THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Mended Hearts: Savings Lives of Heart Patients Through Genetic Testing

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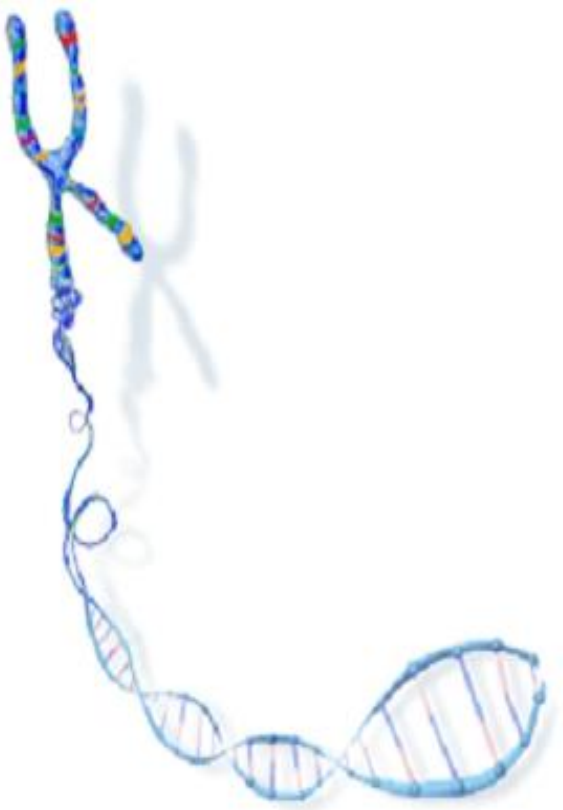
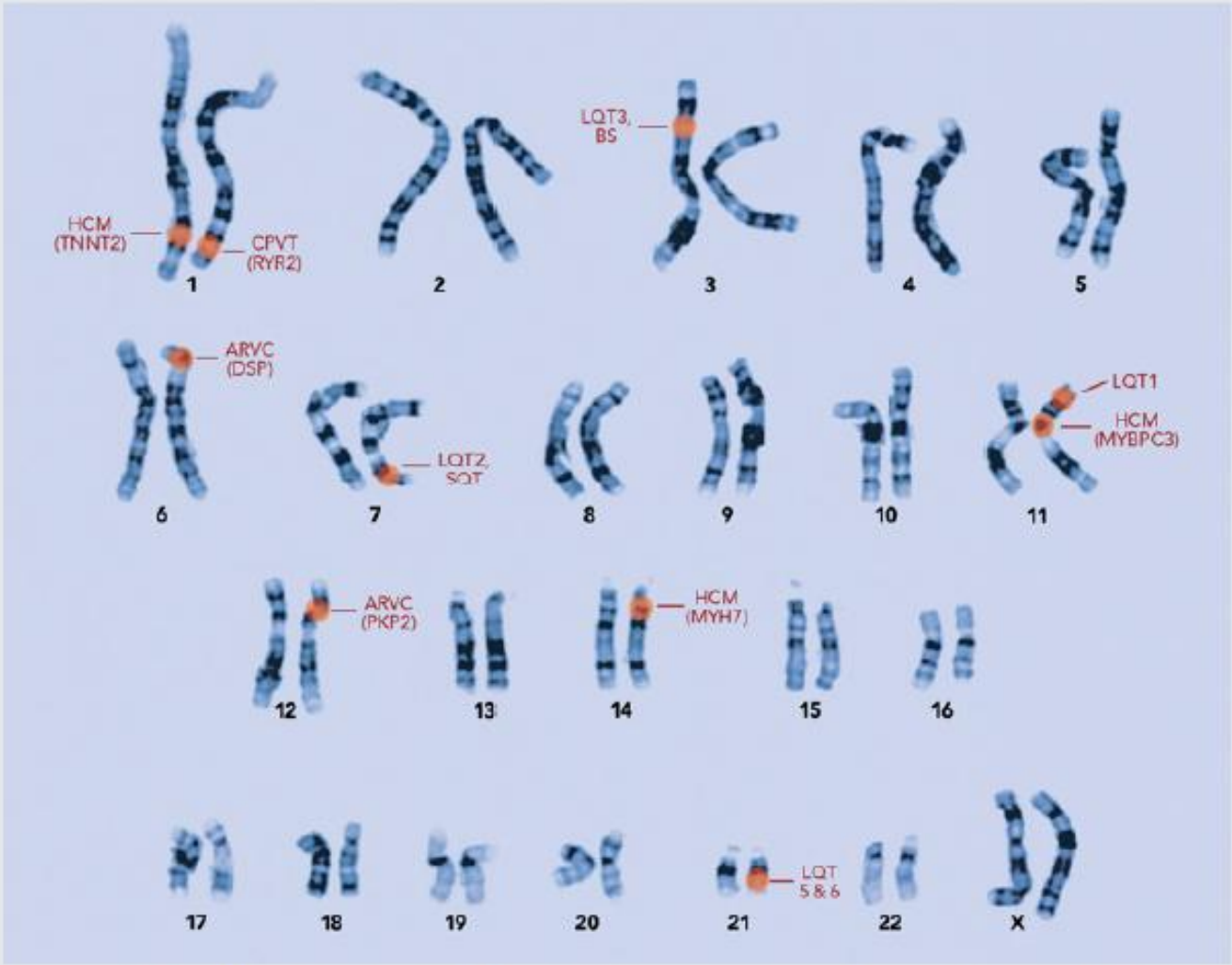
Why Genetics is Important in Heart Disease: Taking Heredity to Heart



