# The ethical implication of genetic diagnosis

Yann Joly, PhD

# AFFILIATIONS

- Quebec Network for Personalized Healthcare (QNPHC) – Advisory board
- VERITAS ethics commitee – Member

No other potential conflict to declare

# LEARNING OBJECTIVES

- At the conclusion of this activity, participants will be able to list the main ethical challenges associated with the genetic testing in the context of familial hypercholesterolemia
- At the conclusion of this activity, participants will be able to assess the pros and cons of different screening models for familial hypercholesterolemia
- At the conclusion of this activity, participants will be able to identify the opportunities and risks associated with the development of gene editing as a one and done treatment for coronary heart disease.

# OUTLINE

- Genetic testing/screening for Hypercholesterolemia
- Pharmacogenetics of PCSK9
- Gene editing

# GENETIC TESTING FOR FAMILIAL HYPERCHOLESTEROLEMIA (FH)

- Up to 1 in 250 individuals carry one abnormal gene associated with FH
- FH is caused most commonly by DNA variants in the LDLR, APOB, or PCSK9 genes. A pathogenic variant in 1 of these genes can be identified in 30%-80% of individuals with clinical FH.
- FH is a signficant risk factor for early onset cardivascular disease, a leading cause of death globally
- Identification of FH remains primarily by clinical diagnosis that can be confirmed by genetic testing
- Treatment & preventive measures : statins, changes in lifestyle and diet
- Access to genetic testing of FH for clinical care is limited in Canada outside of Qc


Canadian Cardiovascular Society Position *Statement on Familial Hypercholesterolemia: Update 2018*

# ETHICAL CONSIDERATIONS

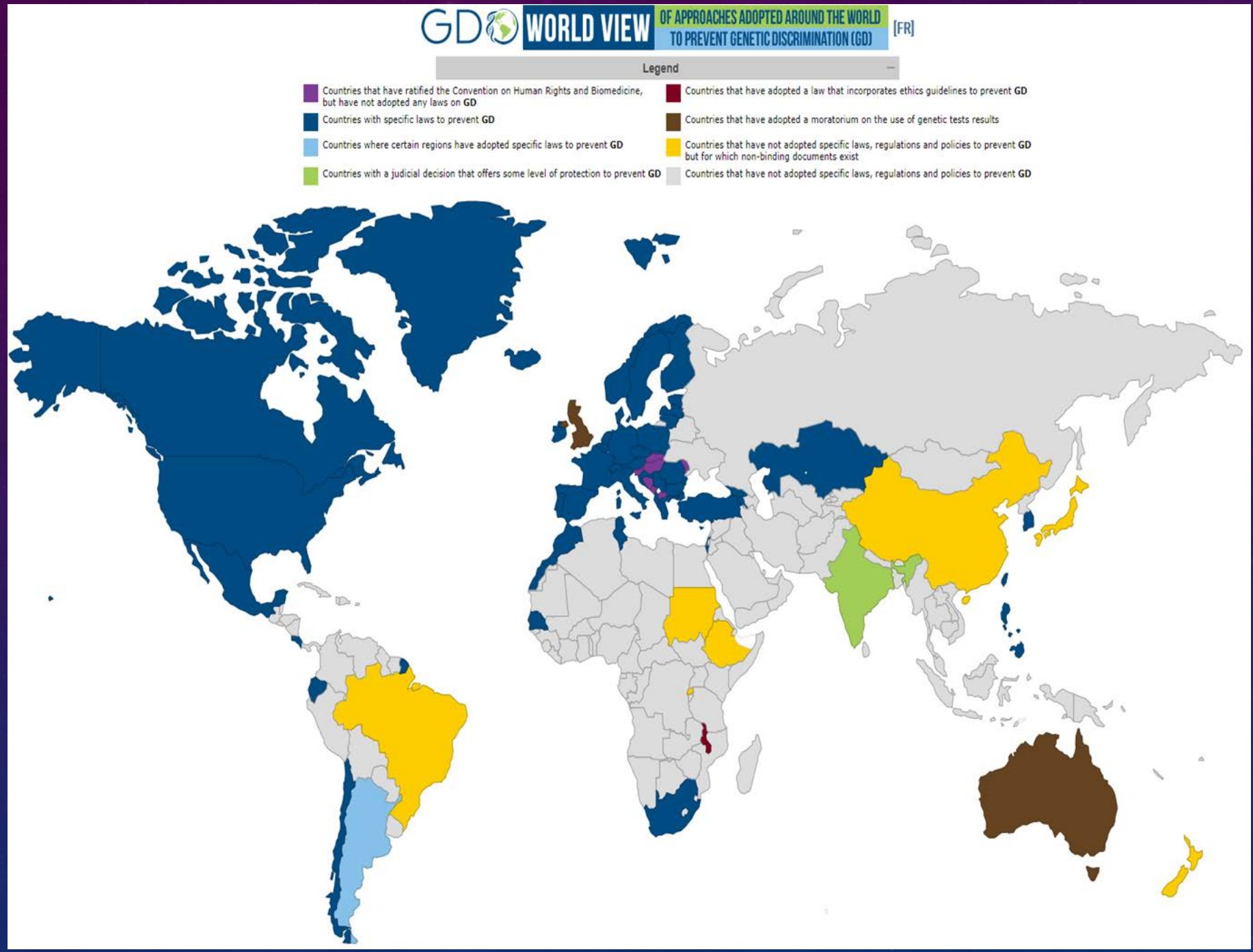
- Confidentiality - Genetic discrimination
- Right not to know
- Duty to warn
- Education and Genetic counseling

