Genomic Medicine in Advanced Heart Failure

Brian D. Lowes, MD PhD

7/8/2014

Conflicts of Interest: None

Goals/Objectives

- Discuss inherited cardiomyopathies and describe their genetics
- Understand current options, strategies, and limitations for genetic testing
- Integrate this knowledge into diagnostic and treatment protocols to improve the care of patients and their families

Prometheus: Greek Mythology

- "Or, like the thief of fire from heaven,
  Wilt thou withstand the shock?
  And share with him- the unforgiven-
  His vulture and his rock?"

SUPREME COURT OF THE UNITED STATES

Syllabus

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, ET AL. *v.* PROMETHEUS LABORATORIES, INC.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 10–1150. Argued December 7, 2011—Decided March 20, 2012

"we conclude that the patent claims at issue here effectively claim the underlying laws of nature themselves. The claims are consequently invalid. And the Federal Circuit's judgment is reversed.

It is so ordered.

Patent on measuring metabolites of thiopurine drugs

SUPREME COURT OF THE UNITED STATES

Syllabus

ASSOCIATION FOR MOLECULAR PATHOLOGY ET AL.
v. MYRIAD GENETICS, INC., ET AL.
CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT
No. 12–398. Argued April 15, 2013—Decided June 13, 2013

"We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material.

For the foregoing reasons, the judgment of the Federal Circuit is affirmed in part and reversed in part. "

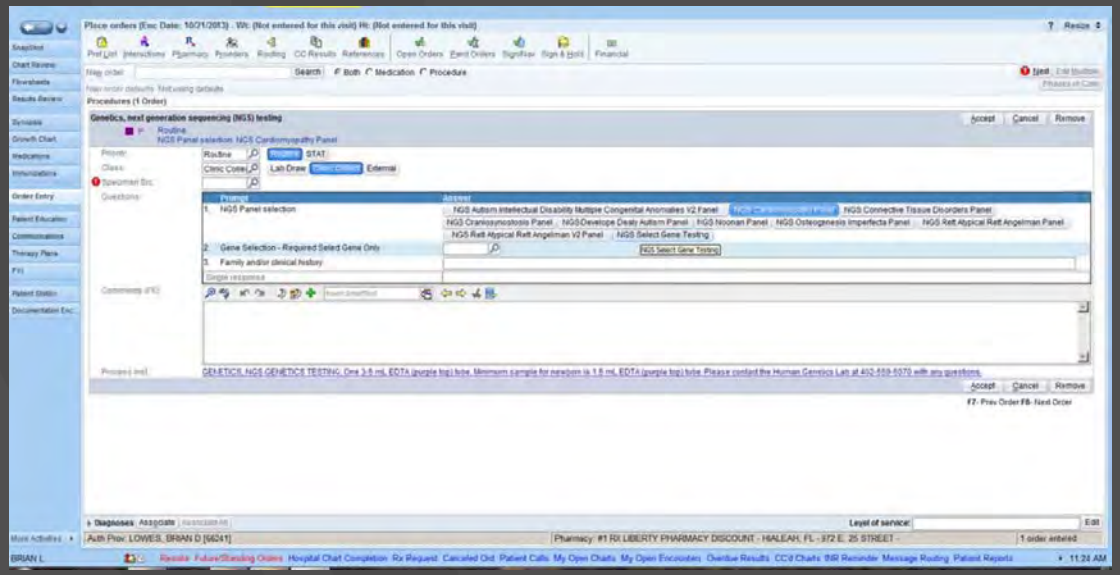
It is so ordered.

Myriad 14 patents on BRCA1/2 genes

Genetics of Cardiomyopathies

- Historically: Testing was expensive, limited to a few genes, interpretation and application of the results was difficult.
- 2013: Rapidly sequence a persons genome at a reasonable cost. Informatics are fundamentally altering our ability to gather, interpret and apply genetic information.

