Genetics for Precision Drug Development

DCR-CTU Lecture Series
October 25th, 2023 - Zoom

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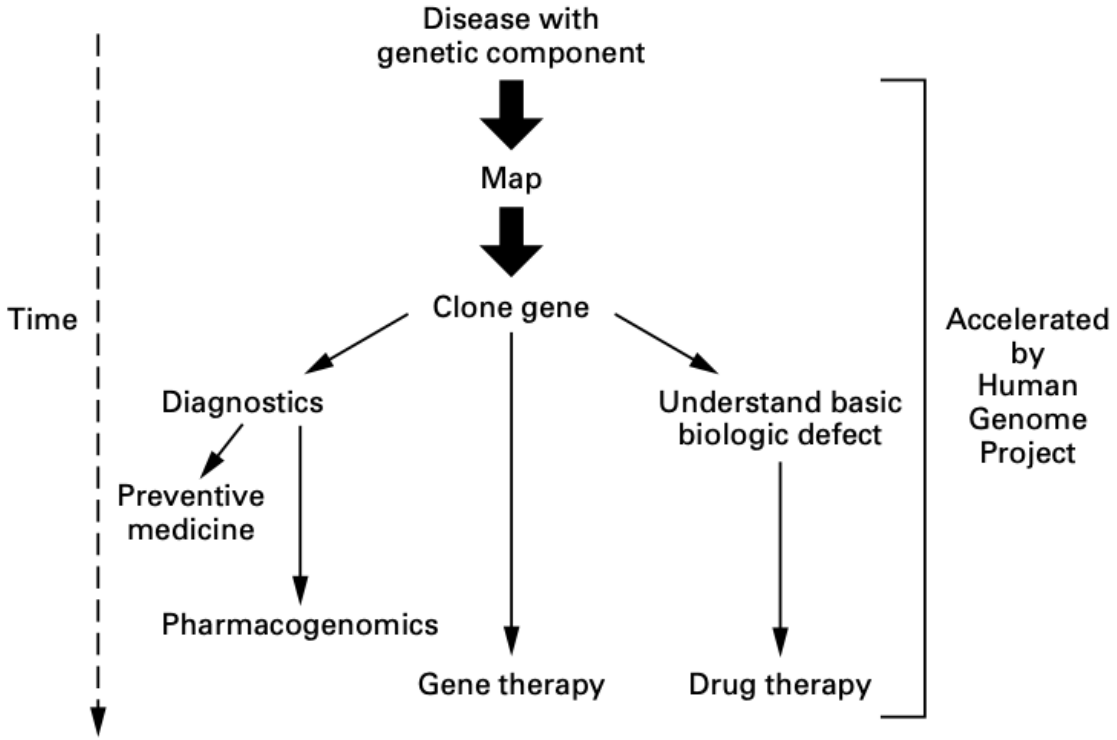
Expectations from the Human Genome Project

SHATTUCK LECTURE — MEDICAL AND SOCIETAL CONSEQUENCES OF THE HUMAN GENOME PROJECT

FRANCIS S. COLLINS, M.D., PH.D.



The New England Journal of Medicine July 1, 1999

Part 1 : Pharmacogenetics (PGx)

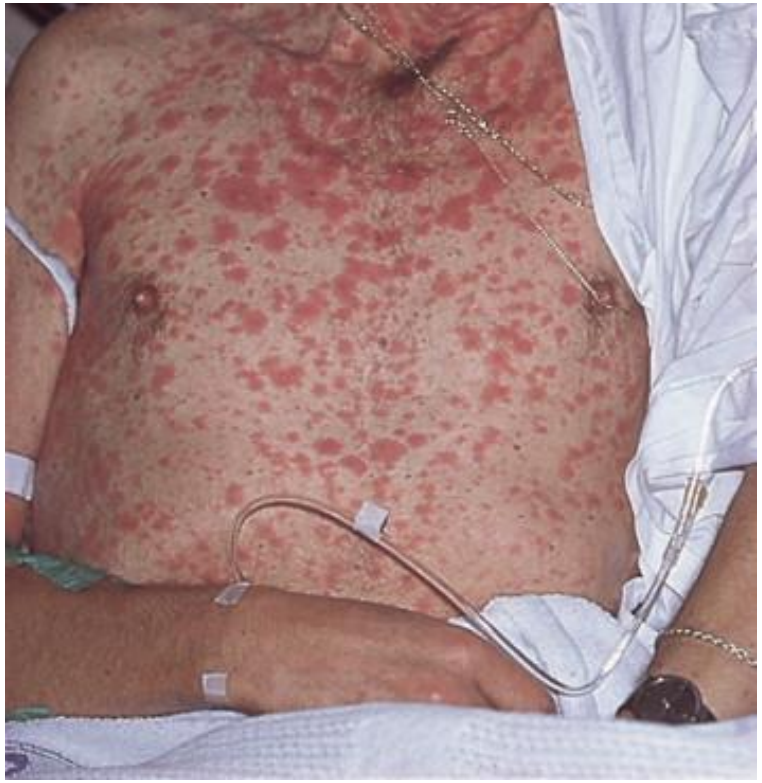
An Emblematic Success Story in PGx

Approved by FDA in 1998

Abacavir Adverse Drug Reaction

3-5 %

Hypersensitivity reaction

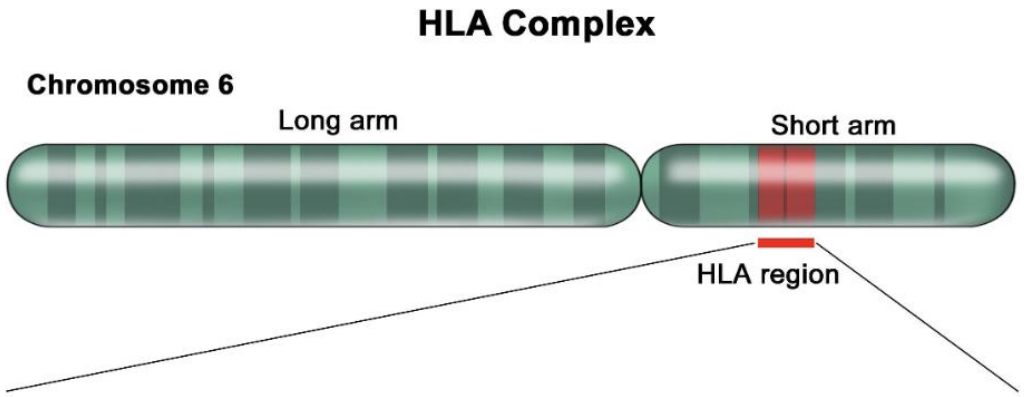


WARNING: HYPERSENSITIVITY REACTIONS/LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

Hetherington *et al.*, 2001, *Clin Ther*

Abacavir – Discovery of Genetic Association



*HLA-B*5701*

Mallal *et al*. 2002. *The Lancet* 359 (9308): 727–32.

Hetherington *et al*. 2002. *The Lancet* 359 (9312): 1121–22.