We all have genetic predispositions

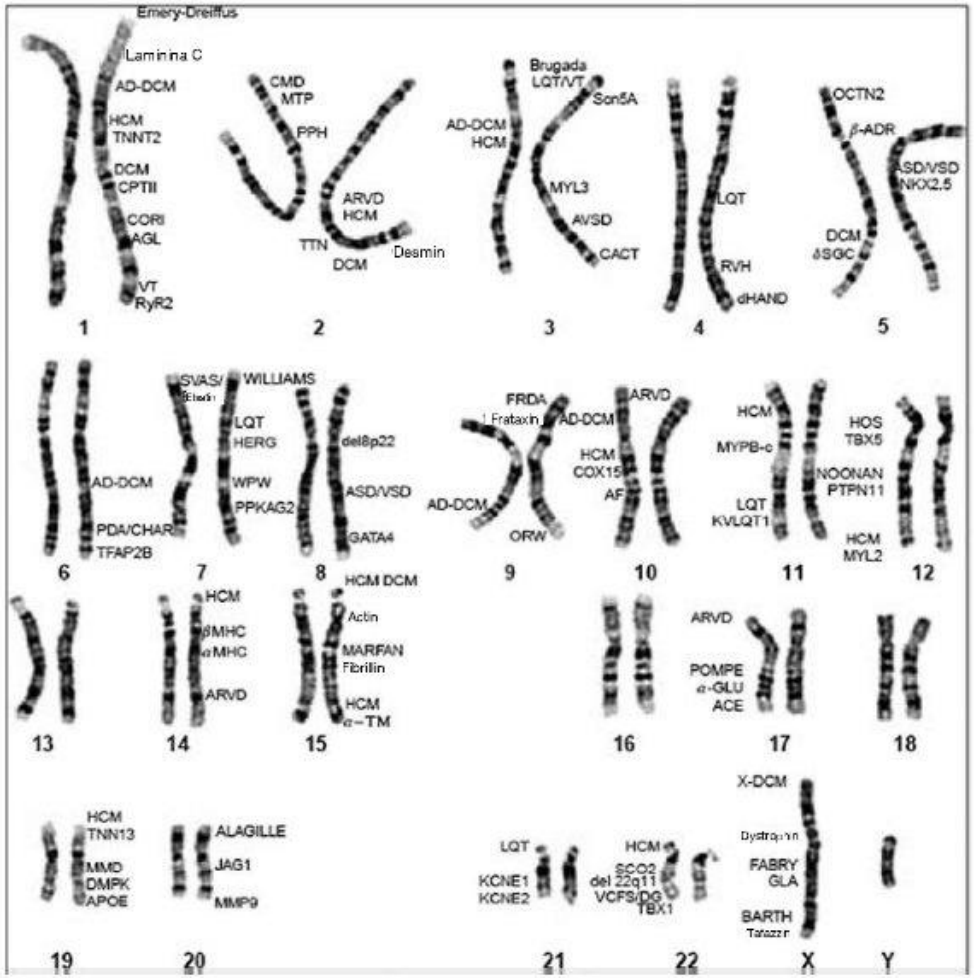


Some genes associated with sudden cardiac death: This image of human chromosomes shows the genes known to be responsible for several inherited conditions that can cause arrhythmias. The name of the condition is followed by the gene abbreviation, indicated in parentheses. See page 3 for full condition 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)

Common Inherited Forms of Heart Disease

- Arrhythmias (isolated and syndromic)
  - Long QT syndrome (LQTS)
  - Brugada syndrome
  - Catecholaminergic polymorphic ventricular tachycardia (CPVT)
  - Familial atrial fibrillation
- Cardiomyopathies (isolated and syndromic)
  - Dilated cardiomyopathy (DCM)
  - Hypertrophic cardiomyopathy (HCM)
  - Restrictive cardiomyopathy (RCM)
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC)
  - Left ventricular noncompaction (LVNC)
- Aneurysm syndromes
  - Familial thoracic aortic aneurysm and dissection syndromes
  - Marfan, Loeys-Dietz, and other connective tissue disorders
- Familial coronary artery disease and dyslipidemias
- Congenital heart disease

Genetic markers of CHDs and other heritable heart diseases



CHDs are caused by

- Chromosome abnormalities
- Microdeletion/duplication syndromes
- Single gene disorders (syndromic and nonsyndromic)
- Somatic mutations?
- Others?
  - The cause for most nonsyndromic CHDs remains unknown – future research utilizing next-generation DNA sequencing may provide more accurate genetic risk information

Clin Genet 2010, *Ann NY Acad Sci* 2010, *Rev Esp Cardiol* 2009

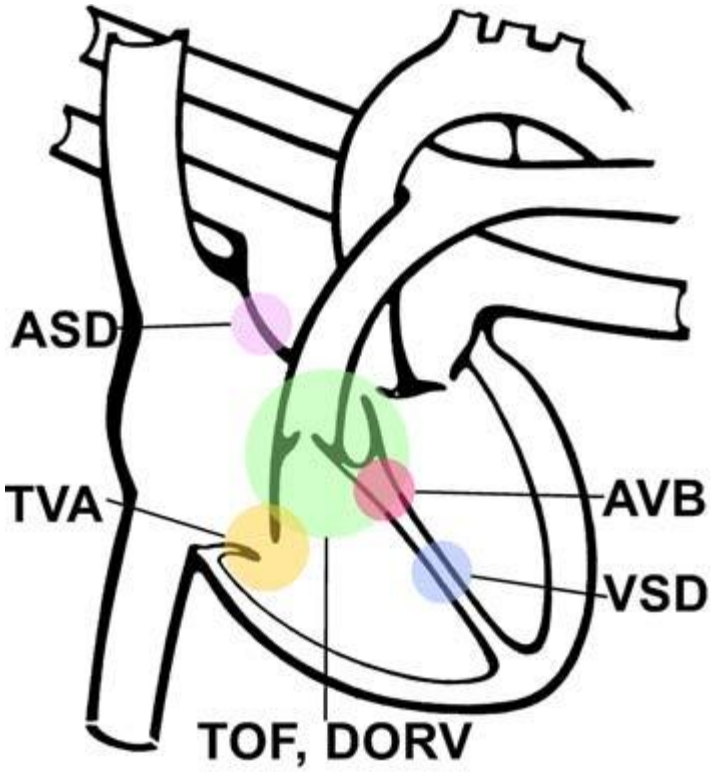
Congenital heart defects (CHDs)