The Future is Now



UNIVERSITY OF NEBRASKA MEDICAL CENTER

HUMAN GENETICS LABORATORY
MUNROE-MEYER INSTITUTE FOR GENETICS AND REHABILITATION
985440 Nebraska Medical Center | Omaha, NE 68198-5440 | 402-559-5070

www.unmc.edu/geneticslab

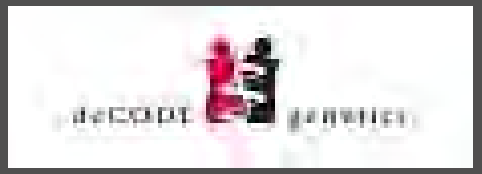
Next Generation Sequencing Report

Result Information:
Order #: 13-2677 NGS Cardiomyopathy panel
Reason for Referral: Cardiomyopathy
INTERPRETATION:

Pathogenic mutation detected in the *LMNA* gene.
Please see detailed interpretation below.

Gene	Chrom	Amino Acid Chg	Nucleotide Chg	NGS Result
LMNA	chr1	NP_733821.1:p.Glu161Lys	NM_170707:c.481G>A	Pathogenic

Genetic Testing



Loss of Function Variants are Common

- Loss of function variants: mutations that are predicted to cause severe disruption in protein coding genes (stop codons, splice, frame shift indel, large deletions..)
- Healthy individuals typically contain between 100 LOF variants

MacArthur et al Science 2012

FDA and 23andMe

- Warning letter: 23andMe failed to supply any indication that it had analytically or clinically validated the PGS for its intended uses

Anna et al NEJM 2014

Clinical Case 1

- 28 y/o male who is referred for f/u from the emergency room
- Previously well, presented to the ER with palpitations that were noticed to be paroxysmal atrial fibrillation
- Dad has a dilated cardiomyopathy and is listed for heart transplant

What to Do?

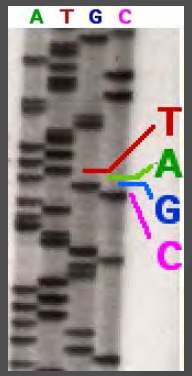
- Event Monitor
- Cardiac MRI
- Next Generation Sequencing for Cardiac Genes (on who?)
- Genetic Counselor
- Ask for more history
- Do nothing

More History

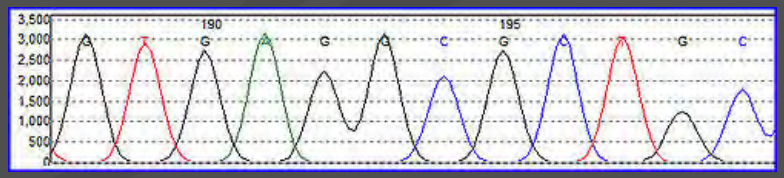
- Dad presented in his 30's with atrial fibrillation, developed a dilated cardiomyopathy and frequent ventricular tachycardia and required a LVAD and heart transplant.
- Dad has a heterozygous nucleotide change (c.481G>A) in exon 2 of the LMNA gene. This nucleotide change predicts an amino acid change from glutamine to lysine (p.E161K) resulting in a missense mutation.

Ask your doctor

History Of DNA Sequencing



- Late 1970's
  - **Maxam-Gilbert Sequencing** – terminally labeled DNA fragments, base-specific cleavage separated by gel-electrophoresis
  - **Sanger Sequencing: Frederick Sanger, 2 nobel prizes in chemistry, 1918-2013**
    - fluorescent labels, capillary gel electrophoresis
    - Predominant DNA sequencing technology for the next 30 years
    - Is still the gold-standard for routine day-to-day molecular diagnostic sequencing
    -Routinely used for sequencing of DNA fragments in a variety of molecular biological research contexts