Abacavir – Prospective Validation

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

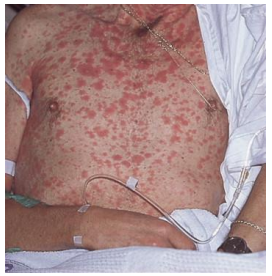
Negative Predictive Value **100%**

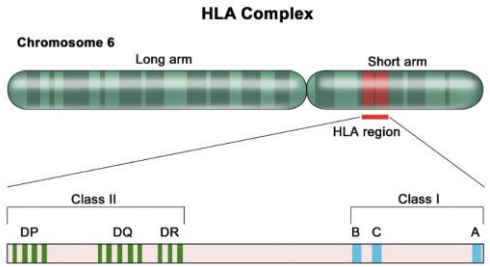
Number Needed to Genotype **25**

Mallal *et al.* 2008. *The New England Journal of Medicine.*

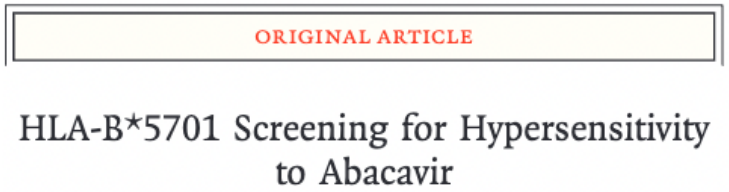
Discovery and Development of PGx Marker

Drug serious adverse event or efficacy → Assay development → Biomarker discovery → Retrospective validation → Prospective validation → Marketed PGx test





*HLA-B*5701*


ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

FDA

1996 -1998 → 2008

Top 10 Prescribed Drugs in the USA

Rank	Drug Name	Total Patients (2020)
1	Atorvastatin	26,640,141
2	Levothyroxine	20,225,373
3	Metformin	20,122,987
4	Lisinopril	19,816,361
5	Amlodipine	16,799,810
6	Metoprolol	15,007,908
7	Albuterol	17,902,020
8	Omeprazole	13,879,629
9	Losartan	12,690,563
10	Gabapentin	10,571,700

https://clincalc.com/DrugStats/Top200Drugs.aspx

PGx Databases

PharmGKB

https://www.pharmgkb.org/

Drug label annotation

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada Santé Canada

swissmedic

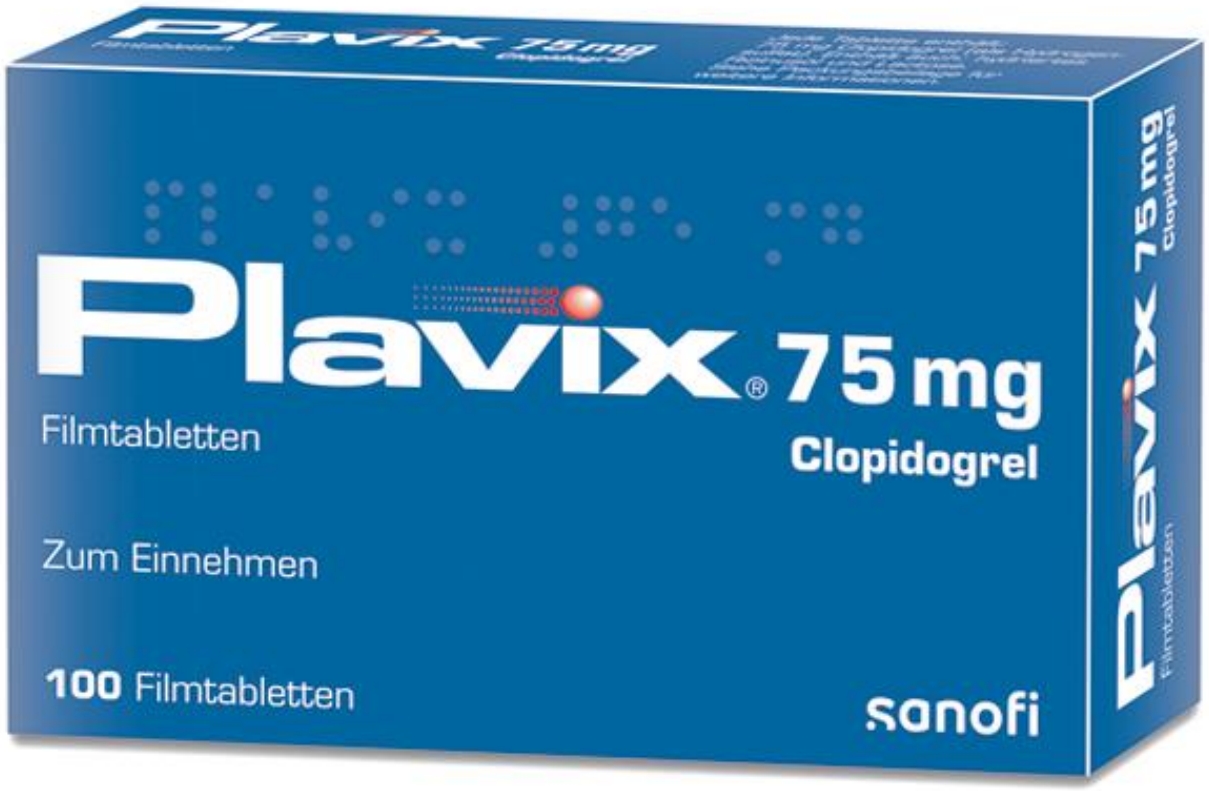
Pmda

Prescribing information

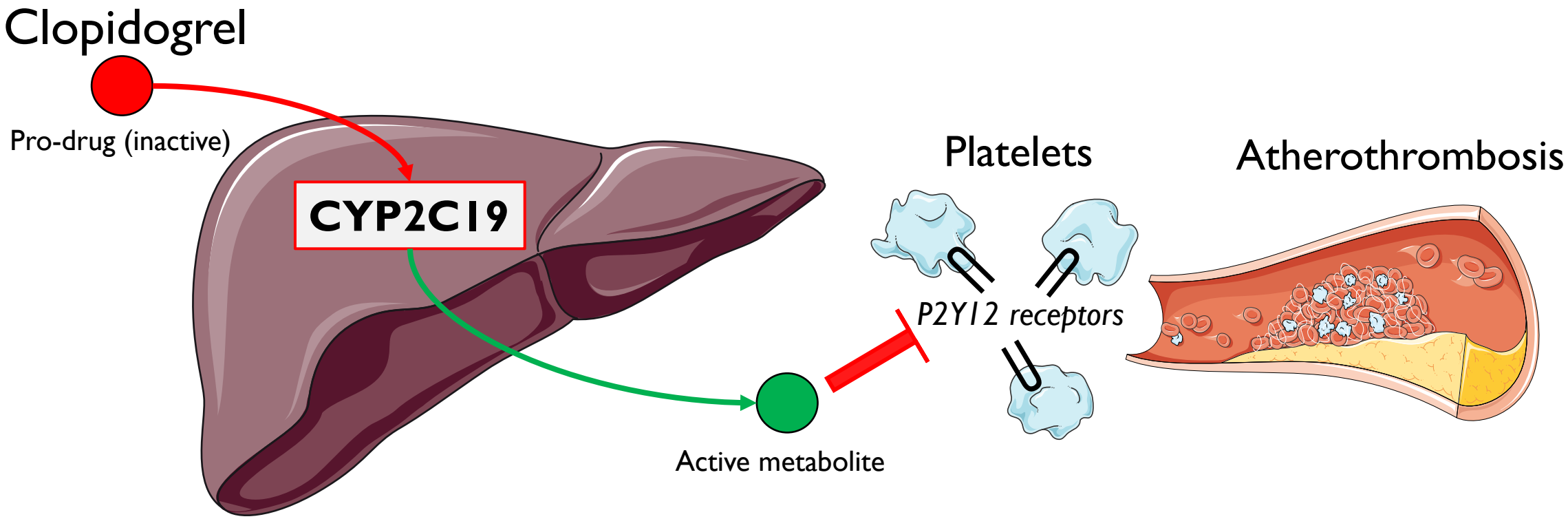
CPIC®
Clinical Pharmacogenetics Implementation Consortium

KNMP
Dutch Pharmacogenetics Working Group (DPWG)

Clopidogrel



Clopidogrel : A Pro-Drug Activated by CYP2C19



GWAS Studies on Response to CV Drugs

32% of the 221 marketed CV drugs were studied

<50% of GWAS reported significant associations

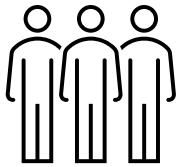
8% of mapped genes have a corresponding drug-gene PGx recommendation