- The most common group of birth defects
  - Account for ~25% of all birth defects
  - CHDs affect ~36,000 children each year in the U.S.
- Multiple studies show CHDs have
  - High heritability
  - Increased recurrence risks (RR)
    - The overall RR of nonsyndromic CHDs is ~2-10%
- A search of the Online Mendelian Inheritance in Man (OMIM) database reveals that the number of genetic syndromes with cardiac involvement is greater than 1300

J Clin Exp Cardiolog 2012,*Clin Genet* 2010

Mutations in the same gene can be associated with diverse cardiac phenotypes

- Prime example: *NKX2.5* gene



Pediatr Cardiol 2010

Cardiac Disorders Predisposing to SCA

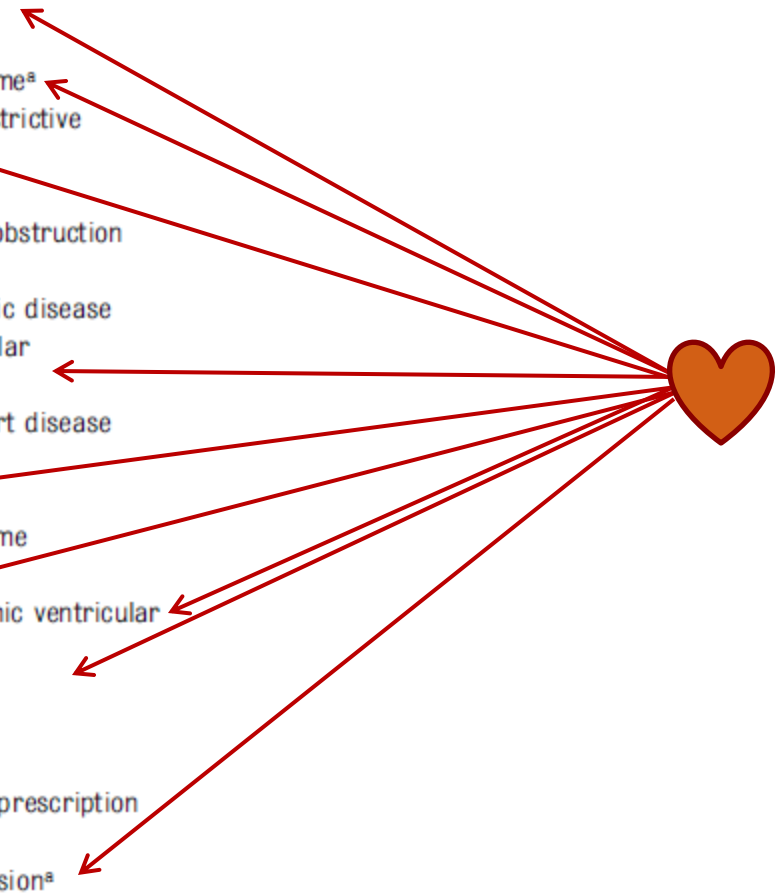
TABLE 1 Cardiac Disorders Predisposing to Pediatric and Young Adult SCA

Structural/functional
1. Hypertrophic cardiomyopathy[a]
2. Coronary artery anomalies
3. Aortic rupture/Marfan syndrome[a]
4. Dilated cardiomyopathy or restrictive cardiomyopathy[a]
5. Myocarditis
6. Left ventricular outflow tract obstruction
7. Mitral valve prolapse
8. Coronary artery atherosclerotic disease
9. Arrhythmogenic right ventricular cardiomyopathy[a]
10. Postoperative congenital heart disease

Electrical
11. LQTS[a]
12. Wolff-Parkinson-White syndrome
13. Brugada syndrome[a]
14. Catecholaminergic polymorphic ventricular tachycardia[a]
15. Short QT syndrome[a]
16. Complete heart block

Other
17. Drugs and stimulants; some prescription medications
18. Primary pulmonary hypertension[a]
19. Commotio cordis

[a] Familial/genetic.



