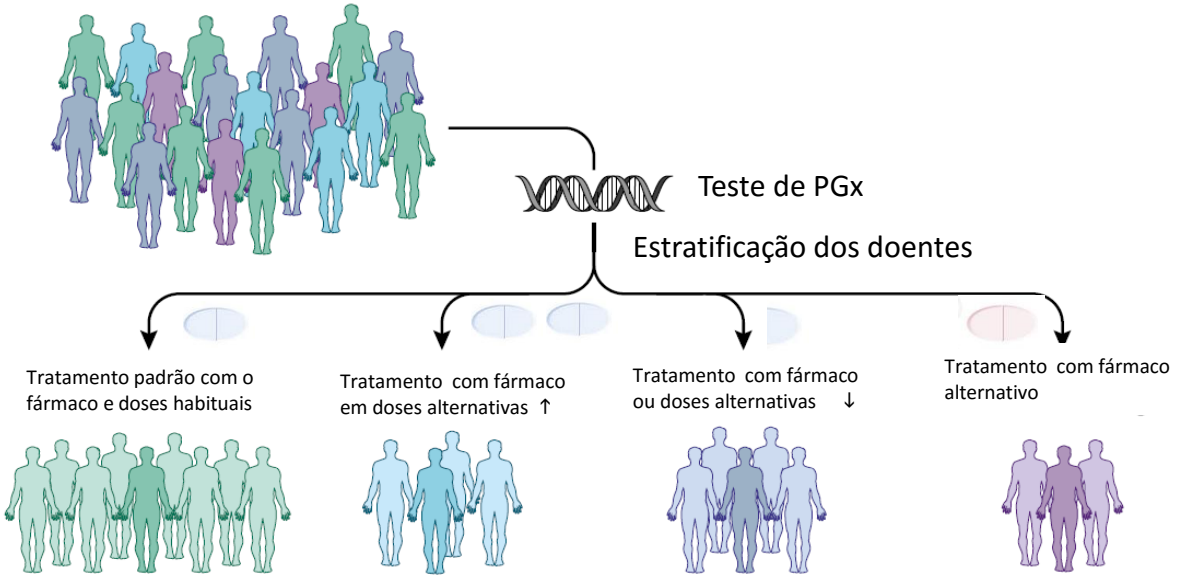
Farmacogenómica

Refere-se à forma como os genes no seu conjunto influenciam a resposta aos medicamentos (efeito terapêutico, neutro, adverso).

1. Modelo terapêutico convencional



2. Modelo baseado na Farmacogenómica (PGx)



Objectivos da Farmacogenómica

- Maximizar o efeito terapêutico do medicamento
- Minimizar a toxicidade do medicamento e reduzir as RAMs
- Ser capaz de predizer que subgrupo de doentes respondem à terapêutica
- Auxiliar no desenvolvimento de novos medicamentos
- O conhecimento do *background* genético dos doentes permitirá **no futuro** seleccionar medicamenos mais apropriados com base nessa informação.