Delabays et al. under revision

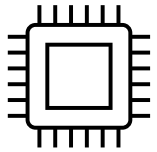
Challenges in Implementing PGx in the Clinic

- Demonstration of clinical validity and clinical utility
- Reimbursement
- Complexity in the interpretation of PGx results
- ELSI of PGx
- Turnaround time and return of PGx results

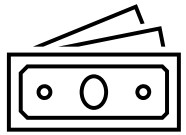
Opportunities for Implementing PGx in the Clinic



- ≥ 95% of us carry actionable PGx variants

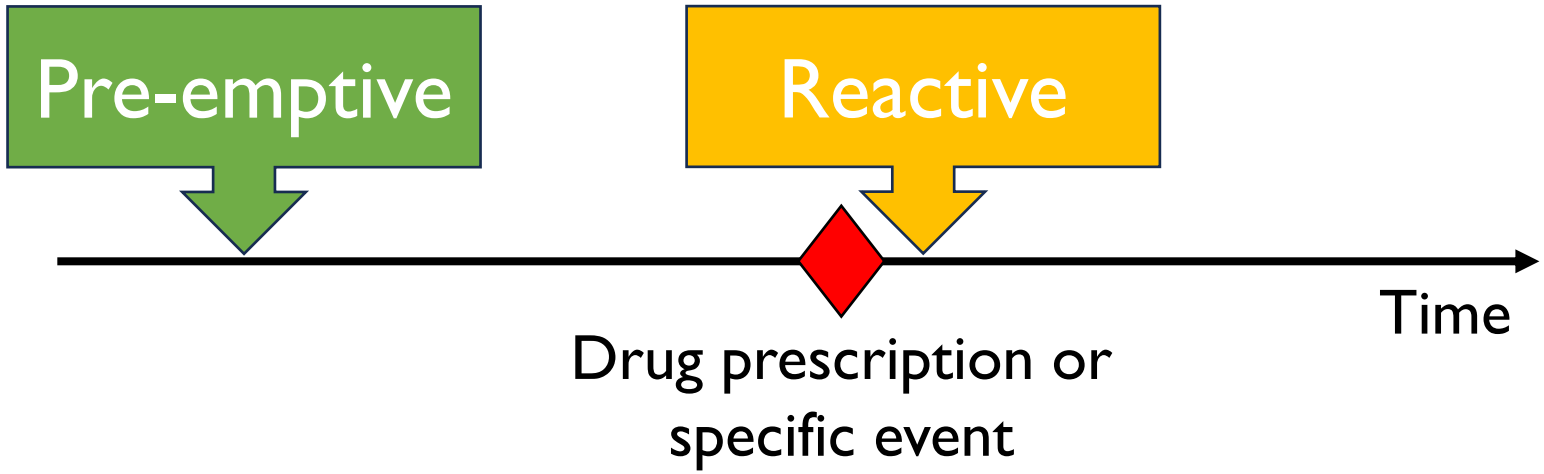


- IT breakthroughs

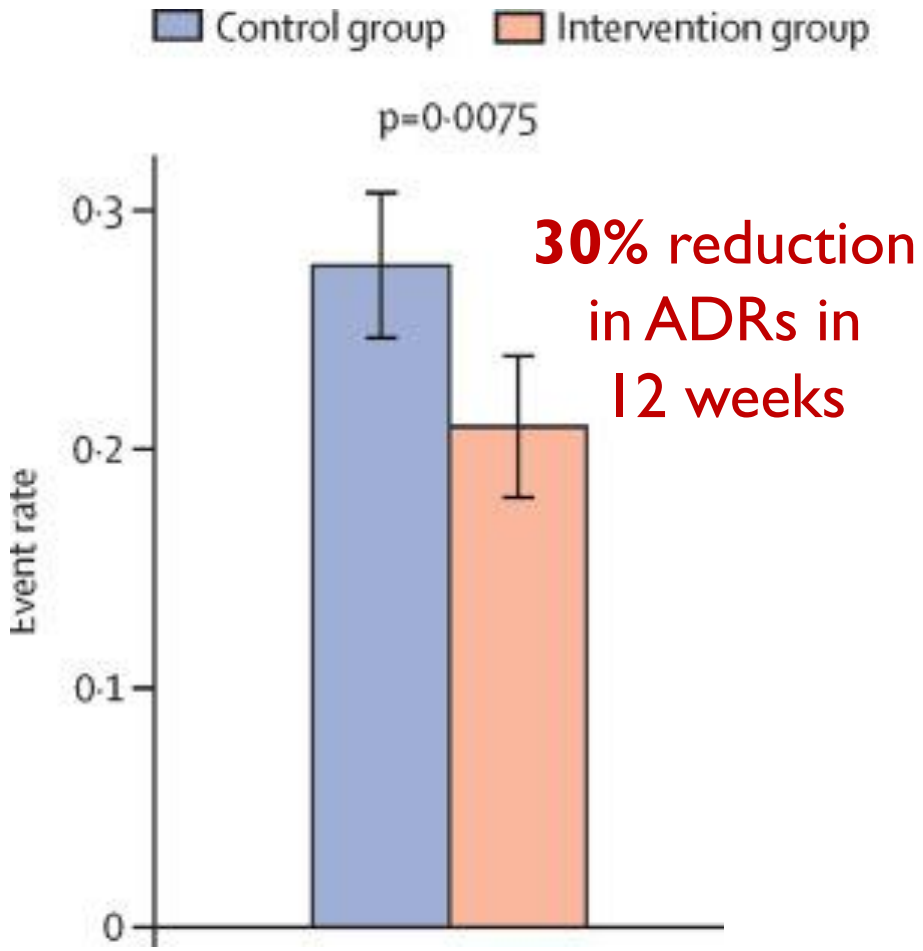


- Decreasing costs of sequencing

Pre-Emptive vs Reactive PGx



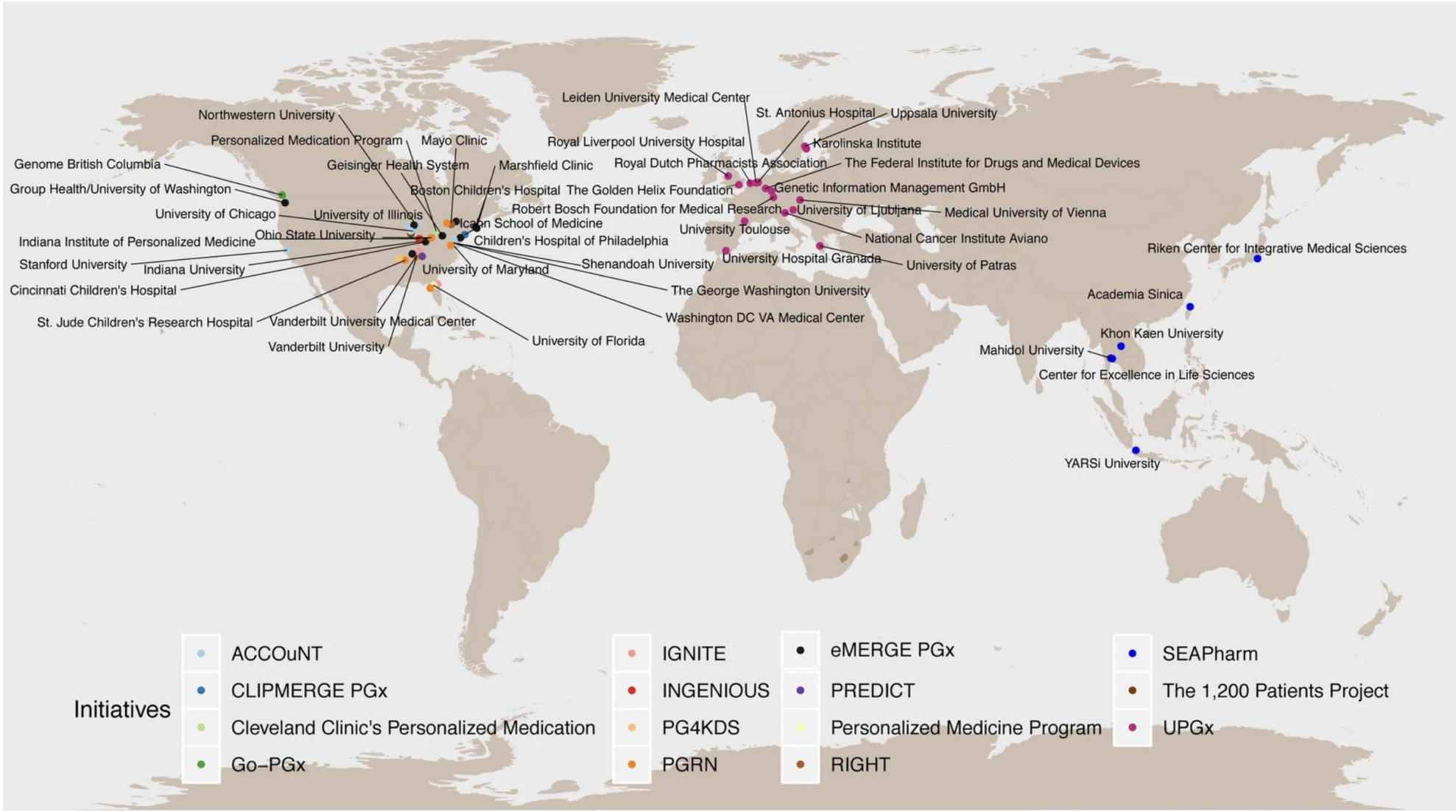
Pre-Emptive PGx Reduces Adverse Drug Reactions