# GENETIC DISCRIMINATION

- Test results should be included in the patients' medical record as it is clinically relevant information. Content of the file is protected by confidentiality and professional secrecy legal provisions

- Canada has a law to prevent genetic discrimination (S-201) but it has been recently invalidated by the Quebec court of appeal. Nevertheless, CLHIA has committed not to ask for test results until the Supreme Court of Canada weigh-in on the matter.

- Data from Netherlands have shown that access to life insurance improved, for familial hypercholesterolemia patients after a genetic diagnosis, especially after the implementation of insurance guidelines stating that the risk assessment should be based on LDL-C levels and that individuals with genetic familial hypercholesterolemia who are free of cardiovascular disease should be offered an unconditional life insurance policy under most conditions


GD WORLD VIEW
OF APPROACHES ADOPTED AROUND THE WORLD TO PREVENT GENETIC DISCRIMINATION (GD)
[FR]
Legend
Countries that have ratified the Convention on Human Rights and Biomedicine, but have not adopted any laws on GD
Countries with specific laws to prevent GD
Countries where certain regions have adopted specific laws to prevent GD
Countries with a judicial decision that offers some level of protection to prevent GD
Countries that have adopted a law that incorporates ethics guidelines to prevent GD
Countries that have adopted a moratorium on the use of genetic tests results
Countries that have not adopted specific laws, regulations and policies to prevent GD but for which non-binding documents exist
Countries that have not adopted specific laws, regulations and policies to prevent GD

# RIGHT NOT TO KNOW


- UNESCO's *Universal Declaration on the Human Genome and Human Rights* (1997), Article 5c affirms: "The right of every individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected"

- But, genetic testing for genes associated with FH is a clinical genetic test whose results carry significant healthcare consequences and where preventive action is possible

- Patient can ask for the procedure to be stopped until test has been analyzed and sent back to clinician. Once it is back with the clinician result should be deposited in the medical record (no right not to know at this point)

- Children: Right not to know in this context must be set aside to respect the fundamental principle of the best interest of the child

- Answer could be different if results was an incidental finding from a WGS, WES

# EDUCATION AND GENETIC COUNSELLING

- Substantial public/patient engagement work is needed to improve uptake of genetic test and prevention measures following positive test results

# DUTY TO WARN?

- Is there a physician’s duty to inform close relatives of patients with heritable genetic conditions in spite of a patient’s refusal
- First step should be to ask an adult patient to voluntarily communicate its results to close relatives.
- At the moment, a duty to inform patients' relatives of genetic risks is not recognized in Quebec. Duty of confidentiality towards patient applies
- But in a case where : 1) There is an elevated risk for the family members in developing a serious illness; 2) The biological family members are identifiable; and 3) The illness can be avoided by preventative measures or controlled by approved treatments; a strong ethical argument could be made that this information should be disclosed