Pharmacogenomics:
the future
is now

THE LANCET

Series from the Lancet journals View all Series

Genomic medicine

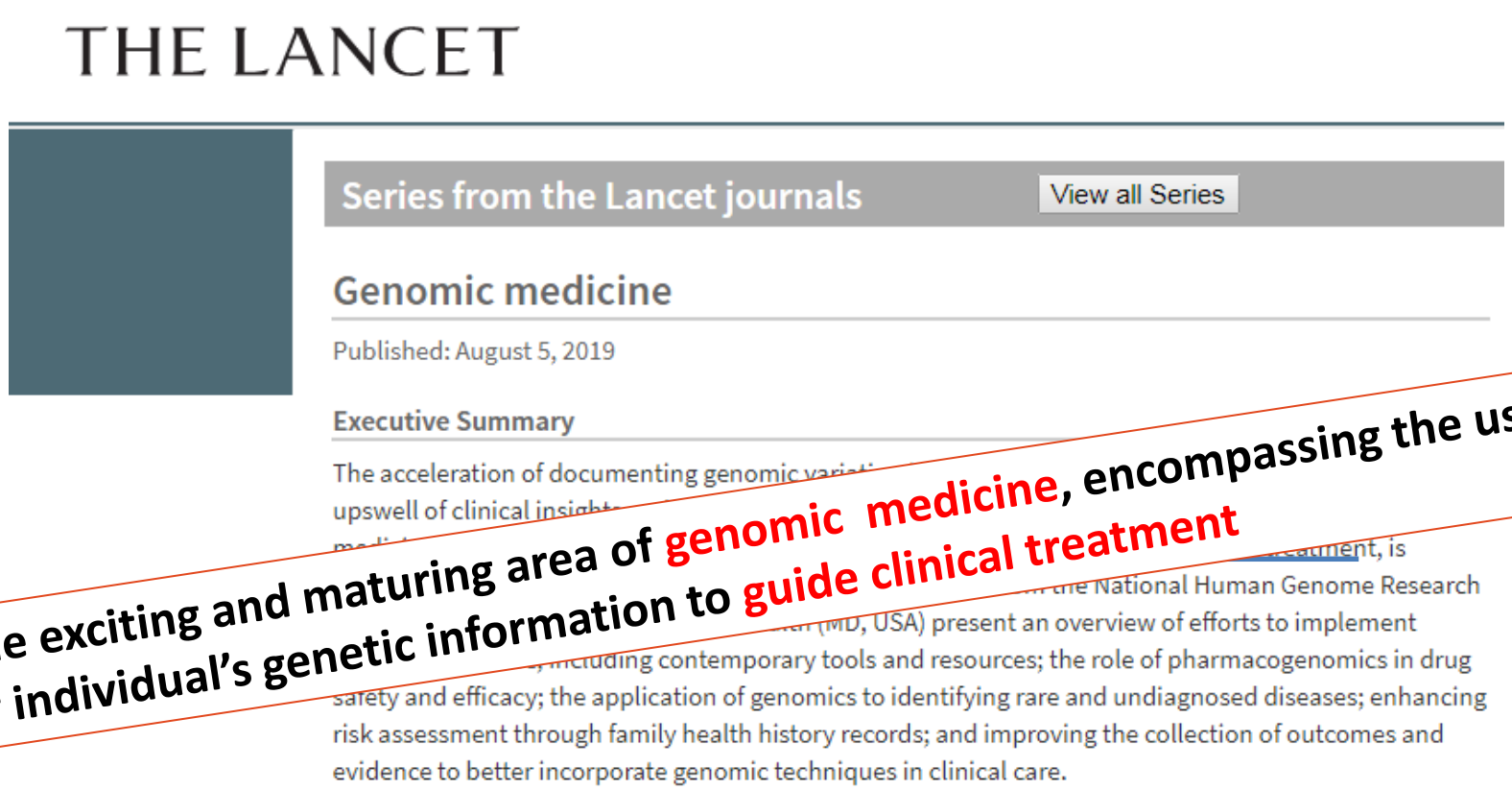
Published: August 5, 2019

Executive Summary

The acceleration of documenting genomic variation in disease states and health outcomes has led to an upswell of clinical insights and avenues of exploration. The exciting and maturing area of genomic medicine, encompassing the use of individuals' genetic information to guide clinical treatment, is featured in this Series. In these five, timely reviews, authors from the National Human Genome Research Institute at the National Institutes of Health (MD, USA) present an overview of efforts to implement genomic medicine, including contemporary tools and resources; the role of pharmacogenomics in drug safety and efficacy; the application of genomics to identifying rare and undiagnosed diseases; enhancing risk assessment through family health history records; and improving the collection of outcomes and evidence to better incorporate genomic techniques in clinical care.

1. **Opportunities, resources, and techniques for implementing genomics in clinical care**
2. **Pharmacogenomics**
3. **Genomic medicine for undiagnosed diseases**
4. **Family health history: underused for actionable risk assessment**
5. **Building evidence and measuring clinical outcomes for genomic medicine**

Published: August 5, 2019*The Lancet*, Vol. 394, No. 10198



The exciting and maturing area of genomic medicine, encompassing the use of individual's genetic information to guide clinical treatment

1. **Opportunities, resources, and techniques for implementing genomics in clinical care**
2. **Pharmacogenomics**
3. **Genomic medicine for undiagnosed diseases**
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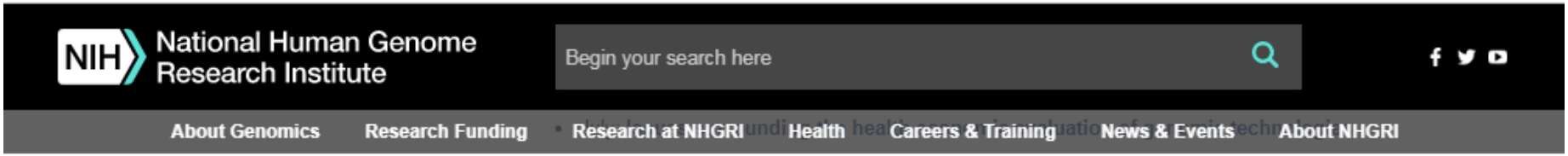
Published: August 5, 2019*The Lancet*, Vol. 394, No. 10198



Pharmacogenomics

2019

- September: September: A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI
- August: Pharmacogenomics
- July: Frequency and clinical outcomes of CYP2C19 genotype-guided escalation and de-escalation of antiplatelet therapy in a real-world clinical setting
- July: Australian genomics: A federated model for integrating genomics into healthcare
- June: A decision-theoretic approach to panel-based, preemptive genotyping