30% reduction in ADRs in 12 weeks

Swen *et al.*, 2023, *Lancet*

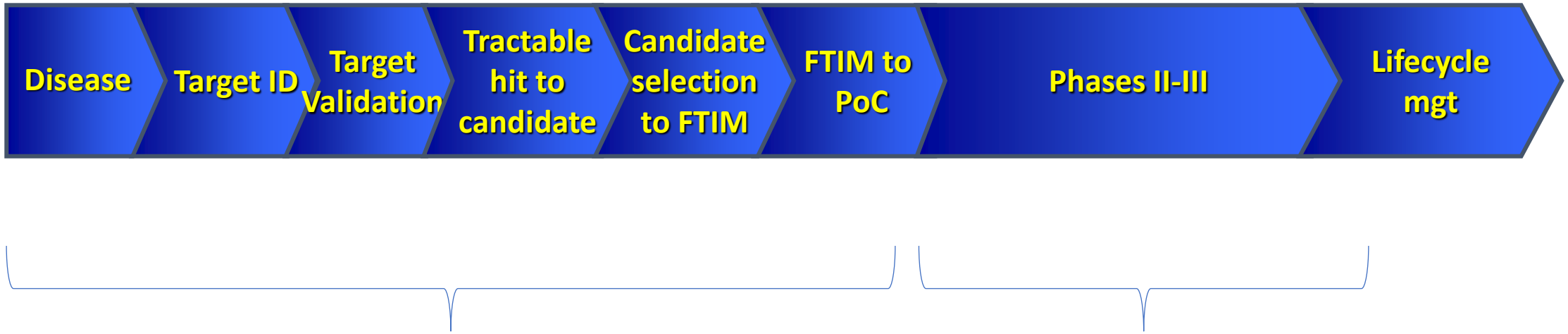
Pre-Emptive PGx Initiatives



Krebs *et al.*, 2019, *Hum Genomics*

Part 2 : New Therapeutics

DDD : A Series of Well-Defined Steps



PCSK9 : An Emblematic Example

"The *PCSK9* story is a terrific example of an up-and-coming pattern of translational research."

Single-minded: Helen Hobbs and Jonathan Cohen's approach to heart-disease genetics yielded a target for drugs that could compete with statins.

PCSK9 : An Amazing Success Story

2003 2006 2015 2022

PCSK9 : An Amazing Success Story

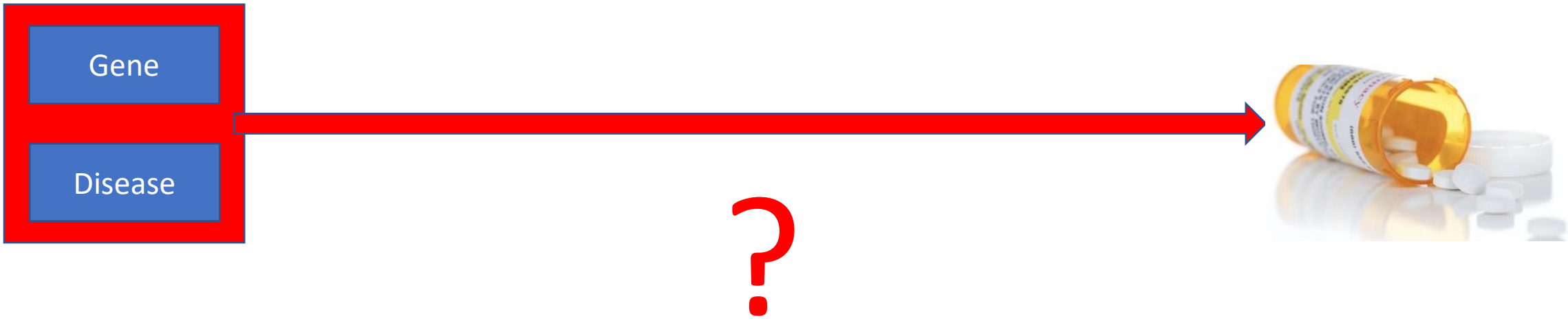
More CRISPR In Human Subjects

12 JUL. 2022 • BY DEREK LOWE • 3 MIN READ • COMMENTS

Science

If you follow the progress of gene editing therapies in human disease, today is an interesting day. Verve Therapeutics has started a trial using CRISPR base editing technology to modify the PCSK9 gene in people with a disease called heterozygous familial hypercholesterolemia (HeFH).

