THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Mended Hearts
FH – It's a Family Affair

Amy Sturm, LGC

Licensed Genetic Counselor

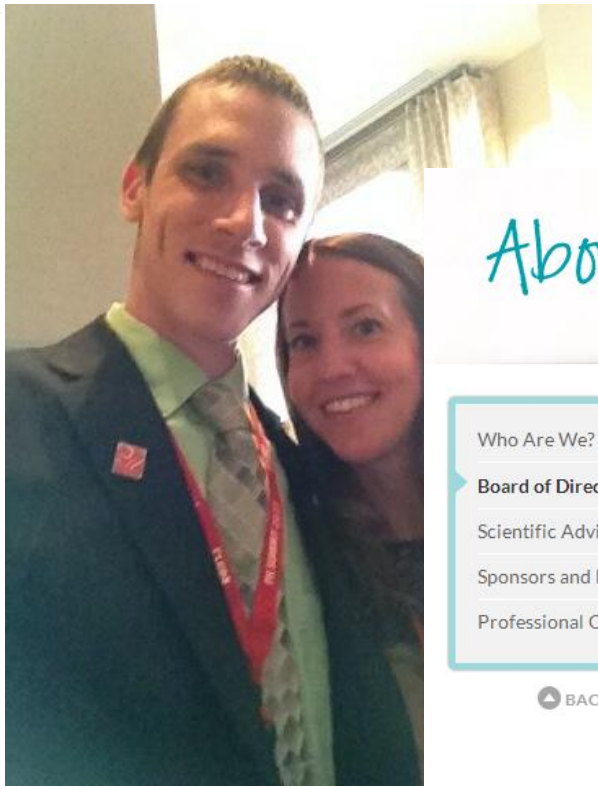
Associate Professor

Division of Human Genetics

Department of Internal Medicine

Ohio State University Wexner Medical Center

It all started with…



FH FOUNDATION
Raising Awareness. Saving Lives.

- Who Are We?
- **Board of Directors**
- Scientific Advisory Board
- Sponsors and Partners
- Professional Organizations

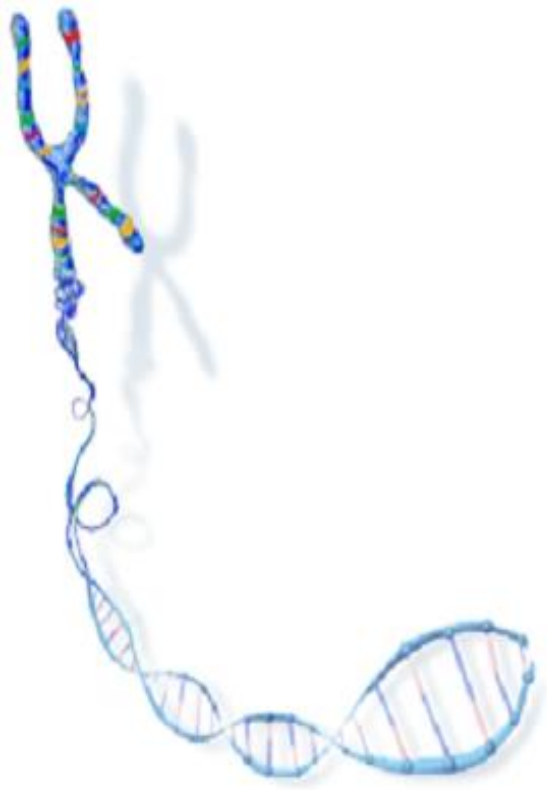
BACK TO TOP

Board of Directors

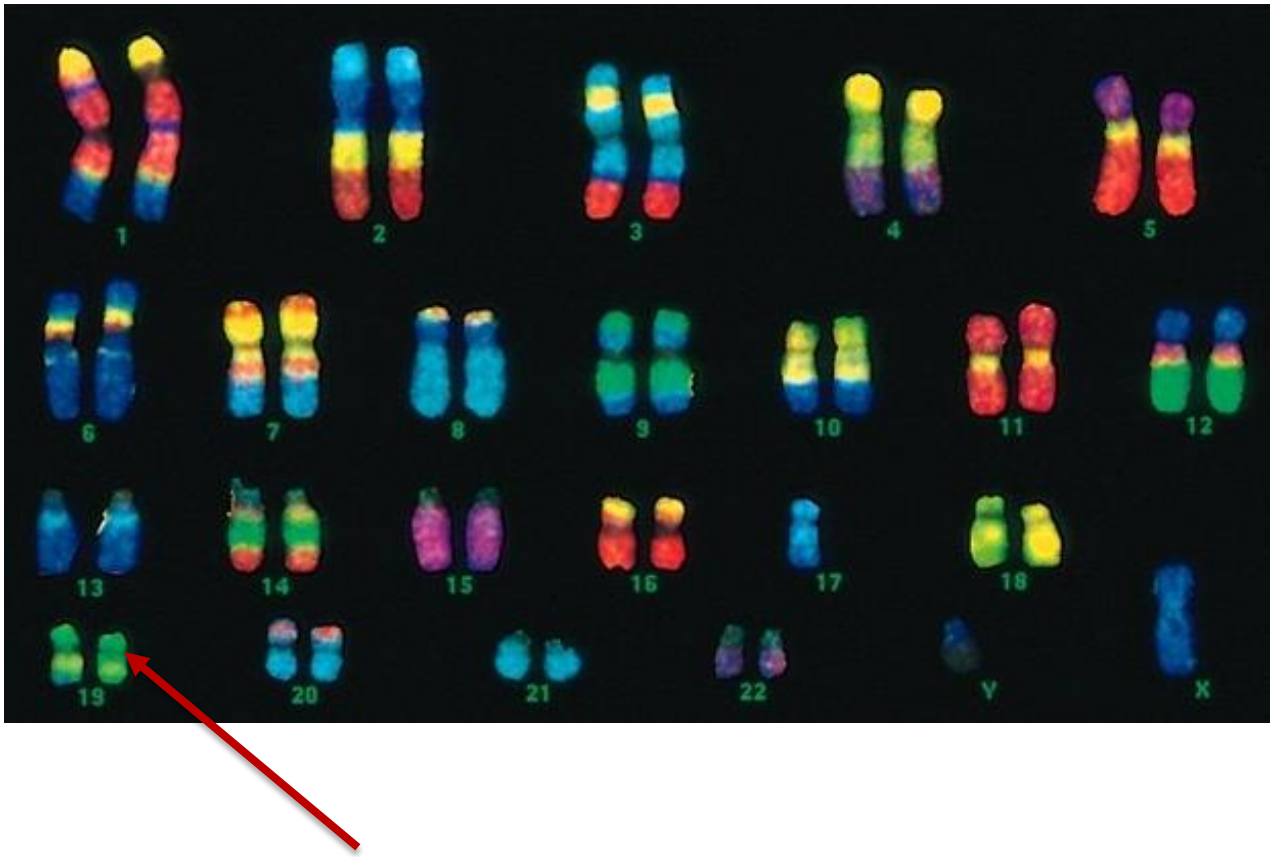
dOfDirectors.jpeg

Overview – The Genetics of FH Knowledge is Power

- Genetics 101
- The Genetics of FH
  - The Family Tree, or Pedigree
  - Inheritance
  - Genetic testing
  - FH Genetics
  - Genetic and genomic testing advances
  - Genetic testing and the guidelines
- Genetic counseling
- Genetic counselors
- CASCADE FH Registry
- Cascade testing
- Family dynamics and privacy
- Genetic discrimination
- Resources