2018

- October: Multisite investigation of strategies for the implementation of CP2C19 genotype-guided antiplatelet therapy
- October: Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: challenges and solutions
- September: Effects of Delivering SLCO1B1 Pharmacogenetic Information in Randomized Trial and Observational Settings
- September: SLCO1B1 and Statin Therapy
- July: Genotype-guided versus traditional clinical dosing of warfarin in patients of Asian ancestry: a randomized controlled trial
- April: Association of HLA-A*31:01 screening with the incidence of Carbamazepine-induced cutaneous adverse reactions in a Japanese population

https://www.genome.gov/health/Genomics-and-Medicine/accomplishments#pharmacogenomics

AJGP Australian Journal of General Practice
Formerly *Australian Family Physician (AFP)*

CLINICAL

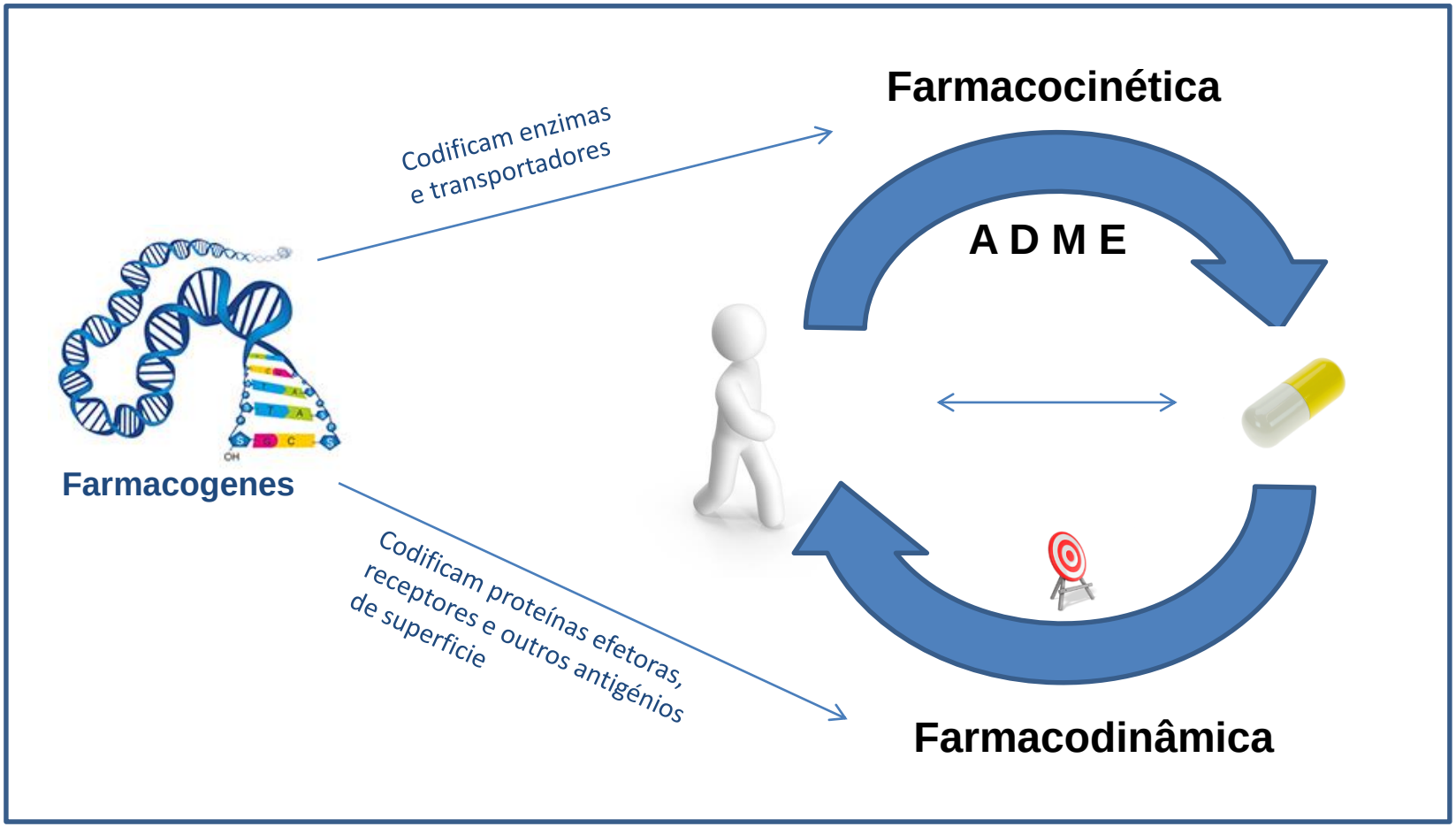
Volume 48, Issue 3, March 2019

Pharmacogenomics in general practice: The time has come

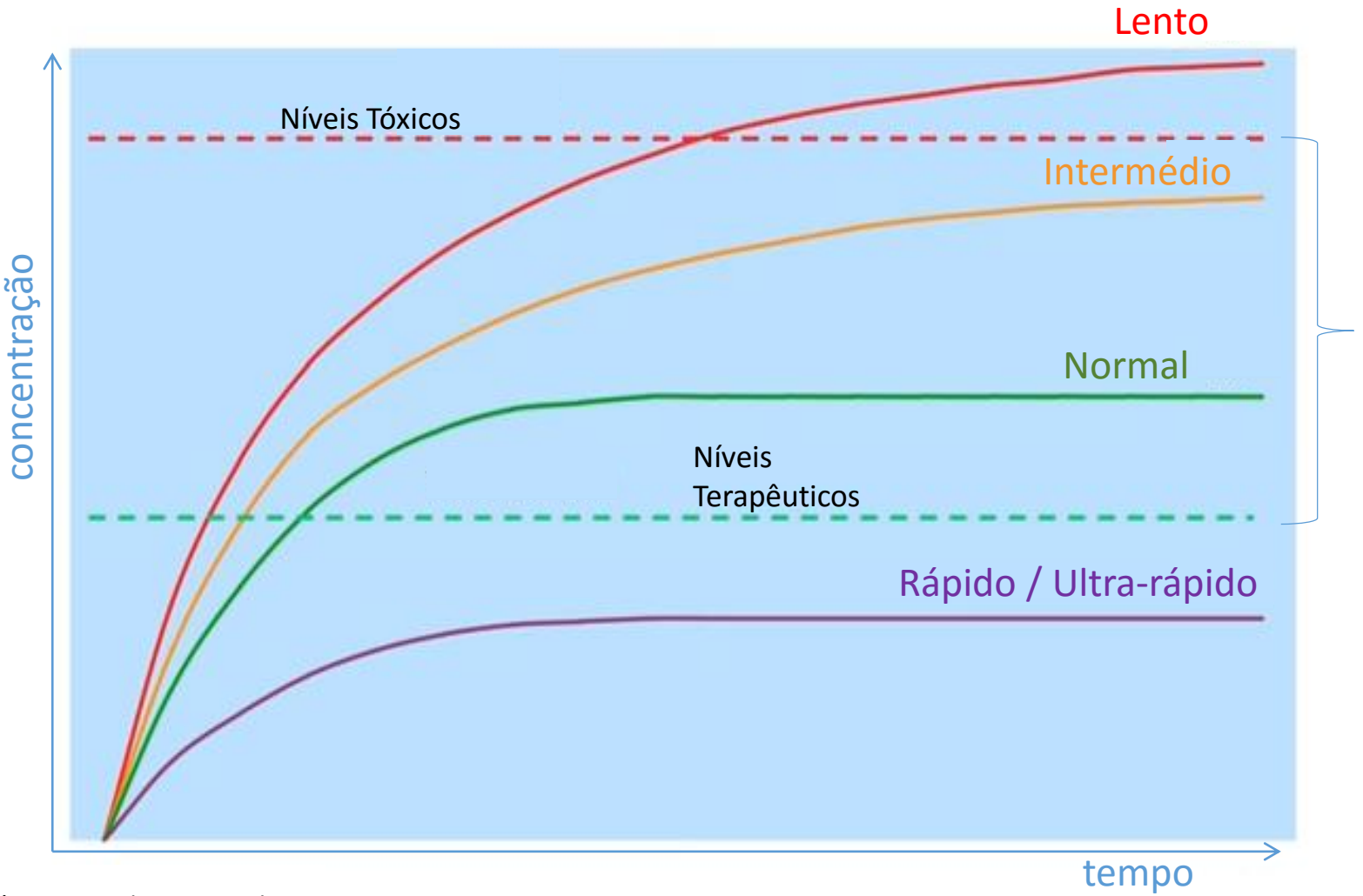
Thomas M Polasek Kym Mina Graeme Suthers

Farmacogenética
Farmacogenómica

Farmacocinética
Farmacodinâmica


Farmacocinética
Codificam enzimas
e transportadores
A D M E
Farmacogenes
Codificam proteínas efetoras,
receptores e outros antigénios
de superficie
Farmacodinâmica

Existem 4 tipos de metabolizadores resultantes da combinação das variantes genéticas presentes