Genetically-Driven Drugs



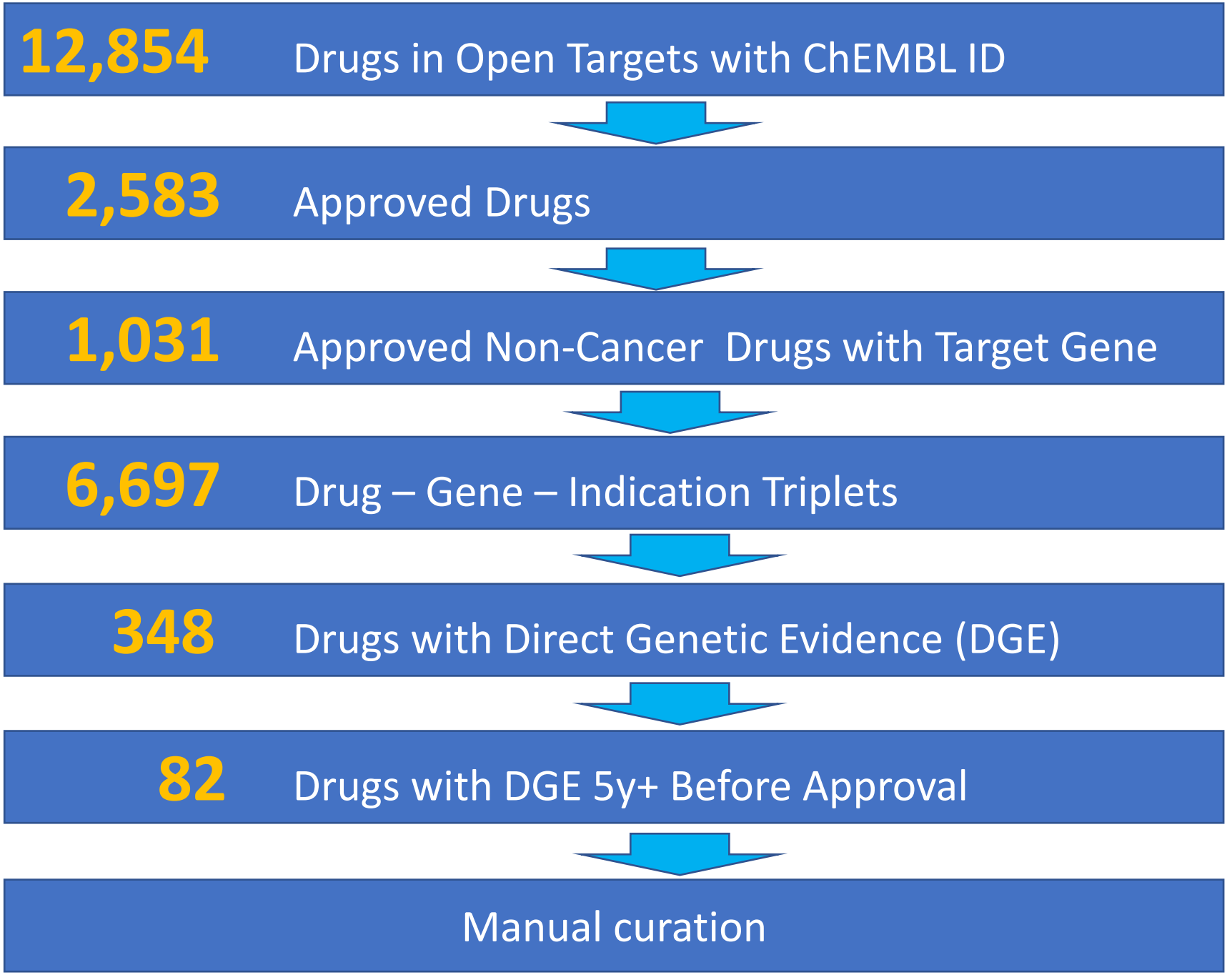
Review

From target discovery to clinical drug development with human genetics

Katerina Trajanoska[1], Claude Bhérer[1], Daniel Taliun[1], Sirui Zhou[1], J. Brent Richards[2,3] & Vincent Mooser[1]✉

Nature | Vol 620 | 24 August 2023

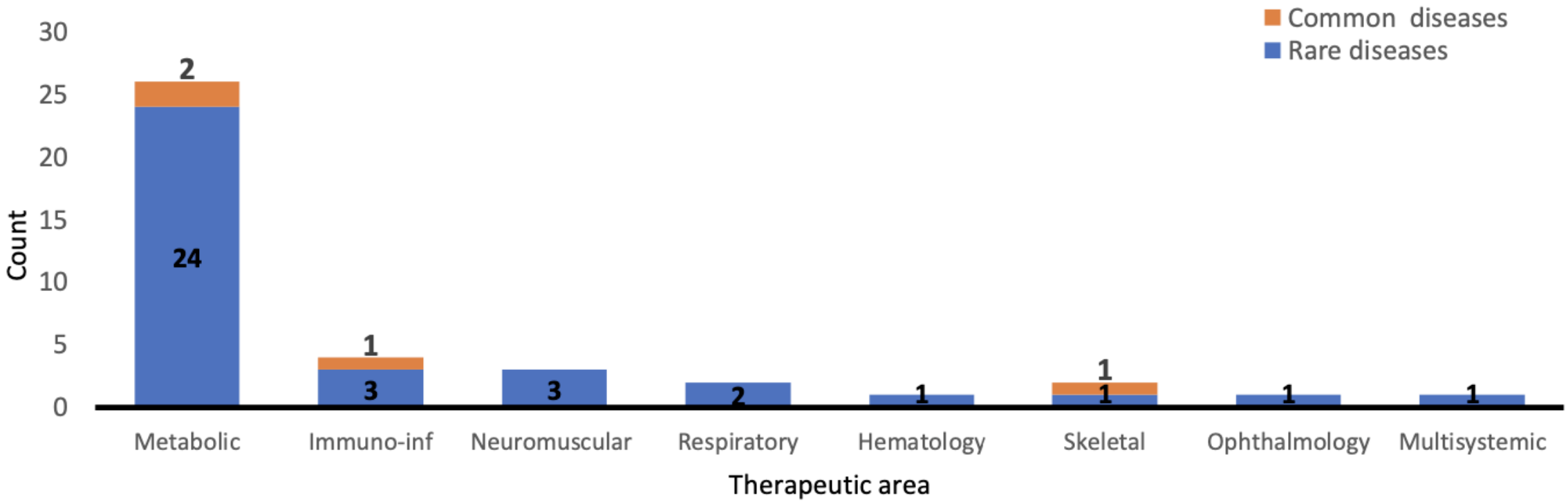
Methods


12,854
Drugs in Open Targets with ChEMBL ID
2,583
Approved Drugs
1,031
Approved Non-Cancer Drugs with Target Gene
6,697
Drug – Gene – Indication Triplets
348
Drugs with Direct Genetic Evidence (DGE)
82
Drugs with DGE 5y+ Before Approval
Manual curation

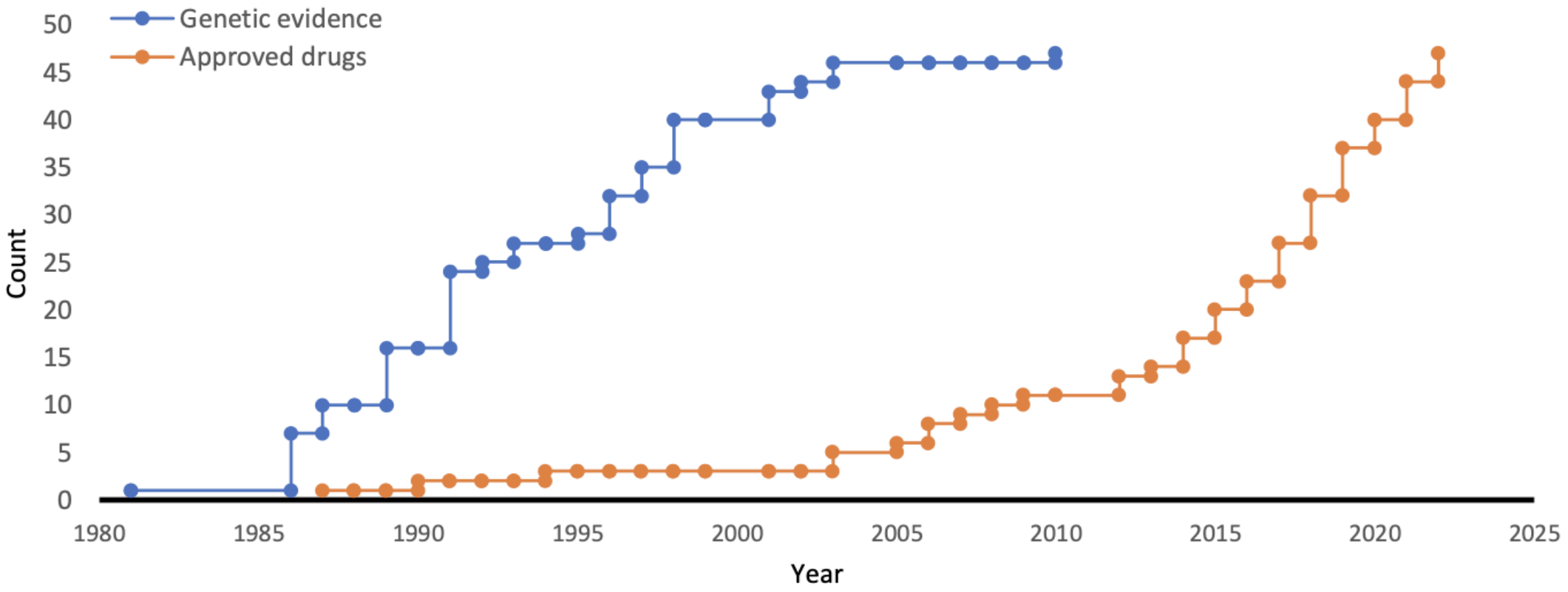
Genetically-Driven Approved Non-Cancer Drugs