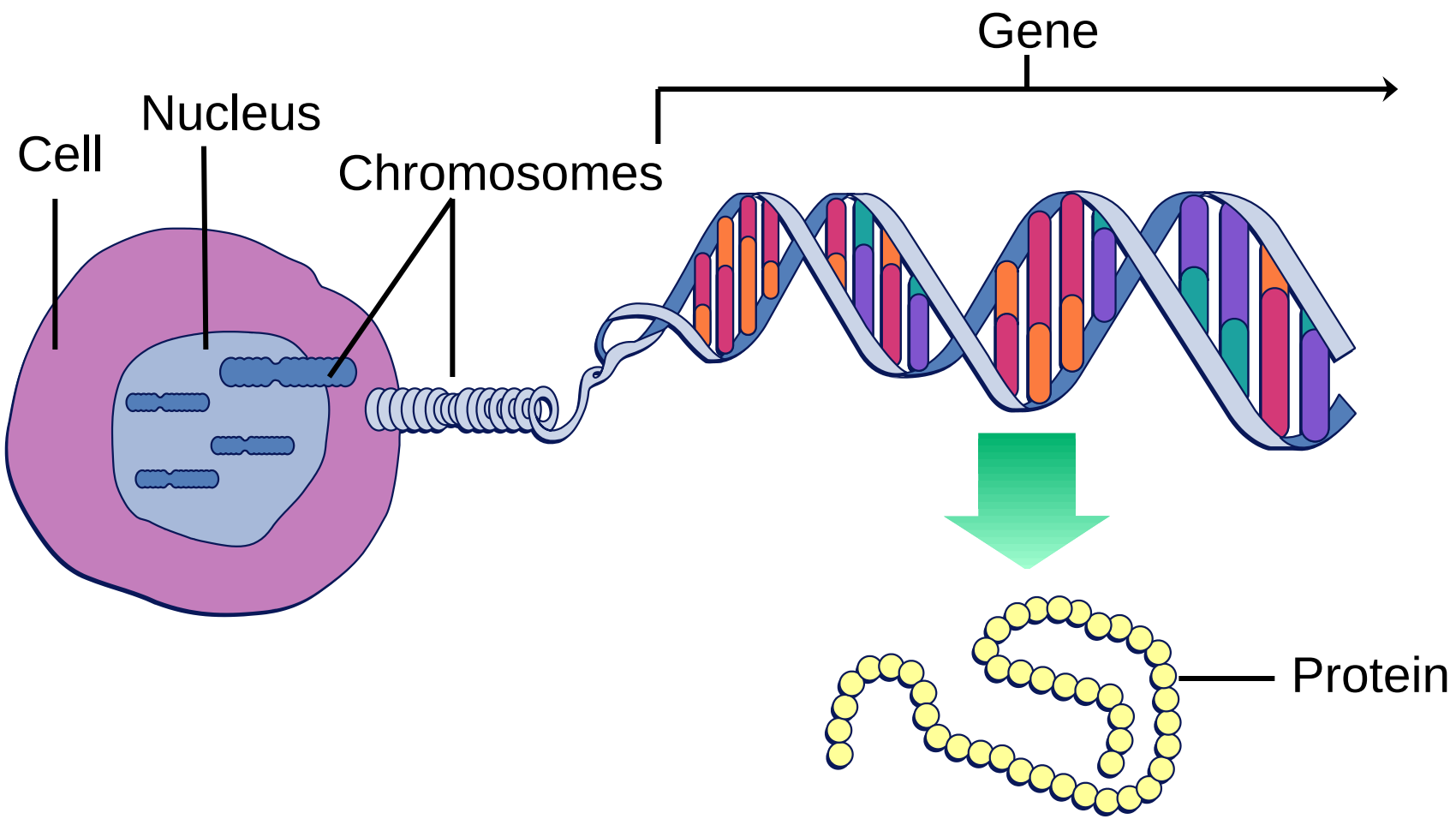


Genetics 101

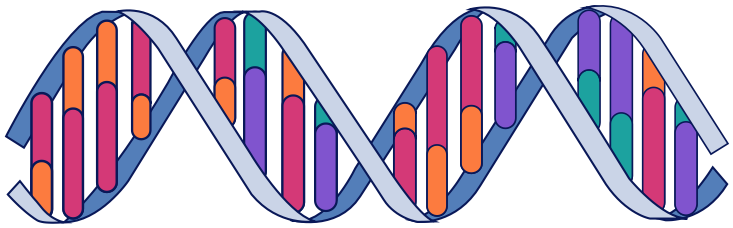


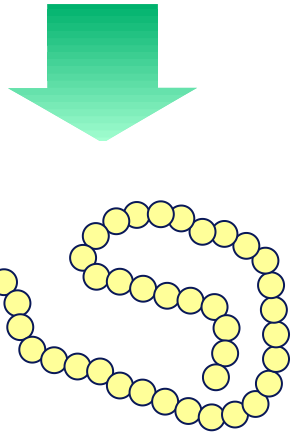
19p13.2: location of *LDLR* gene

Genetics 101: Chromosomes, Genes, and DNA

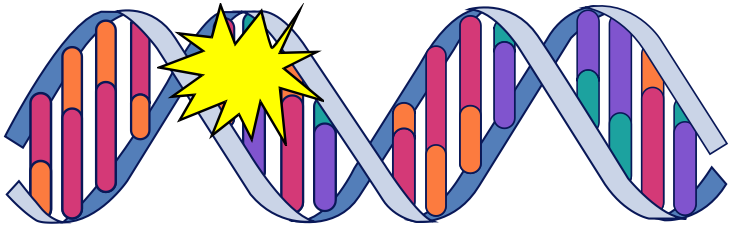


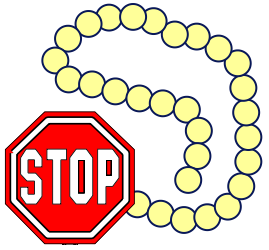
Disease-Associated Genetic Variations Alter Protein Function