# GENETIC SCREENING

- Universal screening: evaluate all individuals in a particular segment of the population (ex. children in certain age groups) for parameters associated with FH
- Targeted screening: focus on individuals meeting specific risk criteria (ex. family history of early onset cardiovascular disease)
- Cascade screening: identify an FH patient (proband) then implement active cholesterol testing, genetic testing, or both for all potentially affected relatives. Repeat for each relative diagnosed with FH to expand the number of potential cases detected
- Use of genetic in screening programs: DNA testing can improve accuracy of screening however challening to select optimal genetic platform (variety of mutations, mutation patterns differ between countries). Use of NGS

# ETHICAL CONSIDERATIONS

*Wilson and Jungner criteria* for broad screening endeavours:

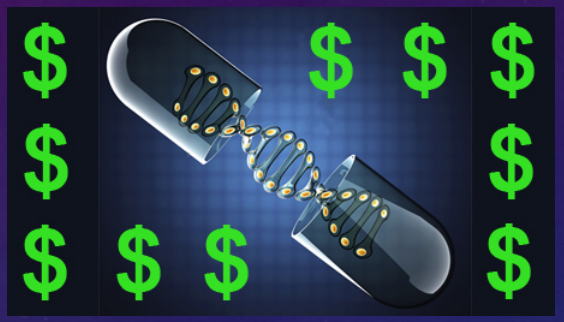
- An important health problem? (frequent/serious)
- History of the condition is adequately understood?
- Treatment is available?
- Cost – benefit ratio of screening? (reliability and cost of test)

- To consider in the case of children:
- Predictive genetic testing for adult onset conditions should be deferred unless an intevention initiated in childhood may reduce morbidity or mortality

# ETHICAL CONSIDERATIONS

- Autonomy – consent vs. beneficence (especially for mandatory programs)
- Possible stigmatization and anxiety post test, psychosocial implications of “labelling” children with a positive diagnosis
- Cost of implementing a screening program
- Education and counselling should be made available to ensure tested individuals can truly benefit from knowing their results
- Genetic discrimination

# PHARMACOGENETICS OF PCSK9



- Statins are the drug class of choice for FH, on the basis of landmark trials in the non- FH population that have shown that statins are the best treatment available for lowering LDL-C in patients with increased ASCVD risk. The yearly cost of generic statins is approximately CAD $300
- Monoclonal antibodies inhibitors of PCSK9 can reduce LDL cholesterol and cardiovascular risk in patients with elevated cholesterol despite high-intensity statin therapy. These are costly medications, CAD $4,500 to $8,000 a year, that should be used judiciously in a cost-constrained medical system

# ETHICAL CONSIDERATIONS

- Population (ethnicity) guided pharmacogenetics
- Access to new pharmacogenetics drugs

# GENE EDITING

- CRISPR/Cas9 targeting of genes in the mouse liver can beneficially modify lipid traits, heralding possible one-shot, lifelong treatments for dyslipidemia and coronary heart disease
- Survey Results From 301 Total Respondents at a Plenary Session on Genome Editing at ATVB/PVD Scientific Sessions 2017: If you had the opportunity to receive a one-shot somatic genome-editing therapy that would permanently reduce your risk of coronary heart disease, would you do so (assuming the therapy is 100% safe)? Y 69%, N 19%, DK 12%
- 2019, Dr Kathiresan funded Verve Therapeutics to develop CRISPR gene editing therapies as a one-and-done treatment for heart disease. Verve's first target will be homozygous FH

# ETHICAL AND HTA CONSIDERATIONS

- Efficacy, safety
- Cost- benefit vs. existing therapy?
- Access and reimbursement
- Pleiothropy, limited data on long term risks
- Slippery slope towards children or germline gene editing?

# THANK YOU!

YANN.JOLY@MCGILL.CA