60 Drugs / 40 Targets

Distribution of Genetically-Driven Drugs by Therapy Area and Prevalence of Disease Indication



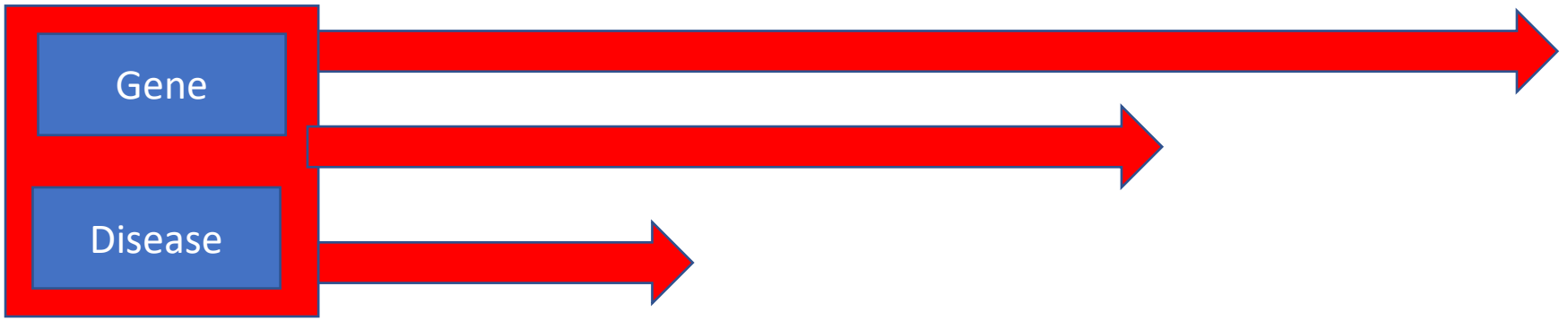
Median 25-Years Separate Target Discovery from Regulatory Approval of Derived Drug



A Word of Wisdom

MS Brown, JL Goldstein, J Clin Invest 1997

Coming up on the Horizon



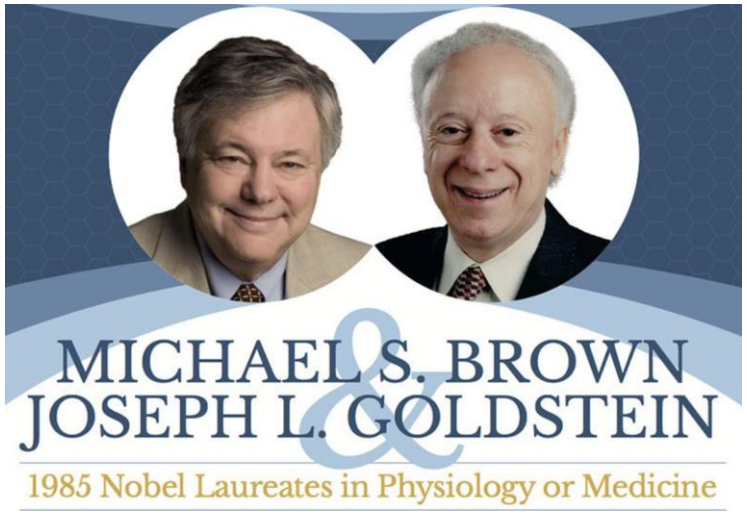
Many genetically well-validated new targets

The Need to Invigorate Drug Development to :

-Prioritize the portfolio
- Accelerate time to approval
- Improve early attrition
- Reduce trial size and costs

→ “Precision Clinical Development"

Genetically Enriched Proof-of-Concept Study



EFFECTS OF AN INHIBITOR OF 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE ON SERUM LIPOPROTEINS AND UBIQUINONE-10 LEVELS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

HIROSHI MABUCHI, M.D., TOSHIHIRO HABA, M.D., RYZO TATAMI, M.D., SUSUMU MIYAMOTO, M.D., YASUYUKI SAKAI, M.D., TAKANOBU WAKASUGI, M.D., AKIRA WATANABE, M.D., JUNJI KOIZUMI, M.D., AND RYOYU TAKEDA, M.D.

Abstract We studied the effects of ML-236B, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, on serum levels of lipoproteins and ubiquinone-10 in seven heterozygous patients with familial hypercholesterolemia. ML-236B terol, and LDL triglyceride decreased significantly ($P<0.01$, $P<0.02$, $P<0.001$, and $P<0.001$, respectively). However, there were no significant changes in very-low-density-lipoprotein (VLDL) cholesterol and triglyceride or high-density-lipoprotein (HDL) choles-

First Description of *PNPLA3*
Am J Hum Gen - Oct 2008

REPORT

Population-Based Genome-wide Association Studies Reveal Six Loci Influencing Plasma Levels of Liver Enzymes

Xin Yuan,[1] Dawn Waterworth,[1] John R.B. Perry,[3] Noha Lim,[1] Kijoung Song,[1] John C. Chambers,[4] Weihua Zhang,[4] Peter Vollenweider,[5] Heide Stirnadel,[2] Toby Johnson,[6,7,8] Sven Bergmann,[6,8] Noam D. Beckmann,[6] Yun Li,[12] Luigi Ferrucci,[9] David Melzer,[3] Dena Hernandez,[10] Andrew Singleton,[10] James Scott,[11] Paul Elliott,[4] Gerard Waeber,[5] Lon Cardon,[1] Timothy M. Frayling,[3] Jaspal S. Kooner,[11] and Vincent Mooser[1,*]

Plasma liver-enzyme tests are widely used in the clinic for the diagnosis of liver diseases and for monitoring the response to drug treatment. There is considerable evidence that human genetic variation influences plasma levels of liver enzymes. However, such genetic variation has not been systematically assessed. In the present study, we performed a genome-wide association study of plasma liver-enzyme levels in three populations (total n = 7715) with replication in three additional cohorts (total n = 4704). We identified two loci influencing plasma levels of alanine-aminotransferase (ALT) (*CPN1-ERLIN1-CHUK* on chromosome 10 and *PNPLA3-SAMM50* on chromosome 22), one locus influencing gamma-glutamyl transferase (GGT) levels (*HNF1A* on chromosome 12), and three loci for alkaline phosphatase (ALP) levels (*ALPL* on chromosome 1, *GPLD1* on chromosome 6, and *JMJD1C-REEP3* on chromosome 10). In addition, we

Precision Drug Development in Action: PoC for PNPLA3 Inhibitors on I14M Carriers

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results > Study Record Detail

Save this study

A Single-Ascending and Repeated Dose Study of LY3849891 in Participants With Nonalcoholic Fatty Liver Disease

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	176 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Basic Science
Official Title:	A Single-Ascending and Repeated Subcutaneous Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3849891 in Participants With Nonalcoholic Fatty Liver Disease Who Have the PNPLA3 I148M Genotype
Actual Study Start Date :	June 8, 2022
Estimated Primary Completion Date :	November 5, 2024
Estimated Study Completion Date :	November 5, 2024

Requirements for Precision Drug Development

→LARGE, DIVERSE, DISEASE-based cohorts

→Patients deeply phenotyped and properly consented for genomic analyses and recall-by-genotype studies