Nota: Profármacos ordem invertida

Projeto Europeu de PGx – UPGx

U-PGx | Ubiquitous Pharmacogenomics

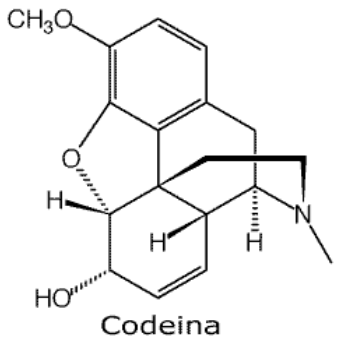
European Pharmacogenomics Implementation Project

Funded by the

European Union's Horizon 2020
research and innovation programme

https://www.youtube.com/watch?v=X2KK_FfsrS4&feature=youtu.be

CODEÍNA e CYP2D6



Codeina

Motherisk Update
Current Practice • Pratique courante

Safety of codeine during breastfeeding

Fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine

Parvaz Madadi Gideon Koren, MD, FRCPC James Cairns, MD David Chitayat, MD Andrea Gaedigk, PHD
J. Steven Leeder, PHARMD, PHD Ronni Teitelbaum, MSC Tatyana Karaskov, MD Katarina Aleksa, PHD

ABSTRACT

QUESTION Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers?

ANSWER When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, newborns might be exposed to toxic levels of morphine when breastfeeding. Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.

Curr Opin Anaesthesiol. 2017 Jun;30(3):349-356. doi: 10.1097/ACO.0000000000000455.

Codeine and opioid metabolism: implications and alternatives for pediatric pain management.

Chidambaran V[1], Sadhasivam S, Mahmoud M.

Author information

1 Department of Anesthesiology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio, USA.

Abstract