Functional protein

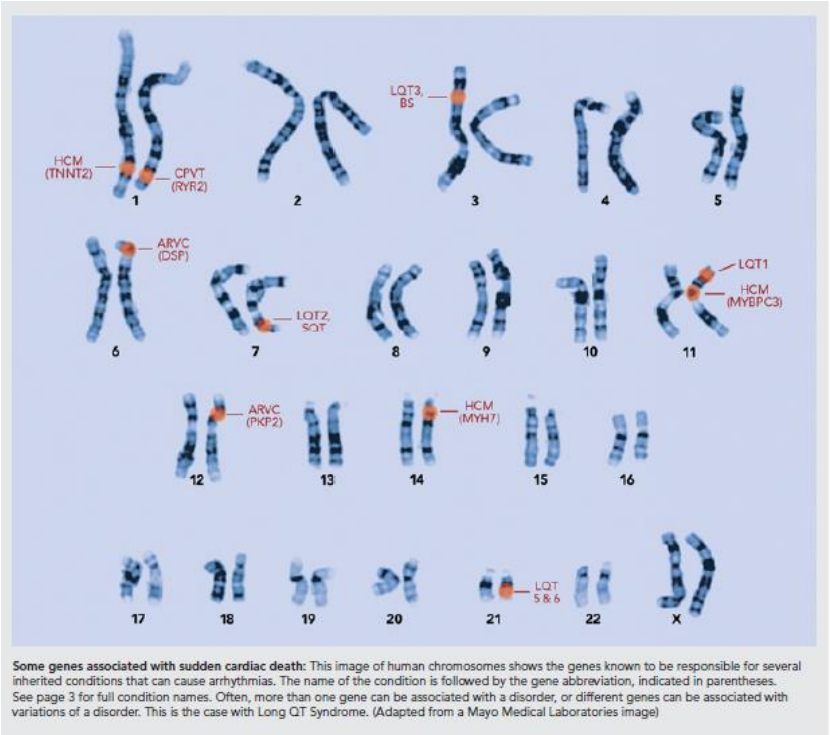




Nonfunctional or missing protein

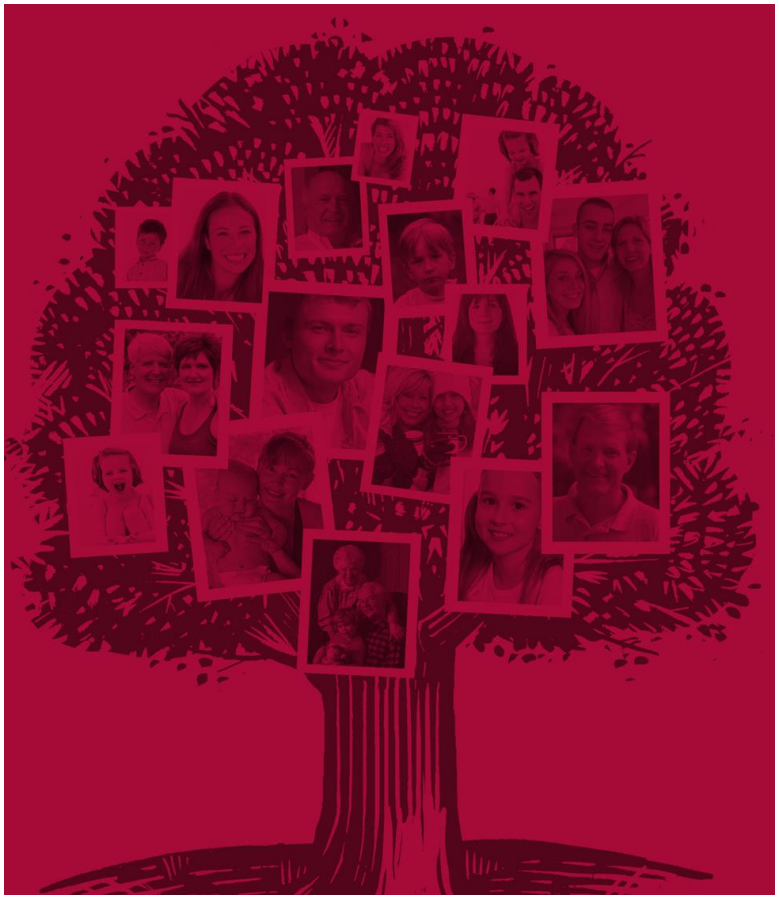
Nobody is “perfect”

All of us, regardless of ethnic or religious background, carry an estimated 5-50 significant genetic variants, or mutations.



Some genes associated with sudden cardiac death: This image of human chromosomes shows the genes known to be responsible for several inherited conditions that can cause arrhythmias. The name of the condition is followed by the gene abbreviation, indicated in parentheses. See page 3 for full condition names. Often, more than one gene can be associated with a disorder, or different genes can be associated with variations of a disorder. This is the case with Long QT Syndrome. (Adapted from a Mayo Medical Laboratories image)

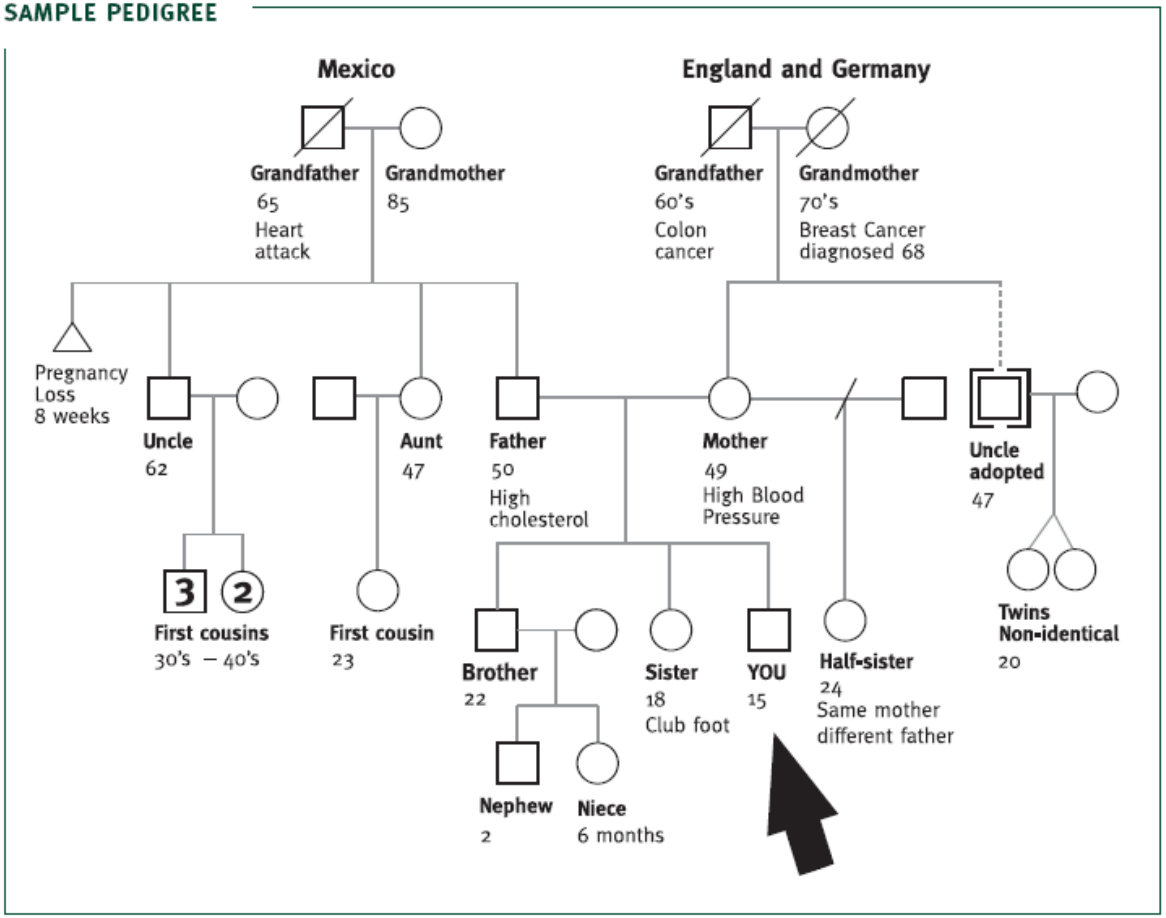
The Family Tree, or Pedigree



Why is Family History Important?

- Family history is a powerful tool that can focus your personal health promotion and disease prevention efforts
- Family history reflects shared genetic susceptibilities, shared environment, and common behaviors
- Knowing your family's health history can save your life!