→Interoperable for (international) collaborations

→Ethically and socially responsible

Paving the Way to Precision Drug Development

Established in 1871
Swiss Medical Weekly
Formerly: Schweizerische Medizinische Wochenschrift
The European Journal of Medical Sciences

Review article: Current opinion | Published 4 December 2014, doi:10.4414/smw.2014.14033
Cite this as: Swiss Med Wkly. 2014;144:w14033

The Lausanne Institutional Biobank: A new resource to catalyse research in personalised medicine and pharmaceutical sciences

Vincent Mooser[a], *Christine Currat*[b]

Paving the Way to Precision Drug Development

Original article | Published 20 October 2017 | doi:10.4414/smw.2017.14528
Cite this as: Swiss Med Wkly. 2017;147:w14528

High participation rate among 25 721 patients with broad age range in a hospital-based research project involving whole-genome sequencing – the Lausanne Institutional Biobank

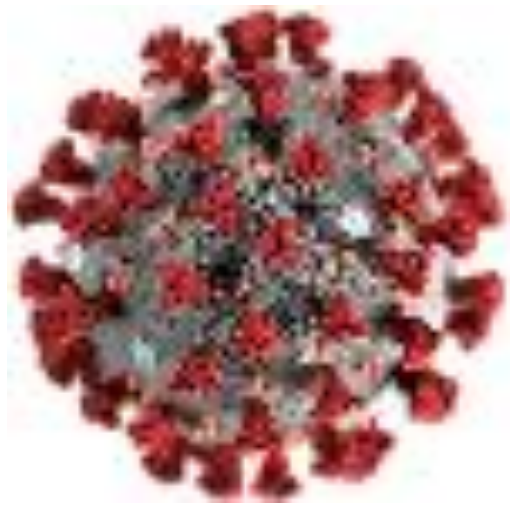
Bochud Murielle[a], Currat Christine[b], Chapatte Laurence[b], Roth Cindy[c], Mooser Vincent[cd]

[a] Institute for Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland
[b] Swiss Biobanking Platform, Lausanne, Switzerland
[c] Valuation of Clinical Data and Biological Samples Unit, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Switzerland
[d] Service of Clinical Chemistry, Centre Hospitalier Universitaire Vaudois, Lausanne Switzerland

From CHUV to McGill – August 2019

Canada Excellence Research Chairs

Chaires d'excellence en recherche du Canada



BIOBANQUE QUÉBÉCOISE DE LA COVID-19

Mars 2020

- **19 mars 2020 :** Mandat du FRQ et de Génome Québec
- **21 mars 2020 :** Mise en place de la Task Force (Comité directeur)
- **31 mars 2020 :** Approbation par le Comité d'éthique du CHUM

Avril 2020

- **1er avril 2020 :** Recrutement du 1er patient

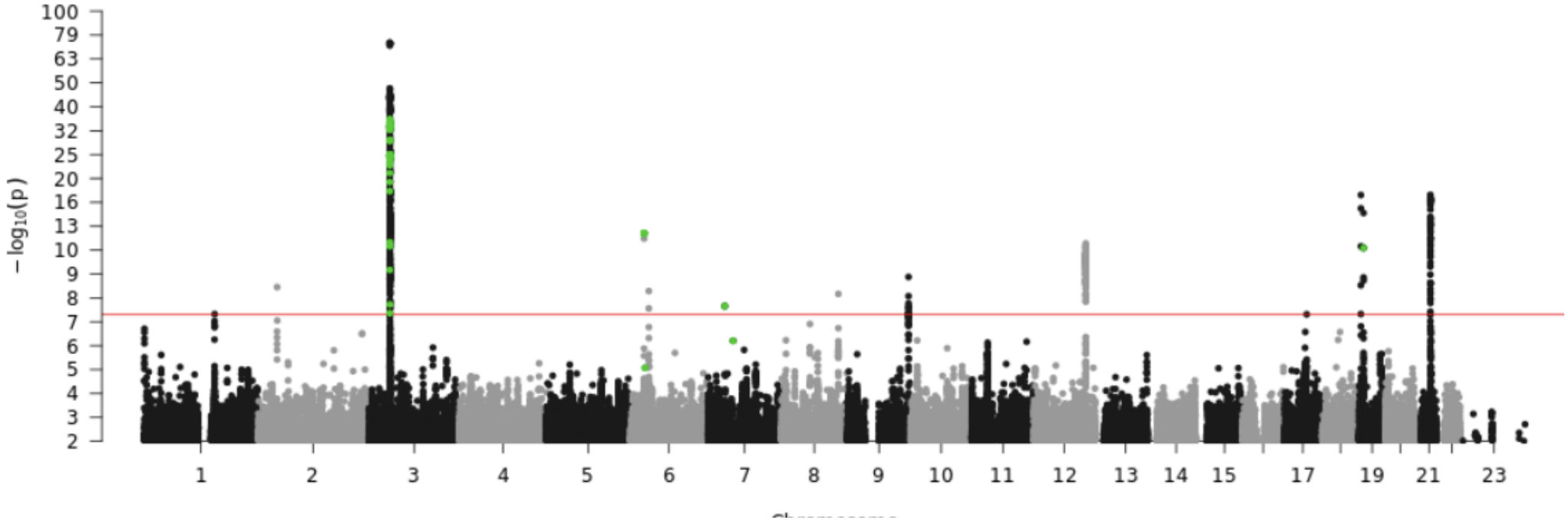
Juin 2020

- **6 juin 2020 :** Recrutement du 1000ème patient
- **10 juin 2020 :** Contrat avec l'Agence de Santé Publique du Canada
- **15 juin 2020 :** Approbation des analyses de base par le Comité de Gouvernance

Juillet 2020

- **17 juillet 2020 :** Libération des premières données

GWAS – COVID-19 Host Genome Initiative



nature

https://doi.org/10.1038/s41586-021-03767-x

Accelerated Article Preview

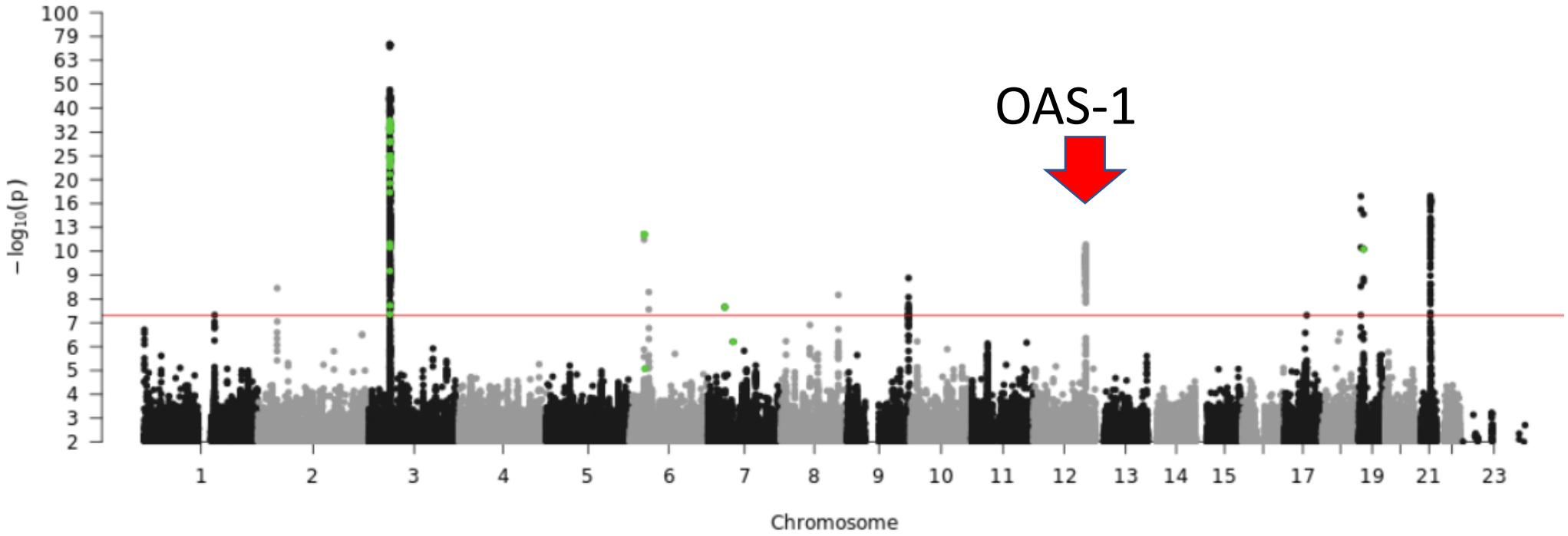
Mapping the human genetic architecture of COVID-19