PURPOSE OF REVIEW: Use of perioperative opioids for surgical pain management of children presents clinical challenges because of concerns of serious adverse effects including life-threatening respiratory depression. This is especially true for children with history of obstructive sleep apnea. This review will explore current knowledge of clinically relevant factors and genetic polymorphisms that affect opioid metabolism and postoperative outcomes in children.

RECENT FINDINGS: Within the past several years, an increasing number of case reports have illustrated clinically important respiratory depression, anoxic brain injuries and even death among children receiving appropriate weight-based dosages of codeine and other opioids for analgesia at home setting particularly following tonsillectomy. Several national and international organizations have issued advisories on use of codeine in pediatrics, based on cytochrome P450 family 2 subfamily D type 6 (CYP2D6) pharmacogenetics. We have discussed the pros and cons of alternatives to codeine for pain management.

SUMMARY: Although routine preoperative genotyping to identify children at risk and personalized opioid use for pediatric perioperative pain management is still a distant reality, current known implications of CYP2D6 pharmacogenetics on codeine use shows that pharmacogenetics has the potential to guide anesthesia providers on perioperative opioid selection and dosing to maximize efficacy and safety.

Published in final edited form as:
Methods Mol Biol. 2013 ; 1015: 311–320. doi:10.1007/978-1-62703-435-7_20.

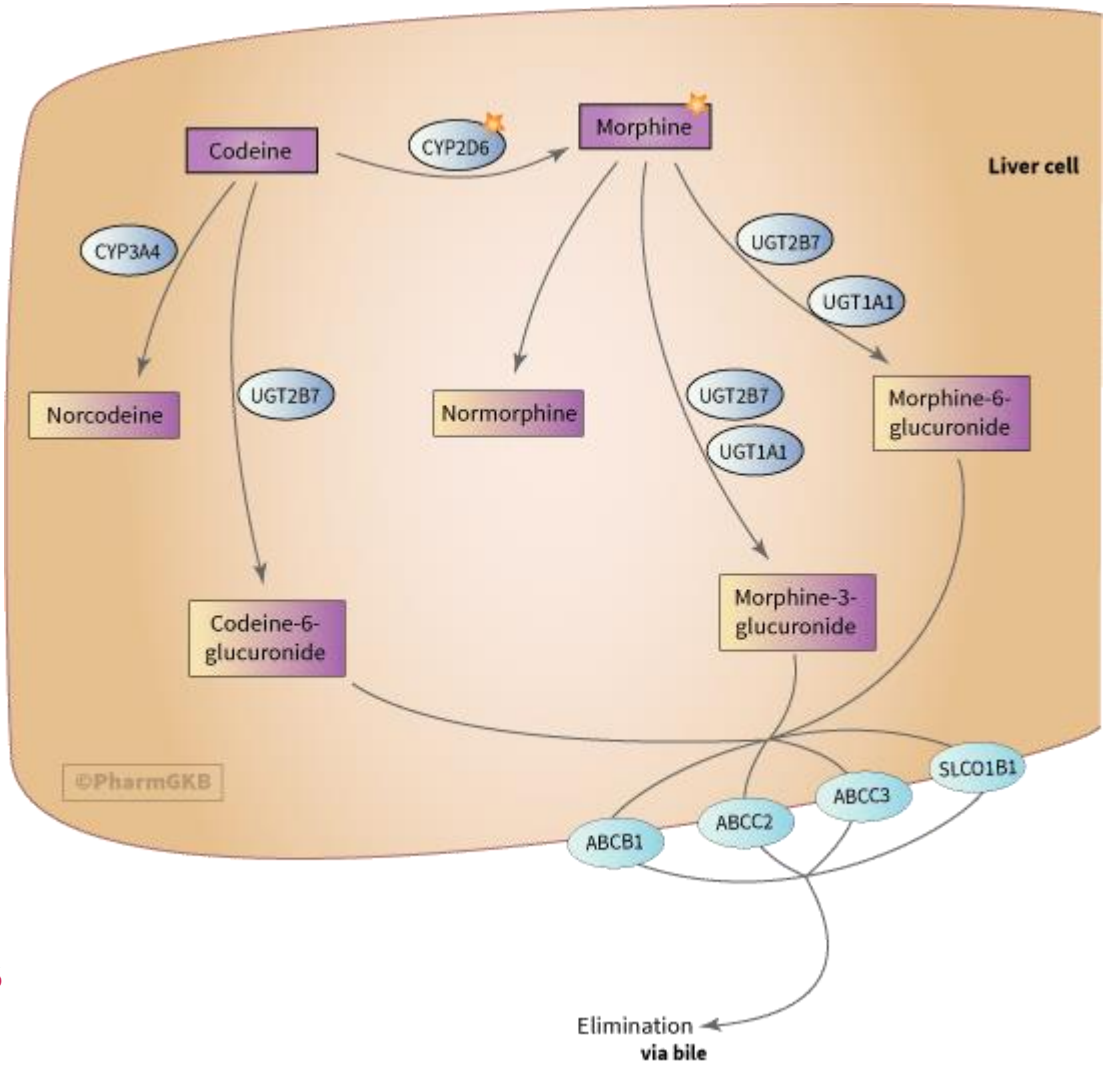
PharmGKB: The Pharmacogenomics Knowledge Base