Constructing an Informative Pedigree



- ≥3 generations

Questions should include:

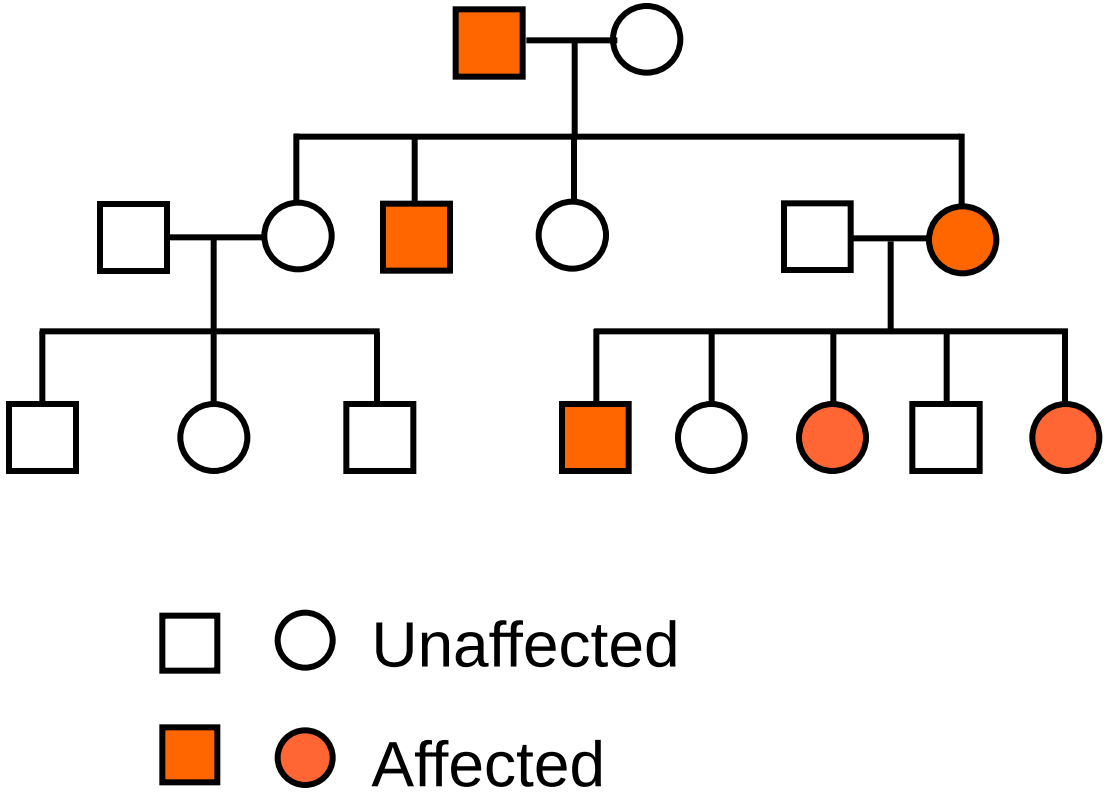
1. Current ages
2. Health status and age at diagnosis
3. Age and cause of death
4. Focus on "red flags" (e.g. premature CAD, SCD)
5. Family's racial/ethnic background

Family history is imperative in:

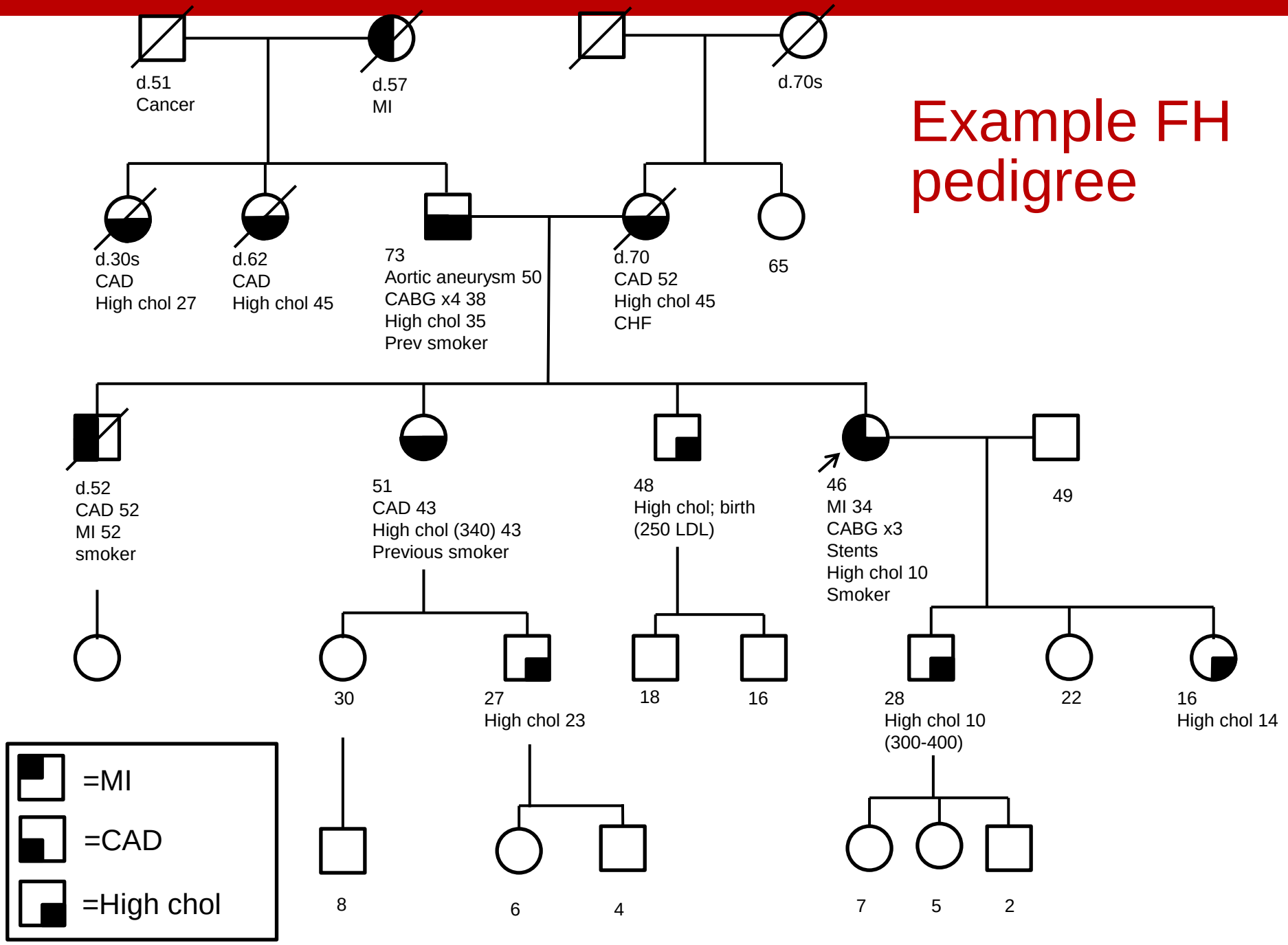
1. aiding diagnosis
2. determining inheritance pattern
3. identifying at-risk relatives
4. selecting the most informative family member for genetic testing initiation

Autosomal Dominant Inheritance

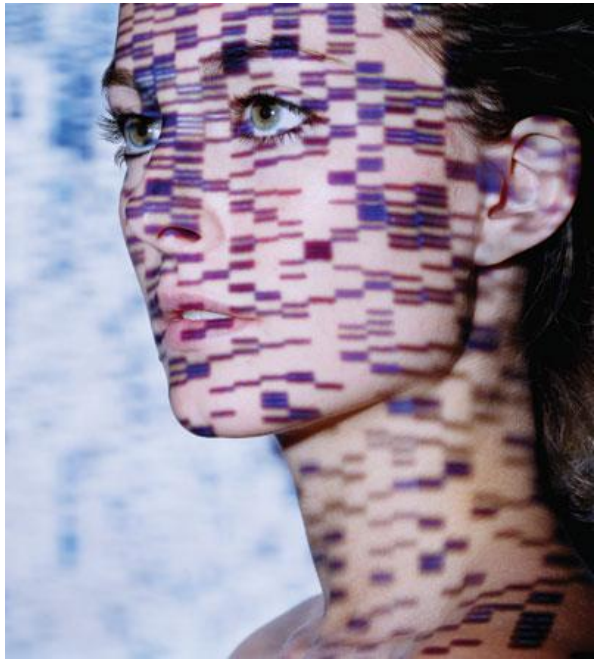
- First degree relatives (FDRs) have 50% chance of inheriting predisposing genetic variant
- Genetic variant does not skip generations
- Transmitted by men and women