Received: 2 March 2021

Accepted: 23 June 2021

COVID-19 Host Genetics Initiative

GWAS – COVID-19 Host Genome Initiative



nature

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Mapping the human genetic architecture of COVID-19

Received: 2 March 2021

Accepted: 23 June 2021

COVID-19 Host Genetics Initiative

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-021-01281-1

Check for updates

A Neanderthal OAS1 isoform protects individuals of European ancestry against COVID-19 susceptibility and severity

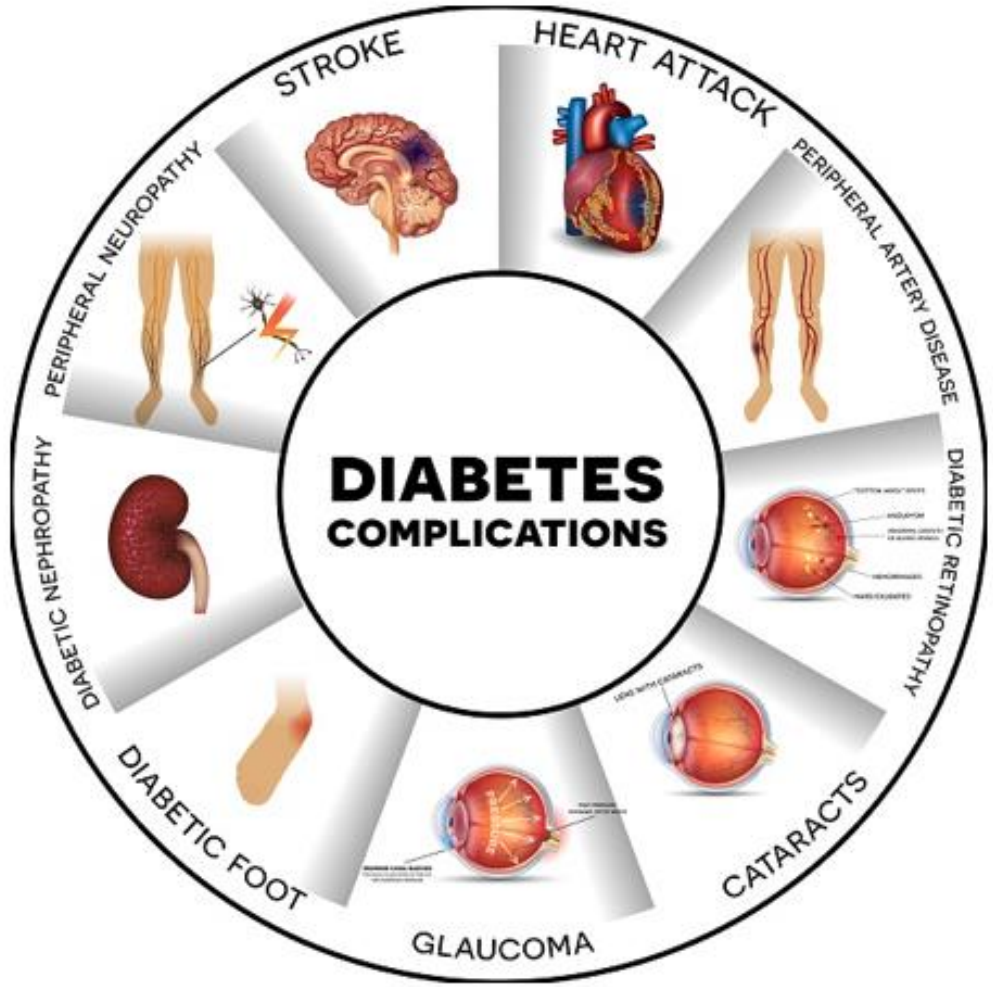
Sirui Zhou[1,2,23], Guillaume Butler-Laporte[1,2,23], Tomoko Nakanishi[1,3,4,5,23], David R. Morrison[1], Jonathan Afilalo[1,2,6], Marc Afilalo[1,7], Laetitia Laurent[1], Maik Pietzner[8], Nicola Kerrison[8], Kaiqiong Zhao[1,2], Elsa Brunet-Ratnasingham[9,10], Danielle Henry[1], Nofar Kimchi[1], Zaman Afrasiabi[1], Nardin Rezk[1], Meriem Bouab[1], Louis Petitjean[1], Charlotte Guzman[1], Xiaoqing Xue[1], Chris Tselios[1], Branka Vulesevic[1], Olumide Adeleye[1], Tala Abdullah[1], Noor Almamlouk[1], Yiheng Chen[1,3], Michaël Chassé[9], Madeleine Durand[9], Clare Paterson[11], Johan Normark[12], Robert Frithiof[13], Miklós Lipcsey[13,14], Michael Hultström[13,15], Celia M. T. Greenwood[1,2,16], Hugo Zeberg[17], Claudia Langenberg[8,18], Elin Thysell[19], Michael Pollak[1,20], Vincent Mooser[3], Vincenzo Forgetta[1], Daniel E. Kaufmann[9,21] and J. Brent Richards

Screenshot

Paving the Way to Precision Drug Development
Recycling the Plans at McGill

- Mission : Improve care of Jewish General Hospital (JGH) patients using genomic medicine
- PI: Brent Richards, Co-PI : Vincent Mooser
- Partners : JGH – CERC – Industry (TBD)
- Funding : JGH Foundation, CERC, industry (TBD)
- Recruitment started : Aug 2023
- Goal : 3500+ patients / yr

BIO-PORTAL


DIABETES
COMPLICATIONS
STROKE
HEART ATTACK
PERIPHERAL ARTERY DISEASE
DIABETIC RETINOPATHY
CATARACTS
GLAUCOMA
DIABETIC FOOT
DIABETIC NEPHROPATHY
PERIPHERAL NEUROPATHY

Summary

- Genetics has delivered new markers of drug safety and new drugs !!!
- Much more to come on the horizon
- Need to demonstrate clinical utility, i.e. from observation studies to intervention trials
- Infrastructures under construction at McGill for “precision clinical development” of new therapeutics
- Active collaborations with UniBE to foster

Collaborations with UniBE on Genomic Medicine

- Development of new, cost-effective, technologies to sequence whole genomes (in press)
- Genomic architecture of Peripheral Artery Disease (ms in preparation)
- Demonstration of clinical utility of PRS in dyslipidemic patients (Drs Elisavet Moutzouri – Nicolas Rodondi – FNRS funded)
- Under planning : McGill as genomic medicine arm for Digital Twin in Diabetes Project (Jose Garcia, Chistoph Stettler, DCR)

Acknowledgments

Claude Bhérer PhD
Daniel Taliun PhD
Sirui Zhou PhD
Raquel Cuella Martin PhD

Kate Trajanoska MD PhD
Benoît Delabays MD

Brent Richards MD PhD
Dave Morrison PhD

And many others

https://www.keepcalmandposters.com/poster/5907208_keep_calm_and_love_genetics