Caroline F. Thorn, **Teri E. Klein**, and **Russ B. Altman**

Abstract

The Pharmacogenomics Knowledge Base, PharmGKB, is an interactive tool for researchers investigating how genetic variation affects drug response. The PharmGKB Web site, http://www.pharmgkb.org, displays genotype, molecular, and clinical knowledge integrated into pathway representations and Very Important Pharmacogene (VIP) summaries with links to additional external resources. Users can search and browse the knowledgebase by genes, variants, drugs, diseases, and pathways. Registration is free to the entire research community, but subject to agreement to use for research purposes only and not to redistribute. Registered users can access and download data to aid in the design of future pharmacogenetics and pharmacogenomics studies.

Genes candidatos para o metabolism da codeína



PHARMGKB

The **C**linical **P**harmacogenetics **I**mplementation **C**onsortium (CPIC) foi criado em 2009 como um projeto conjunto da PharmGKB and the Pharmacogenomics Research Network (PGRN).

A função deste consórcio internacional é estabelecer guidelines clínicas que permitam a translação dos resultados dos testes laboratoriais de farmacogenética em decisões de prescrição clínica para fármacos específico em consonância com o estado atual do conhecimento .

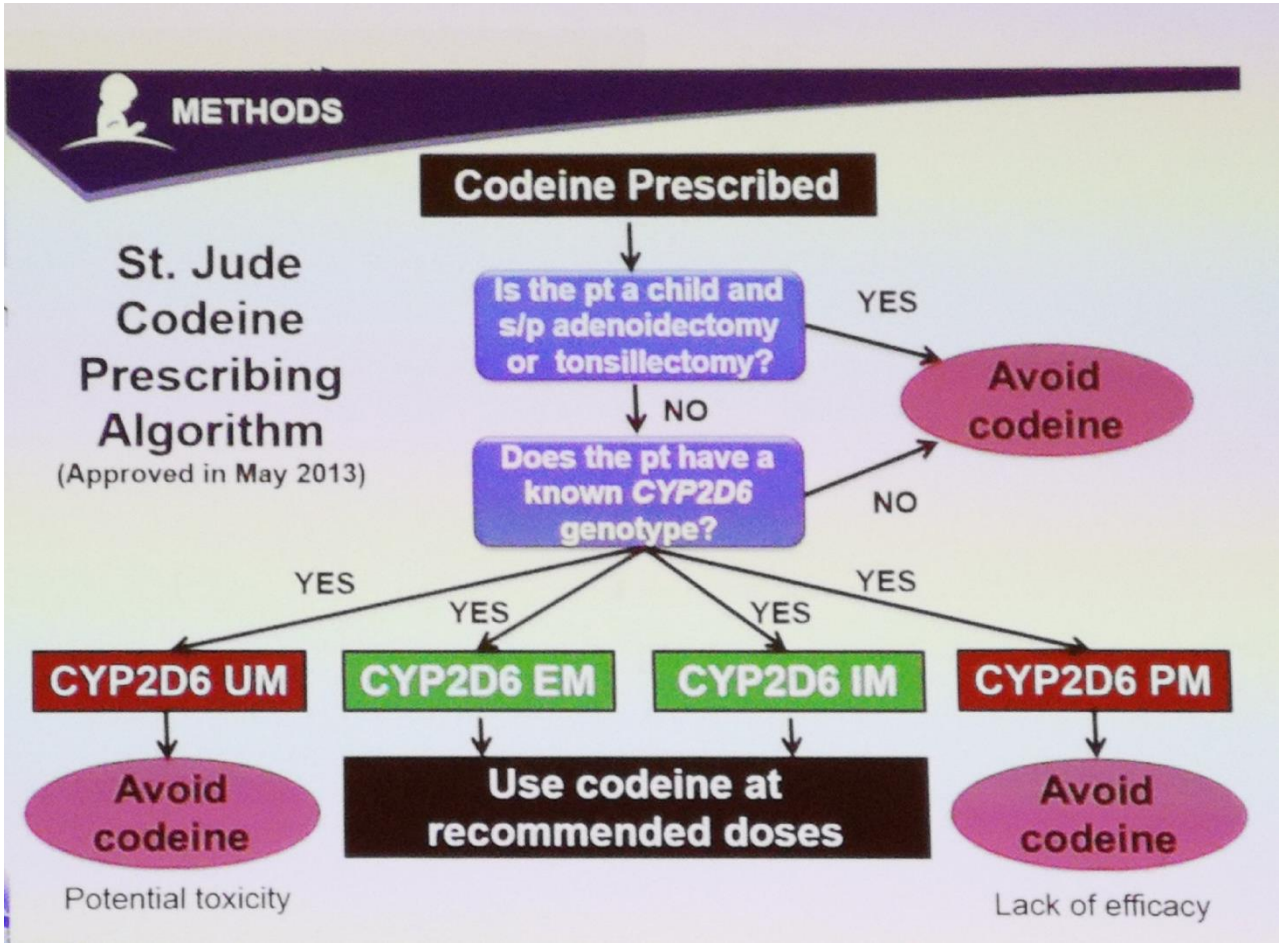
Table 1. Medication and gene combinations for which the Clinical Pharmacogenomic Implementation Consortium has assigned the highest level of evidence for clinical benefits.*

Medication	Estimated prevalence of pharmacogenomic susceptibility	Genes involved in medication exposure
Abacavir	7%	*HLA-B*5701*
Allopurinol	8%	*HLA-B*5801*
Amitriptyline	74%	*CYP2C19, CYP2D6*
Atazanavir	31%	*UGT1A1*
Azathioprine	4%	*TPMT*
Capecitabine	2%	*DPYD*
Carbamazepine	10%	*HLA-A3101, HLA-B1502*
Citalopram	31%	*CYP2C19*
Clopidogrel	31%	*CYP2C19*
Codeine	63%	*CYP2D6*
Doxepin	74%	*CYP2C19, CYP2D6*
Escitalopram	31%	*CYP2C19*
Fluorouracil	2%	*DPYD*
Fluvoxamine	63%	*CYP2D6*
Irinotecan	31%	*UGT1A1*
Mercaptopurine	4%	*TPMT*
Ondansetron	63%	*CYP2D6*
Oxycodone	63%	*CYP2D6*
Paroxetine	63%	*CYP2D6*
Peginterferon	40%	*IFNL3*
Phenytoin	26%	*CYP2C9, HLA-B1502*
Ribavirin	40%	*IFNL3*
Simvastatin	20%	*SLCO1B1*
Tacrolimus	92%	*CYP3A5*
Tamoxifen	63%	*CYP2D6*
Thioguanine	4%	*TPMT*
Tramadol	63%	*CYP2D6*
Tropisetron	63%	*CYP2D6*
Voriconazole	31%	*CYP2C19*
Warfarin	66%	*CYP2C9, CYP4F2, VKORC1*

*Medications not listed on the Pharmaceutical Benefits Scheme in 2017 are excluded.