Example FH pedigree



Genetic Testing



Genetic Testing

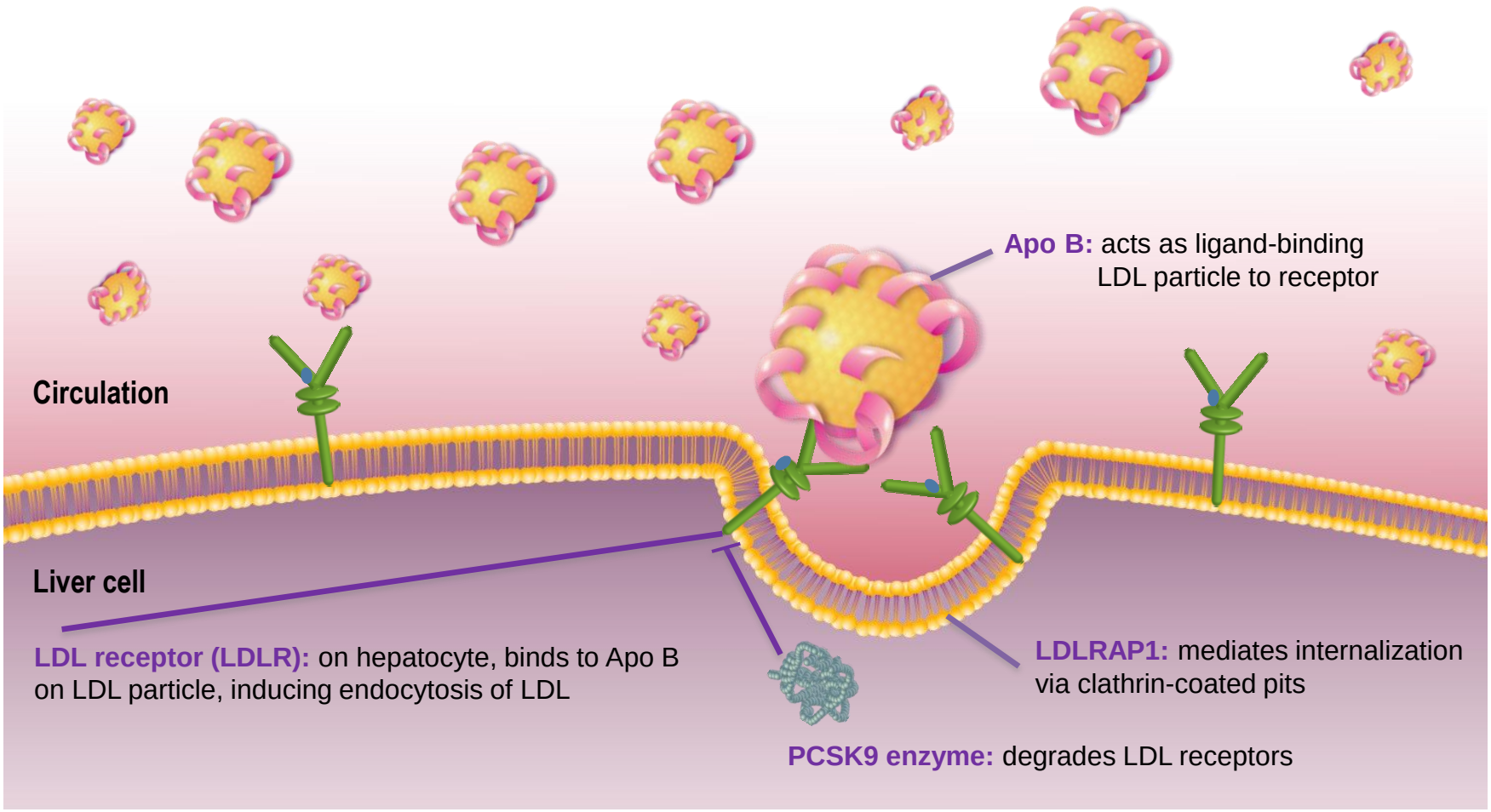
- Clinical & research genetic testing
- Determining the appropriate genetic test and lab is critical
- Genetic tests are often covered by insurance
- Interpretation and implications of genetic tests is not always straightforward

Types of Genetic Testing

- The identification of a gene variant may:
  - Confirm the diagnosis of a genetic condition (diagnostic testing)
  - Identify the risk to develop a condition (predictive or presymptomatic testing)
- Testing should begin with an affected individual
- Targeted genetic testing can be done for at-risk family members once the causative variant has been identified in the proband, or index patient

FH Genetics

Genetic Mutations That Cause FH Impair LDL-C Particle Clearance, Increasing Plasma Cholesterol



LDLRAP1 = low-density lipoprotein receptor adaptor protein 1.

Image reproduced from: Department of Life Sciences and Institute and Institute of Genome Sciences Web site. http://www.dls.ym.edu.tw/ol_biology2/ultranet/Endocytosis.html. Published June 11, 2001. Accessed January 19, 2012.

De Castro-Oros I, et al. *Appl Clin Genet.* 2010;3:53-64.; Rader DJ, et al. *J Clin Invest.* 2003;111:1795-1803.; Hopkins PN, et al. *J Clin Lipol.* 2011;5(3 suppl):S9-S17.

Genetics of FH

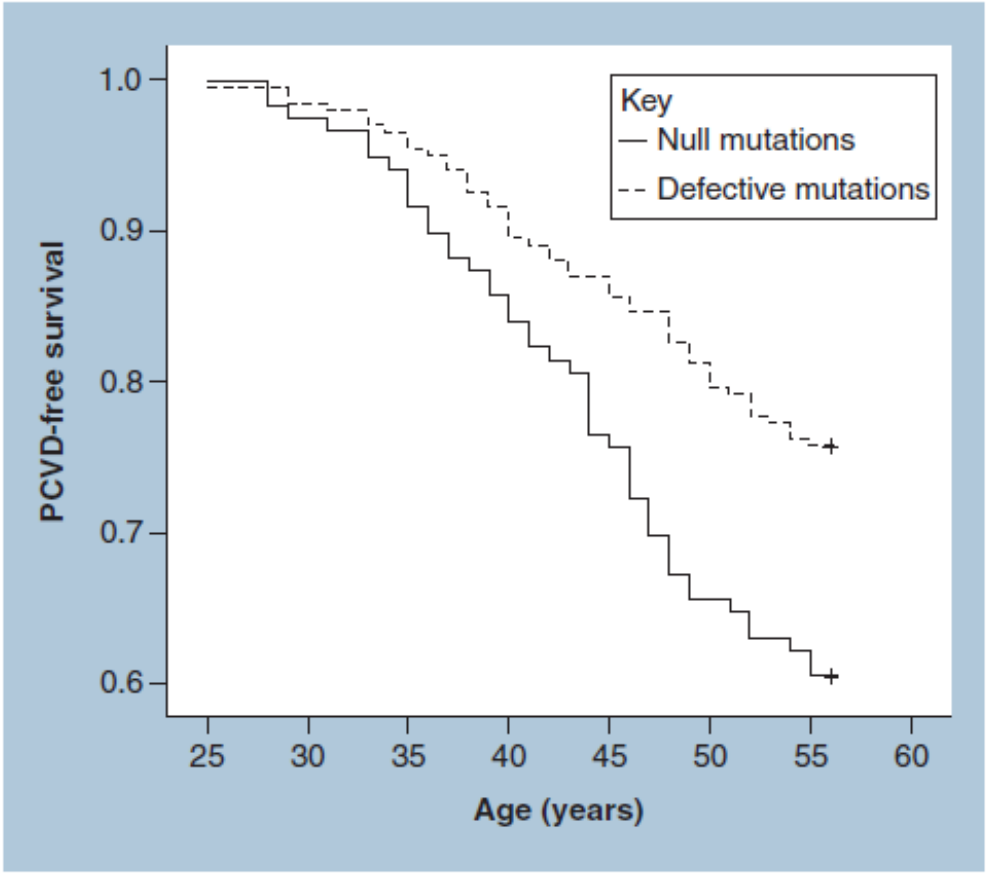
GENE	Chr	# Causal Mutations	% of FH cases*
LDLR (LDL Receptor)	Chr 19	> 1600	60-80%
APOB (Apolipoprotein B)	Chr 2	Handful (esp. Arg3500Gln or R3500Q)	1-10%
PCSK9 (proprotein convertase subtilisin/kexin type 9)	Chr 1	Handful	<5%
Unknown			20-40%