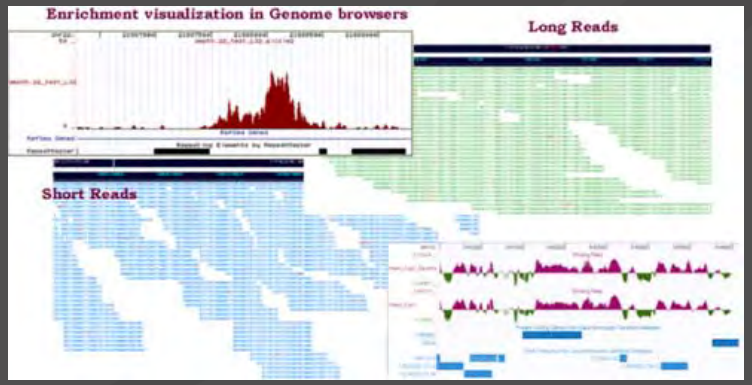


Background: Human Genome Project

- 2003 – First Human Genome Sequenced
  - Sanger Sequencing: Applied Biosystem (ABI) capillary sequencers
  - Time Frame: 1990 – 2003
  - Cost: ~ 2.7 billion dollars

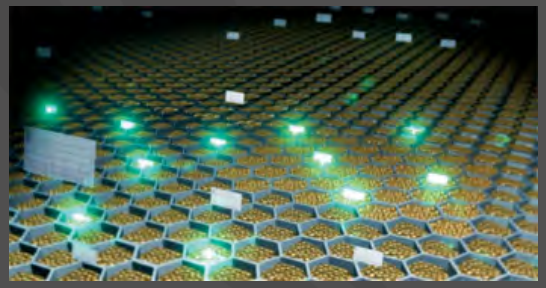
Next Generation Sequencing of Whole Genome

- 2008- First human genome by NGS
  - Time – 5 months
  - Cost – 1.5 million dollars
  - Many individual human genomes sequenced since then in a variety of contexts using NGS.
  - 2011 –6k dollars, 10 days
  - 2013 – 1k dollars, 2-3 day

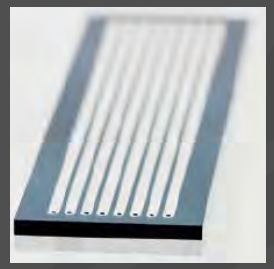


Next Generation Sequencing Platforms

- Massive Parallel Sequencing of Clonal Amplified DNA Fragments – millions
- Output are millions of short reads (relative to Sanger sequencing) of DNA sequence
- Clonal Amplified Fragments Spatially Separated – all fragments sequenced simultaneously