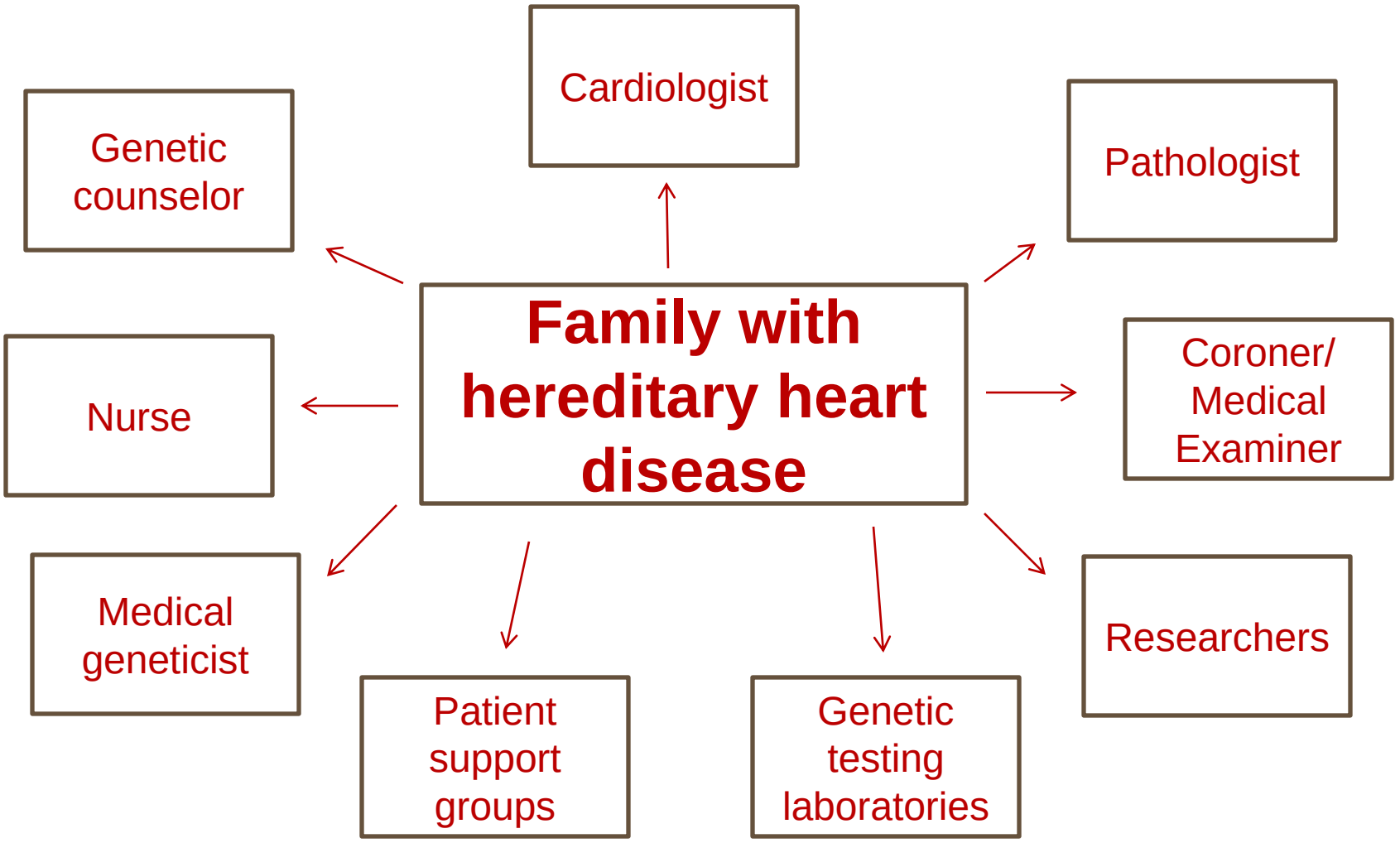
Familial/ Genetic

AAP Policy Statement 2012

Cardiovascular Genetic and Genomic Medicine Program

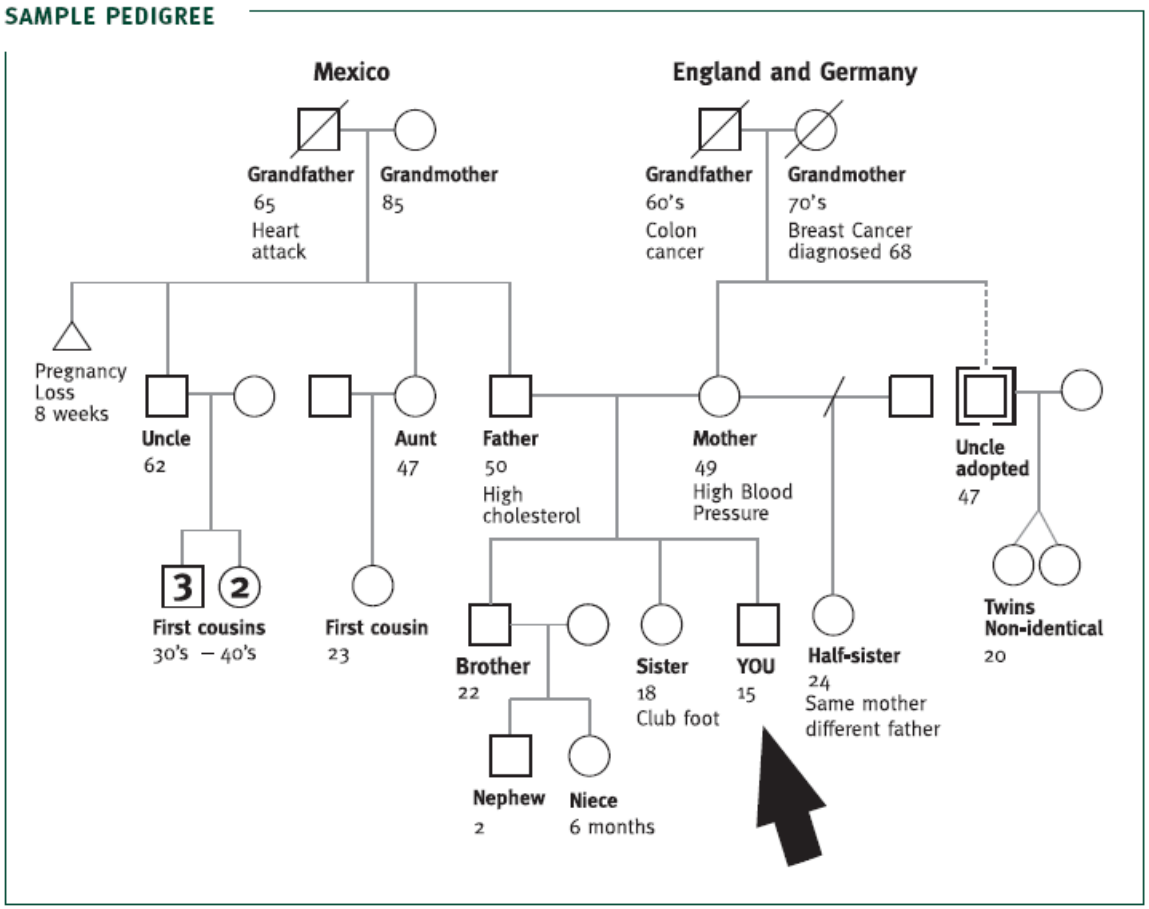
- **Comprehensive, multidisciplinary program at the Richard M. Ross Heart Hospital**
- **CV Genetic and Genomic Medicine Clinic**
  - **Dr. Ray Hershberger**
  - Multidisciplinary clinic for cardiomyopathies, familial hypercholesterolemia, aortopathies, congenital heart disease, others
- **Inherited Arrhythmia Clinic**
  - **Dr. Raul Weiss**
  - Multidisciplinary clinic for genetic types of arrhythmias
- **To schedule an appointment, please call 614-293-6694**