* Yield for genetic testing is higher in “definite” FH (~80%) vs. “probable” and “possible” FH (35-60%)

*Slide modified from Josh Knowles, MD, PhD

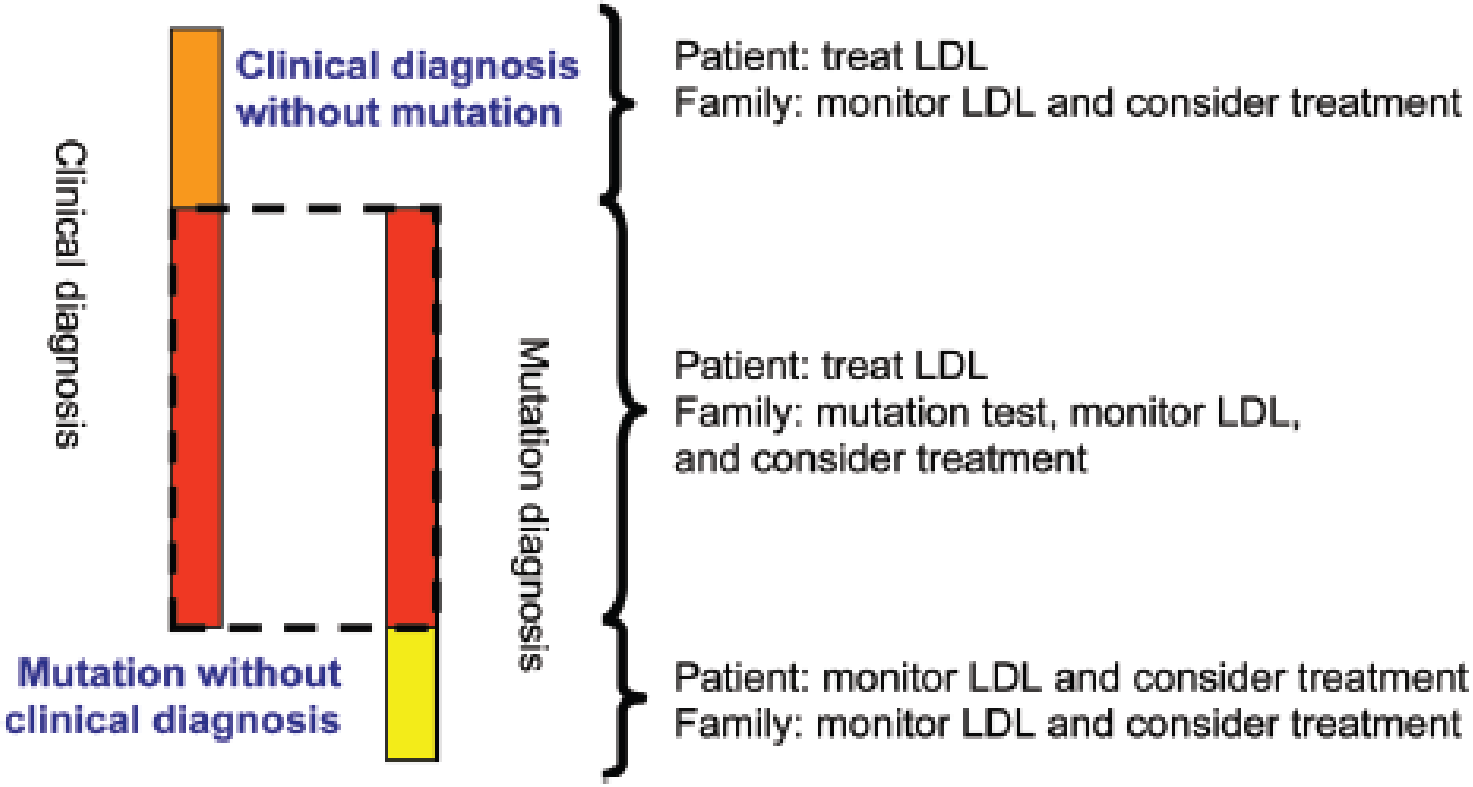
LDLR variant type may affect cardiovascular disease (CVD) risk

- Curves for CVD-free survival in FH men with null and defective *LDLR* variants
- Patients with null variants had significantly higher CVD frequency



Alonso et al. Expert Rev Cardiovasc Ther 11(3), 327-342 (2013).

Overlap of Clinical and Mutation Diagnosis of Heterozygous Familial Hypercholesterolemia



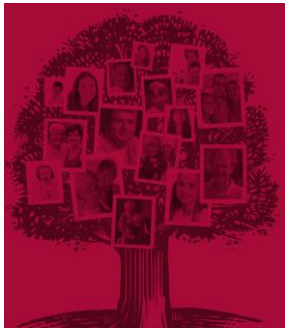
Nordestgaard B G et al. Eur Heart J 2013.

European Heart Journal

Genetic Counseling

The Process of Genetic Counseling

- Medical history
- Family history
  - Collection and review of family members' medical records
    - Cholesterol panels, other medical records, death certificates, autopsy reports
- Physical examination – collaborating physician
  - Evaluation for physical signs of FH
- Risk assessment
  - Inheritance, recurrence risk
- Education
- Genetic testing
  - Informed consent, sample collection, insurance pre-authorization
- Genetic test result interpretation, disclosure, and documentation
- Screening/prevention/management recommendations in collaboration with referring physician
- Discussion of reproductive options

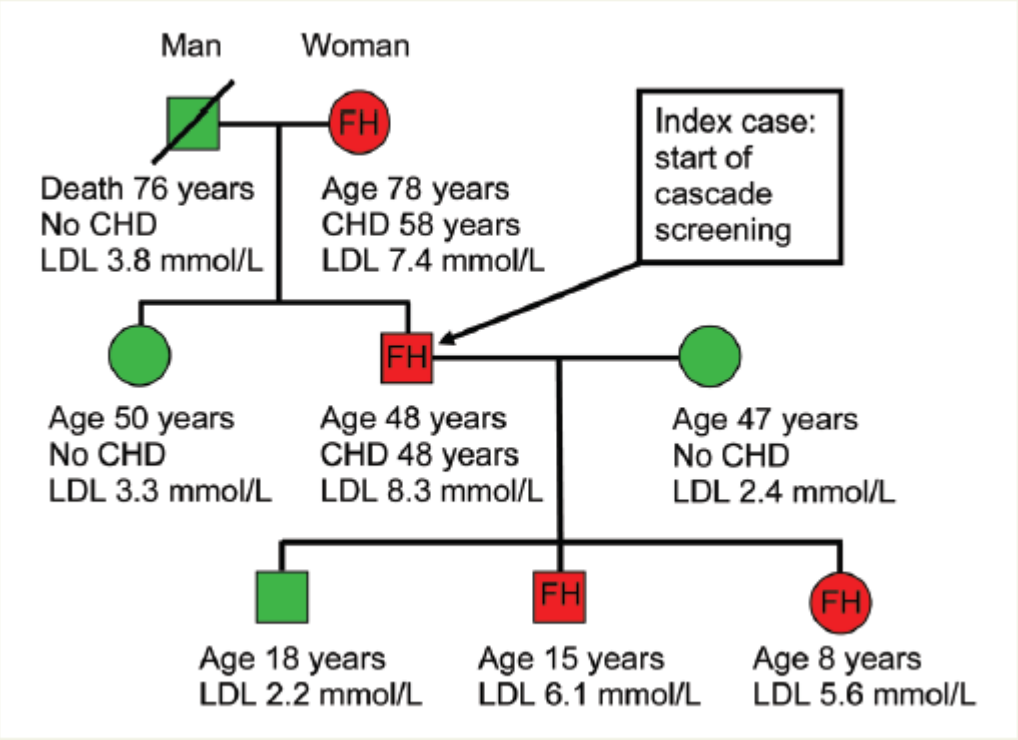


The Process of Genetic Counseling

- Psychosocial counseling and anticipatory guidance
- Provision of resources from national organizations and advocacy groups
- Connection with families with the same condition
- Discussion of DNA banking availability, when applicable
- Discussion of available research options
  - Enrolling FH patients into the CASCADE FH Registry
- Facilitation of family-based care/evaluation of at-risk family members