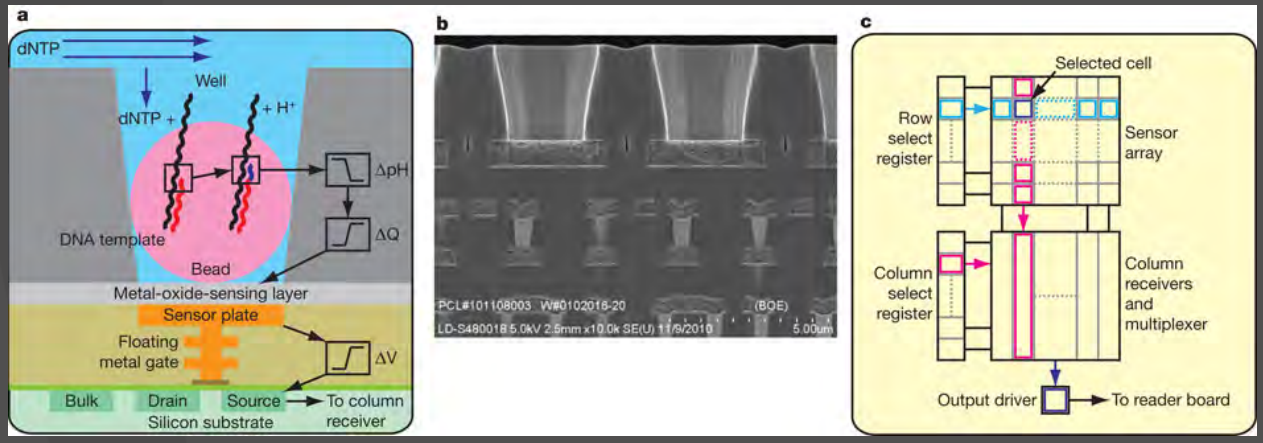


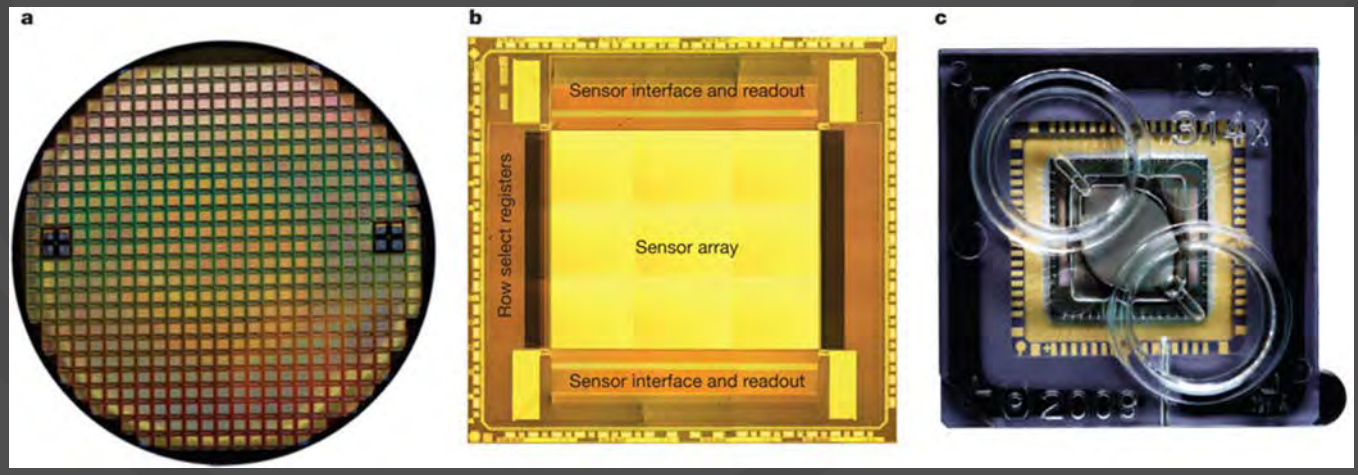
Roche 454 microtiter plate



Illumina flow cell

Semi-conductor Devices Enabling non-optical Genome Sequencing





JM Rothberg *et al. Nature* **475**, 348-352 (2011) doi:10.1038/nature10242

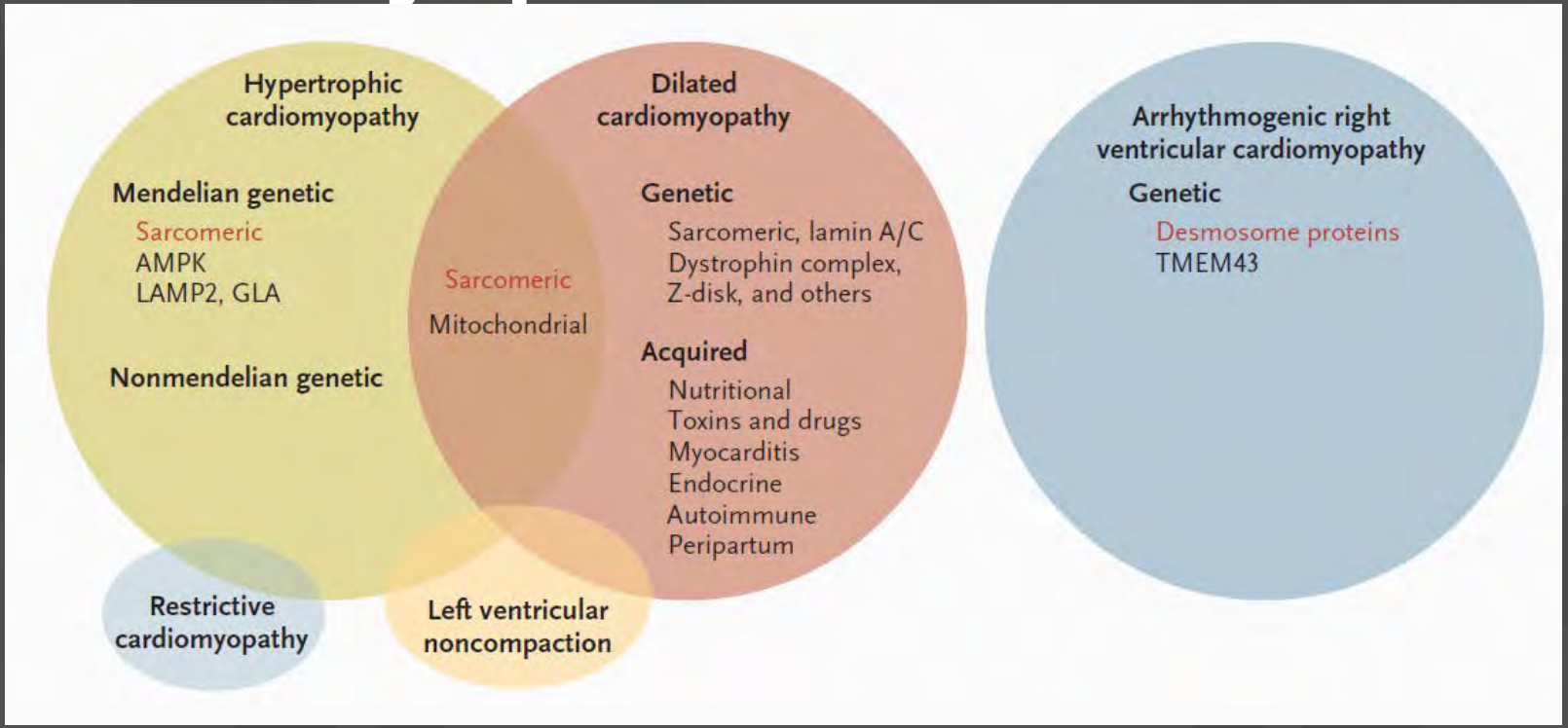
What are the Cardiomyopathies?

- "Cardiomyopathy" first used 1957
- WHO 1980: "Heart muscle disease of unknown etiology"