Specialized Multidisciplinary CV Genetic and Genomic Medicine Clinic Model



Adapted from Semsarian and Hamilton *Heart Rhythm* 2012 and Ingles et al *Heart Rhythm* 2011

Taking an Informative Pedigree
Essential Tool for CV Genetic Medicine



- ≥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. syncope)

Family history is imperative in:

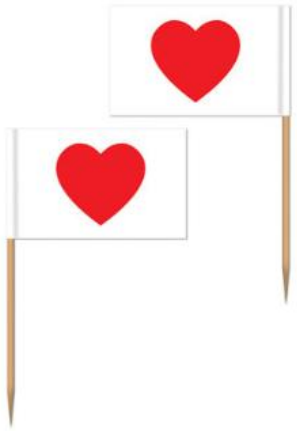
1) aiding diagnosis
2) determining inheritance pattern
3) identifying at-risk relatives
4) selecting the most informative family member for genetic testing initiation

A Few General Rules of Thumb

- ***Most*** Inherited Cardiovascular Conditions
  - Relatively common diseases
    - **Younger** age of onset
    - More **severe**
  - Autosomal dominant
    - However…pedigree may not look dominant
    - Phenotype may not be in every generation
    - Lack of additional diagnoses in family even when genetic due to
      - Reduced penetrance
      - Smaller family sizes
      - Variable expression of signs and symptoms

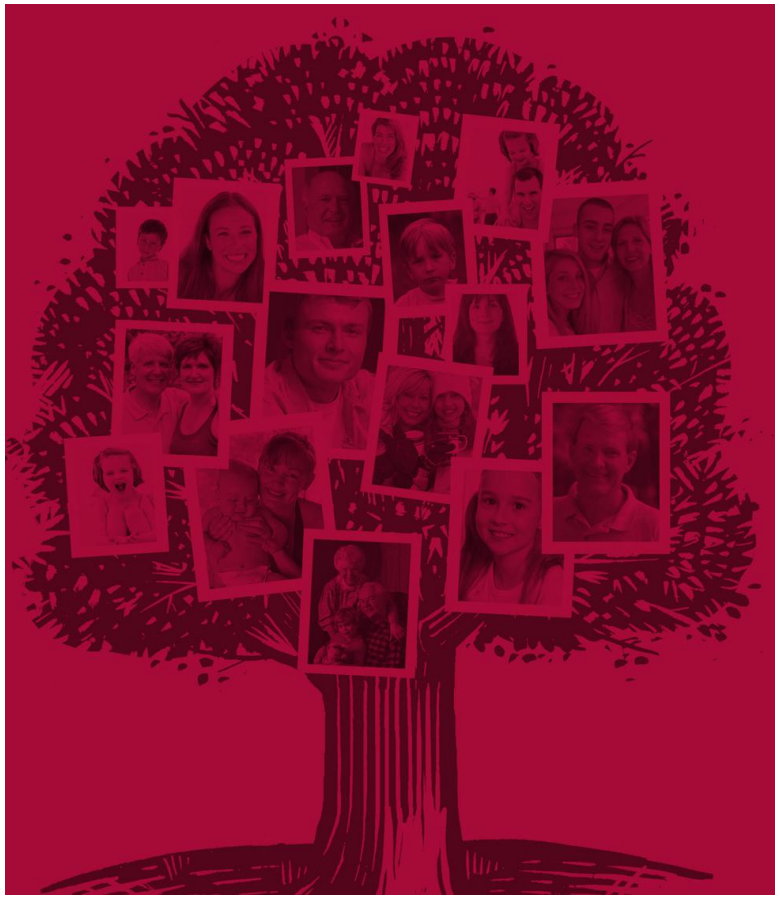
Family History Red Flags

- "Heart attack", <55 yrs men, <65 yrs women
  - Arrhythmia, aortic dissection, cardiomyopathy, early onset CAD
- Sudden death, unexplained & accidental (drowning, unexplained single MVA)
  - Arrhythmia, aortic dissection, cardiomyopathy, early onset CAD
- Syncope or pre-syncope
  - Arrhythmia, cardiomyopathy
- Exercise intolerance
  - Arrhythmia, cardiomyopathy
- Heart transplantation
  - Cardiomyopathy
- Heart failure <60 yrs
  - Cardiomyopathy
- Multiple family members with pacemakers and/or ICDs
  - Arrhythmia, cardiomyopathy
- Sudden Infant Death Syndrome (SIDS)
  - Emerging data suggests ~10-15% of SIDS deaths are associated with mutations in several genes associated with cardiac ion channelopathies
- Seizures