Cascade testing

Cascade Testing: Critical for FH Families

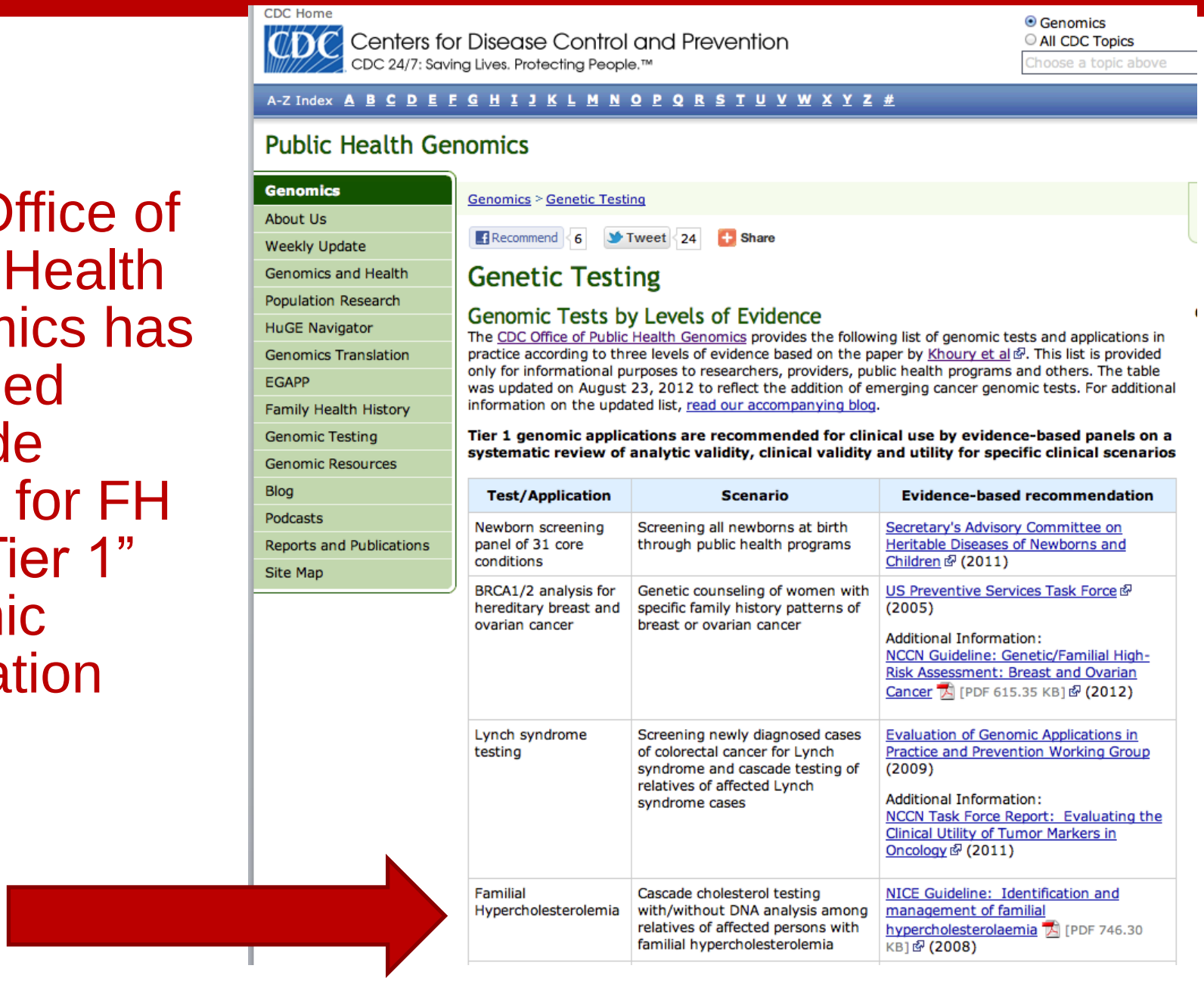


- Process of systematic family tracing to identify at-risk relatives
- Should begin with 1st-degree relatives and then extend to 2nd and 3rd degree in a stepwise fashion
- DNA testing should be used if the pathogenic variant has been identified
- Newly identified FH patients provide additional relatives who should be screened
- Facilitates early detection and treatment
- A cost-effective method for identifying people with FH

After FH has been diagnosed, any family member can have lipid or genetic testing, but a cascade strategy saves resources and headaches!

Nordestgaard et al. European Heart Journal. 2013

CDC Office of Public Health Genomics has classified cascade testing for FH as a "Tier 1" genomic application



CDC Home

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

Genomics
All CDC Topics
Choose a topic above

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Public Health Genomics

- Genomics
- About Us
- Weekly Update
- Genomics and Health
- Population Research
- HuGE Navigator
- Genomics Translation
- EGAPP
- Family Health History
- Genomic Testing
- Genomic Resources
- Blog
- Podcasts
- Reports and Publications
- Site Map