- **AHA 2006: "**Cardiomyopathies are diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy, or dilation and are due to a variety of causes that frequently are genetic."

Not Everything is Genetic "Acquired Cardiomyopathies"

- Differential Dx Heart Failure:
  - Coronary artery disease, valvular, myocarditis, hypothyroidism, stress-induced, etoh, brain injury, nutritional deficiency (beri-beri), chemotherapy, heavy metals…..
  - 5 Classes of Genetic Cardiomyopathies

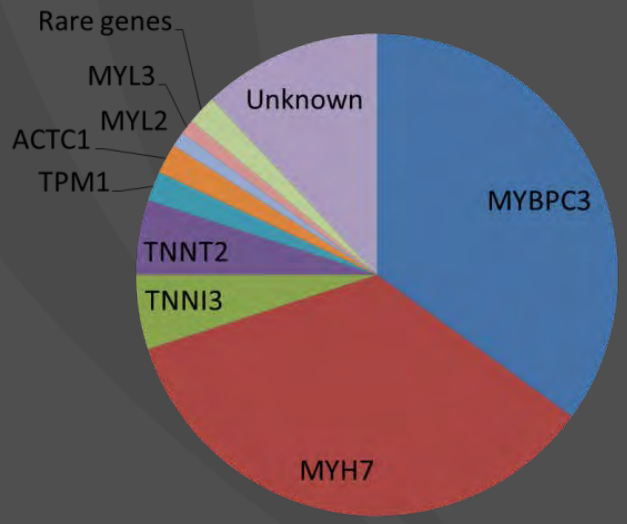
What are the Inherited Cardiomyopathies?