CV Genetic/Genomic Medicine Consultation

- Medical history
- Family history
  - Collection and review of family members' medical records, autopsy reports, etc.
- Physical examination
  - Cardiologist, electrophysiologist, medical geneticist
- Risk assessment
- Education
- Genetic and genomic testing options – now MANY!
  - Informed consent, discussion of possible results, sample collection, insurance preauthorization
- Genetic test result interpretation and disclosure
- Screening/management recommendations

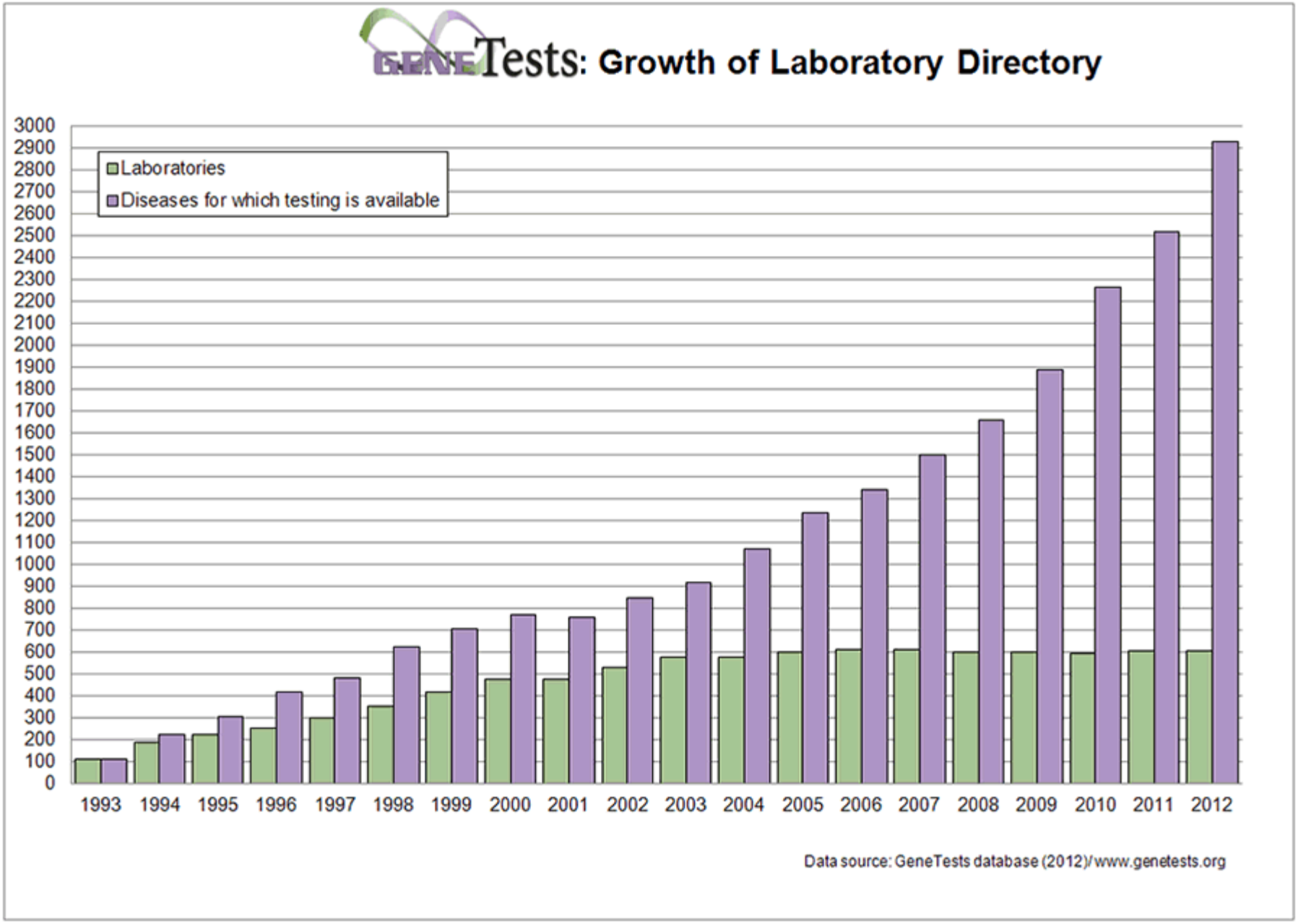