Genomics > Genetic Testing

Recommend 6 Tweet 24 Share

Genetic Testing

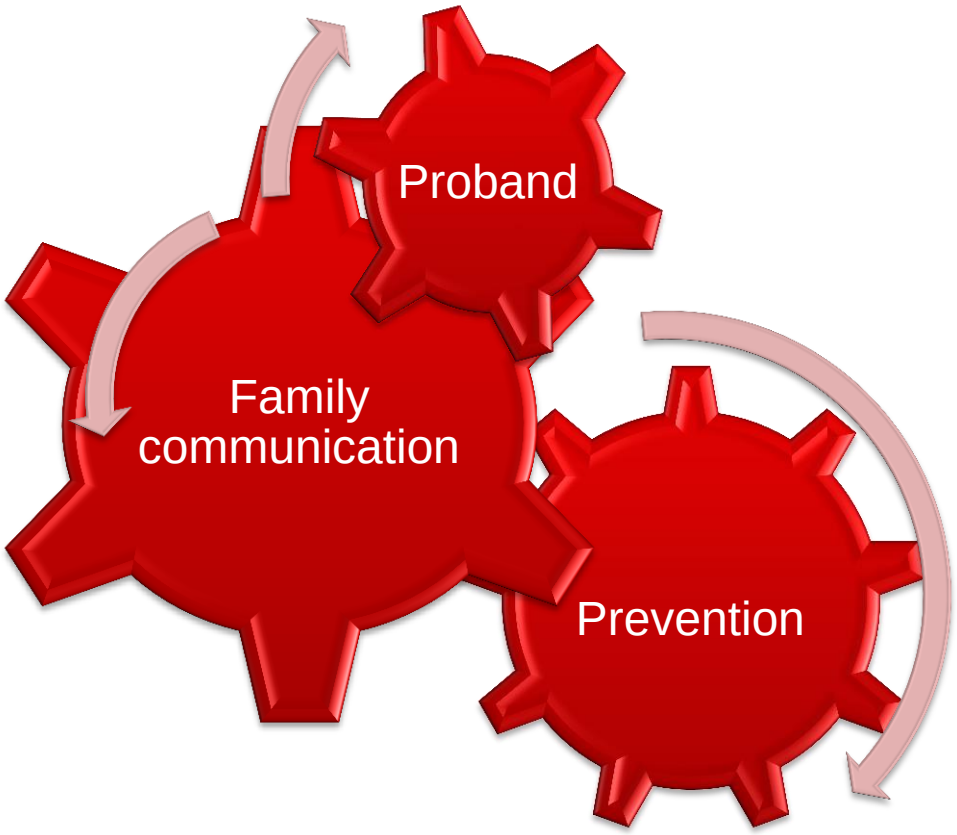
Genomic Tests by Levels of Evidence

The CDC Office of Public Health Genomics provides the following list of genomic tests and applications in practice according to three levels of evidence based on the paper by Khoury et al. This list is provided only for informational purposes to researchers, providers, public health programs and others. The table was updated on August 23, 2012 to reflect the addition of emerging cancer genomic tests. For additional information on the updated list, read our accompanying blog.

Tier 1 genomic applications are recommended for clinical use by evidence-based panels on a systematic review of analytic validity, clinical validity and utility for specific clinical scenarios

Test/Application	Scenario	Evidence-based recommendation
Newborn screening panel of 31 core conditions	Screening all newborns at birth through public health programs	Secretary's Advisory Committee on Heritable Diseases of Newborns and Children (2011)
BRCA1/2 analysis for hereditary breast and ovarian cancer	Genetic counseling of women with specific family history patterns of breast or ovarian cancer	US Preventive Services Task Force (2005) Additional Information: NCCN Guideline: Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer [PDF 615.35 KB] (2012)
Lynch syndrome testing	Screening newly diagnosed cases of colorectal cancer for Lynch syndrome and cascade testing of relatives of affected Lynch syndrome cases	Evaluation of Genomic Applications in Practice and Prevention Working Group (2009) Additional Information: NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology (2011)
Familial Hypercholesterolemia	Cascade cholesterol testing with/without DNA analysis among relatives of affected persons with familial hypercholesterolemia	NICE Guideline: Identification and management of familial hypercholesterolaemia [PDF 746.30 KB] (2008)

Genetic counseling promotes family communication



Dear Family Member Letter

Located on the resources page of the FH Foundation website

National Society of Genetic Counselors

Dear Family Member,

I have been diagnosed with familial hypercholesterolemia (FH). FH is a genetic disorder that causes high cholesterol levels in the blood resulting in a 20-times increase in risk for premature heart disease (including heart attack) if left untreated. Based on my diagnosis, you are at risk for FH. You could have FH without any physical signs or symptoms and may feel and look healthy. If diagnosed, FH needs to be treated through medication and lifestyle changes (not smoking, regular exercise and a healthy diet). The good news is that **HEART DISEASE due to FH CAN BE PREVENTED if you TAKE ACTION** and have your high cholesterol treated by a health care provider who knows about this condition. Knowing your cholesterol level gives you the power to act.

If you already have high cholesterol or heart disease, ask your health care provider if you might have FH. If you do not know whether you have high cholesterol, you can see your health care provider and have a fasting lipid profile. This is a standard blood test that provides information about cholesterol levels. Individuals with FH have high levels of low-density lipoprotein (LDL) cholesterol, also known as the "bad cholesterol". Genetic testing for FH is available and can be useful to assist in diagnosis and identify other family members who may also have FH.

FH is passed down through families in an autosomal dominant manner and can be inherited from a parent. All first-degree relatives (parents, siblings, children) of a person with FH have a 50% chance of also having FH. FH affects people of all ages and high cholesterol levels need to be treated in children as well as adults. Diagnosis of FH in childhood allows for early intervention and treatment and improves chances to prevent heart disease. Therefore we recommend all children at risk for FH have their cholesterol levels checked for the first time between the ages of two and eight years old.

Next Steps

- Take a copy of this letter with you when you meet with your health care provider.
- Ask your health care provider to check your cholesterol.
  - A diagnosis of FH is probable in a family member of an affected individual with FH if:
    - Untreated LDL is greater than 170 mg/dL in adults 20 years of age and older.
    - Untreated LDL is greater than 155 mg/dL in children and adolescents less than 20 years of age (Williams RR et al. *Am J Cardiol.* 1993;72(2)171-176).
  - Initial screening of children at risk for FH should take place between 2 and 8 years of age.
- If you are diagnosed with FH, share this letter with your at-risk parents, siblings and children.
- If your cholesterol levels are normal:

Dear Family Member Letter

- All children should have their cholesterol levels checked by their pediatrician between the ages of 9 and 11, and again between 17 and 21 (AAP guidelines, 2014).
- All adults should have their cholesterol checked every 5 years by their primary care provider (ACC/AHA guidelines, 2013).

Genetic Counseling

Genetic counselors are health care professionals who can help you understand the inheritance of FH and what this diagnosis means for you and your family. Genetic counselors can also facilitate genetic testing and interpret results. To learn more about genetic counselors, visit the website for the National Society of Genetic Counselors, www.nsgc.org.

Learn More About FH

- The FH Foundation (http://www.thefhfoundation.org/)
- FH Journeys (http://www.fhjourneys.com/)
- National Lipid Association (http://www.lipid.org/)
- Preventive Cardiovascular Nurses Association (http://pcna.net/patients/familial-hypercholesterolemia)

Find FH Professionals

Genetic Counselors: nsgc.org/findageneticcounselor
FH Specialists: thefhfoundation.org/find-fh-specialist

The clinic that evaluated me, _____,
would also be happy to evaluate you. You can reach them by calling _____.

Sincerely,

Family Dynamics

- Encourage family involvement and a shared approach to decision making
- Common emotional issues
  - Grief, Guilt, Blame, Responsibility
- Parental guilt
  - Helpful to emphasize benefits of information (i.e. knowledge is power)
- Survivor guilt
  - Family members may have discordant results
- Take care to avoid coercion
  - “Nagging” of children by parents
  - Could lead to relationship breakdown
- Protect and maintain privacy and confidentiality
- Paternity

Genetic Discrimination

- Genetic Information Non-discrimination Act (GINA)
  - Federal Law signed on May 21, 2008
  - Prevents health insurers from denying coverage, adjusting premiums, or otherwise discriminating on the basis of genetic information
    - Group and self-insured policies
  - Employers cannot use genetic information to make hiring, firing, compensation, or promotion decisions
  - No protection for disability or life insurance discrimination

CASCADE FH Registry

"Science tells us what we can do;
guidelines tell us what we should do;
and registries tell us what we're actually doing."

CASCADE FH Registry

CAscade SCreening for Awareness and DEtection of FH

1. PROMOTE AWARENESS OF FH at both the patient and provider levels.
1. IDENTIFY AND ENROLL FH PATIENTS through clinic-based, community-based, and family-based screening initiatives.
1. EVALUATE PATTERNS OF REAL-WORLD CLINICAL PRACTICE AND PATIENT EXPERIENCES
1. CONTRIBUTE TO THE STATE OF SCIENTIFIC KNOWLEDGE OF FH
2. IMPROVE HEALTH OUTCOMES, quality of life, and impact policy decisions.

COLLECT & **TRACK**
longitudinal clinical information

EVALUATE TRENDS
in therapy, clinical outcomes, & patient reported outcomes

FURTHER KNOWLEDGE & **UNDERSTANDING**
of familial hypercholesterolemia

IMPROVE
care, quality of life, & long-term clinical outcomes
of patients with FH and their affected family members