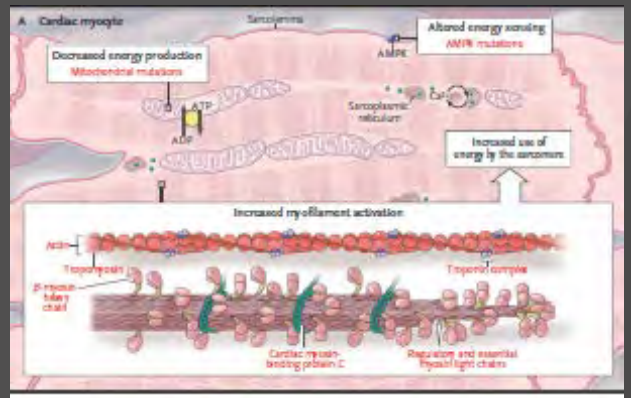


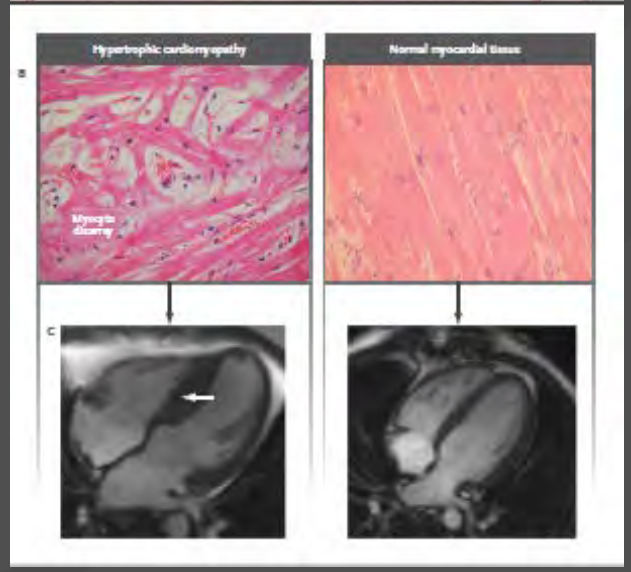
Watkins et al NEJM 2011

Hypertrophic Cardiomyopathies

Prevalence 1/500

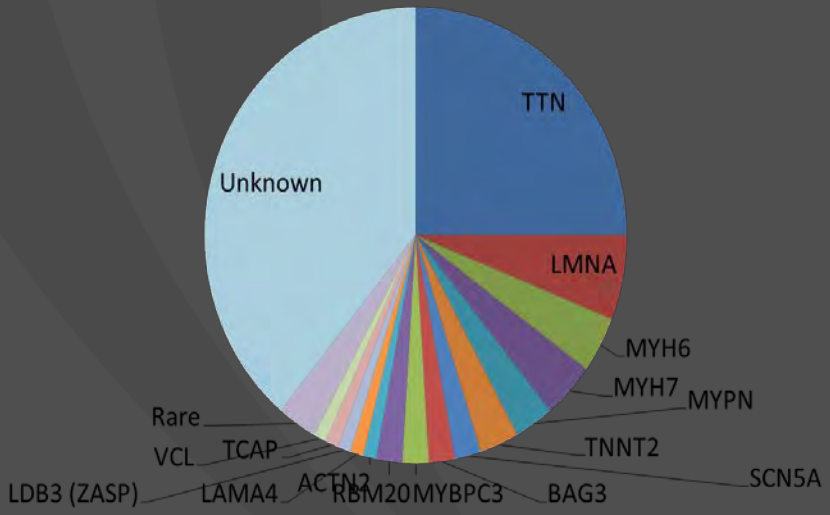


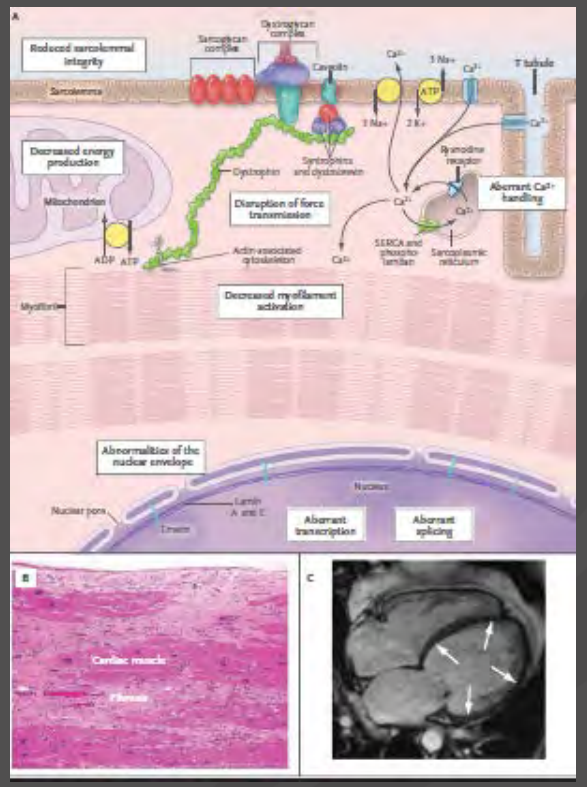




Dilated Cardiomyopathies

Prevalence 1/1000





Watkins et al NEJM 2011