Additional Services

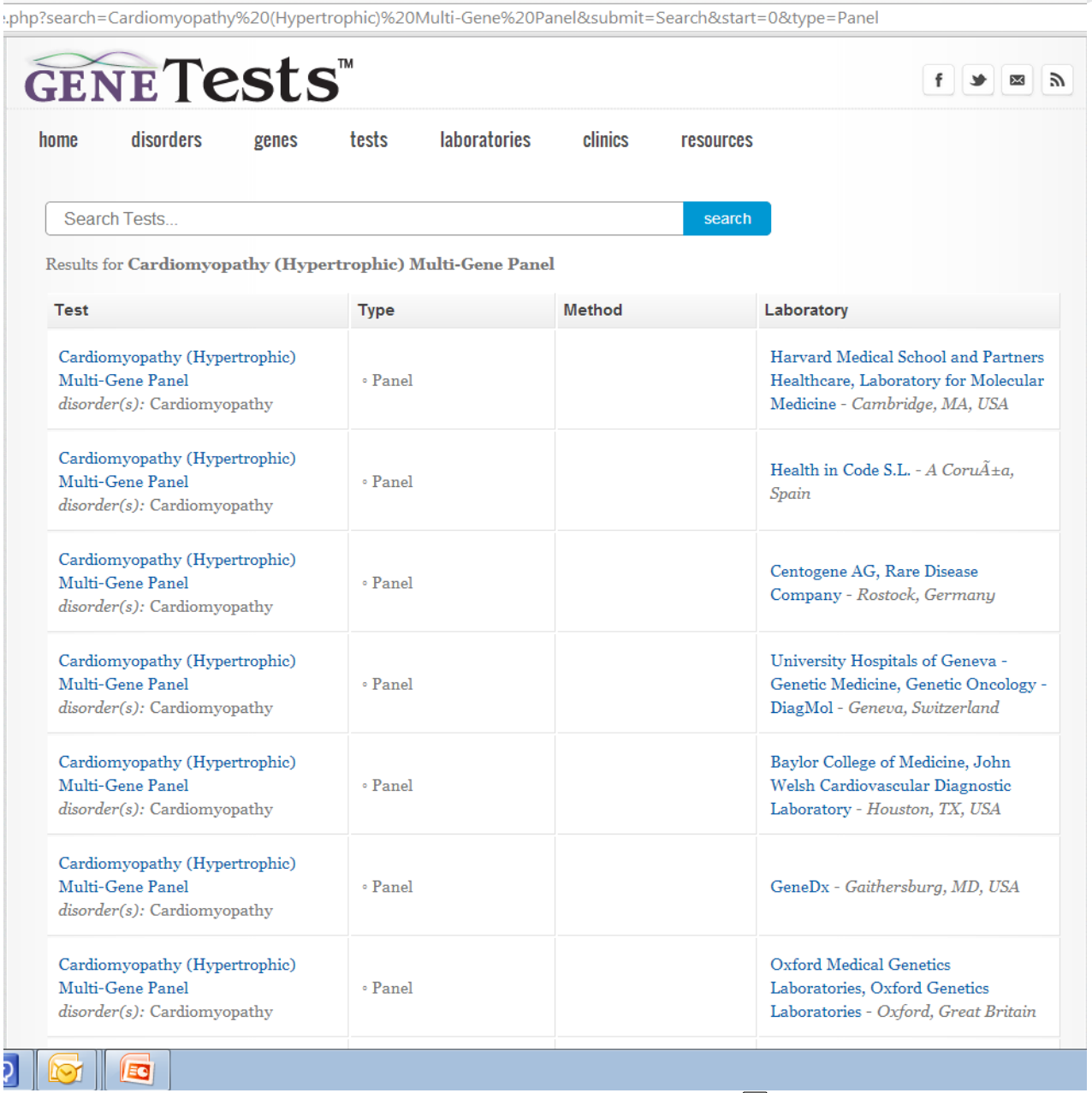
- Psychosocial counseling and anticipatory guidance for issues related to hereditary disease, genetic testing results, etc.
- Referral to support groups and advocacy organizations
- Connection with families with the same condition
- Coordination of DNA banking for future use of patients, families and possibly researchers
- Discussion of available genetics research study options
- Evaluation of at-risk family members

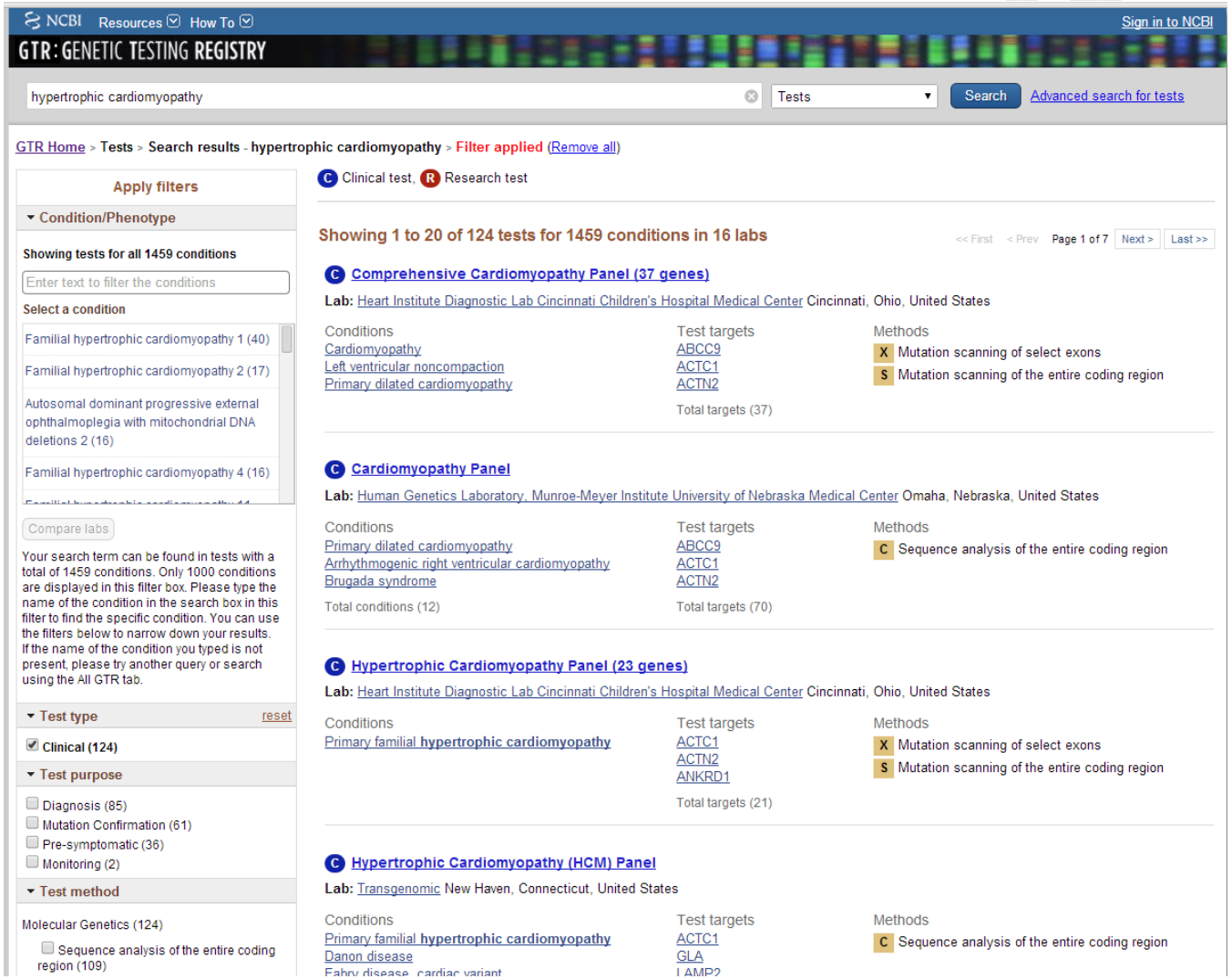
Cascade genetic testing and clinical screening