CPIC®
Clinical Pharmacogenetics Implementation Consortium

Implementation of PGx testing

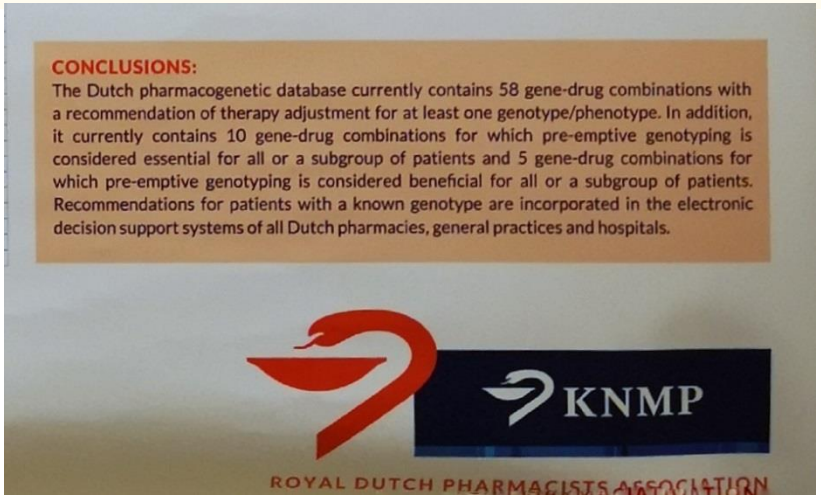


Comparação entre o CPIC e o DPWG

	CPIC	DPWG
Founded	2009	2005
Type of membership	Open for application of new members with a clinical interest in pharmacogenetics, N=206 as of March 2017	By invitation, N=14
Composition	Multidisciplinary	Multidisciplinary
Objectives	1) To address the barriers to implementation of pharmacogenetic tests into clinical practice 2) To provide guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs	1) To develop pharmacogenetics-based therapeutic (dose) recommendations 2) To assist drug prescribers and pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance
Number of gene-drug pairs covered	40	86
Number of gene-drug pairs with therapeutic recommendation	40	47
Frequency of scheduled updates	As needed, reviewed at least every 2 years	If needed, max 4 years
Funding	National Institutes of Health	Royal Dutch Pharmacist's Association and H2020 contract number 668353-I

Clin Pharmacol Ther. 2018 Apr; 103(4): 599–618

DPWG = KNMP



Oct - 2019

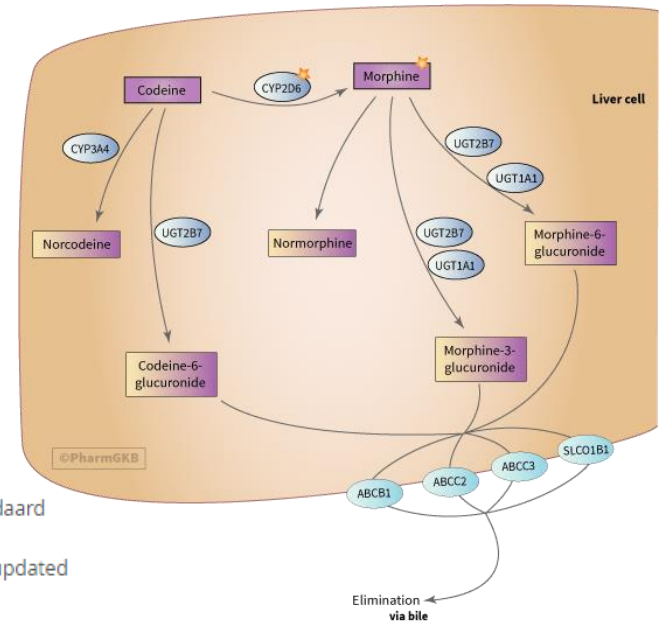
Date 20-11-2017

CYP2D6 UM: codeine 1585

The genetic variation increases the conversion of codeine to morphine. This can result in an increase in side effects. Death has occurred in children who received analgesic doses. One adult with reduced kidney function and co-medication with two CYP3A4 inhibitors became comatose after use of codeine for a cough.

Recommendation:

- DOSES HIGHER THAN 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND/OR ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  Codeine is contra-indicated
  - if possible, select an alternative
    - For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.
      Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.
    - For COUGH: noscapine is not metabolised by CYP2D6.
- DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:
  - no action required



KNMP

Recommendations

In the Netherlands the pharmacogenetic recommendation text is incorporated in the G-Standaard and can be used during prescribing and dispensing. For healthcare professionals outside the Netherlands, we provide the short recommendation text and literature list below. This file is updated after every meeting of the Dutch Pharmacogenetic Working Group of the KNMP.

Pharmacogenomics: the future is now

- Implementação da Metodologia Laboratorial - genes com guideline do CPIC e do DPWG – em curso
- Participação no programa de controlo de qualidade externo estudo piloto ENMQ 2019 - OK
- Primeira sessão de divulgação externa da Farmacogenómica " As potencialidades da Farmacogeómica aplicada à pediatria" – Centro Materno infantil - Porto - Outubro 2019 - OK
- Acordo com a OF para divulgação do inquérito sobre farmacogenómica conseguido ontem.
- 1º Teste de Farmacogenética para Tamoxifeno DPS


Pharmacogenomics:
the future
is now
isn´t it ?