Genetic testing


GeneTests: Growth of Laboratory Directory
Laboratories
Diseases for which testing is available
3000
2900
2800
2700
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012
Data source: GeneTests database (2012)/www.genetests.org

Genetests.org





GTR:
Genetic Testing Registry
http://www.ncbi.nlm.nih.gov/gtr/

Genetic and Genomic Testing Advances

- Next-generation DNA sequencing
  - Rapid analysis of large panels of disease-specific genes
- “Design Your Own” Panels
  - 1,000 genes for $1,000
- Pan Cardio Panels (~80 genes)
- Cardiomyopathy Panels (>70 genes)
- Arrhythmia Panels (>30 genes)
- Whole exome sequencing
  - Information on coding sequence of all ~24,000 genes
  - Clinically available and have ordered on several patients now
- Whole genome sequencing

Ending the diagnostic odyssey, with and without treatment ramifications

Doctors Sift Through Patients' Genomes To Solve Medical Mysteries

by ROB STEIN

Listen to the Story
Morning Edition [7 min 49 sec]
Add to Playlist
Download
Transcript

Eric Kayne for NPR

Sara Terry and her son, Christian, in Spring, Texas. After sequencing Christian's genome, doctors were able to diagnose him with a Noonan-like syndrome.

Sara Terry's first clue that something was wrong with her son, Christian, came just three weeks after he was born.

"We went to check on him, just like any parents go and check on their kids just to make sure they're breathing," says Terry, 34, of Spring, Texas. "And we found him in his crib, and he wasn't breathing. He was blue."

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North County Twins Cured After Whole Genome Sequencing

By Chris Chan | Saturday, Aug 25, 2012 | Updated 11:03 AM PDT

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North County twins Alexis and Noah Beery have seen a drastic improvement in their health since they underwent genetic testing. NBC 7's Chris Chan speaks to the twins, as well as their parents Retta and Joe Beery.

Exome Analysis of a Family With Pleiotropic Congenital Heart Disease

Cammon B. Arrington, MD, PhD; Steven B. Bleyl, MD, PhD; Norisada Matsunami, MD, PhD; Gabriel D. Bonnell, BS; Brith E.M. Otterud, BS; Douglas C. Nielsen; Jeffrey Stevens, BS; Shawn Levy, PhD; Mark F. Leppert, PhD; Neil E. Bowles, PhD

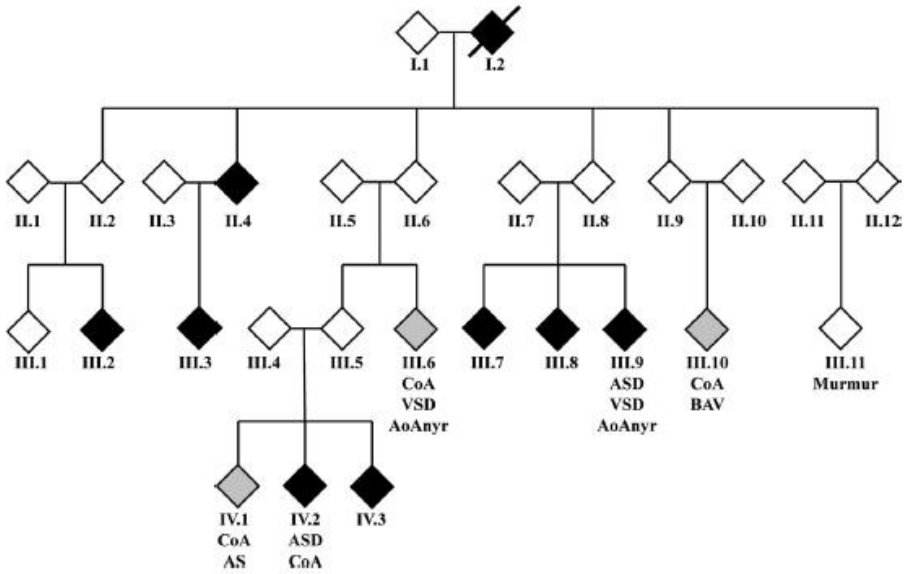

Figure. Family K100165. The gender of family members is not indicated. Black symbols represent patients with ASD or complex phenotypes that include ASD. Gray symbols represent patients with CHD but without ASD. Patient III.11 was diagnosed with a murmur as a child but has not had an echocardiogram to rule out the presence of an ASD and has not experienced any cardiac-related health issues. ASD indicates atrial septal defect; CHD, congenital heart defect; CoA, coarctation of the aorta; VSD, ventricular septal defect; BAV, bicuspid aortic valve; AS, aortic stenosis.

- DNA from two family members were analyzed by WES
- >2000 rare variants were shared
- Of these, 55 were predicted to affect a protein
- None completely segregated with CHD
- MYH6 Ala290Pro was identified in all but one affected individual

Circ Cardiovasc Genet 2012