Dilated Cardiomyopathies and Advanced HF in Nebraska

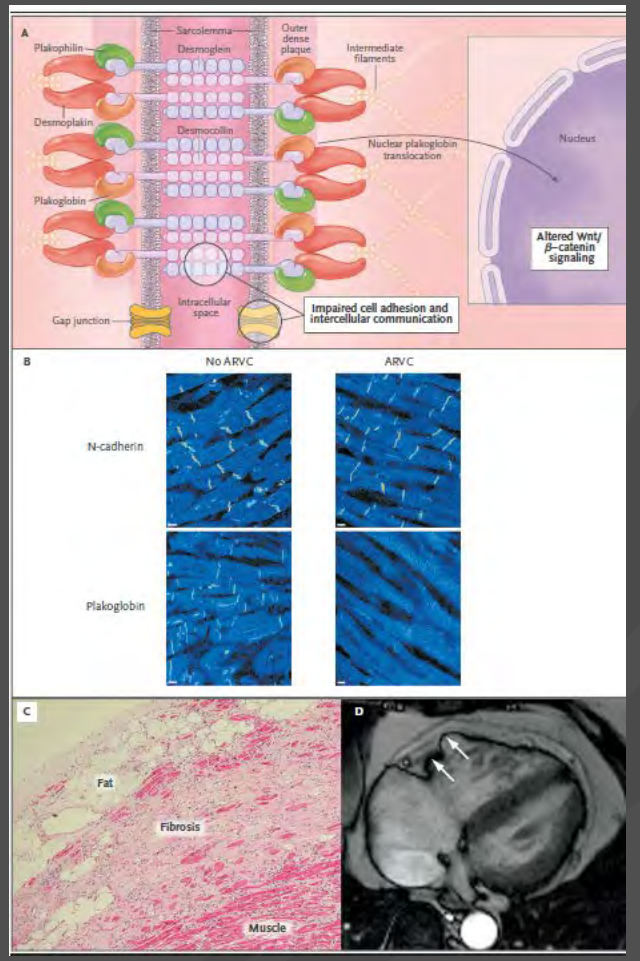
Cardiac Gene	Prevalence	Mutation Type
DSC2	1/10	N
SCN5A	2/10	2 NA
RYR2	1/10	NA
MYH7	1/10	S
DSG2	1/10	N
STARD3	1/10	D
DES	1/10	D
MYH6	1/10	N
AKAP9	1/10	D
MSH2	1/10	D

7 males and 3 females with an average age of 52 and an average EF at presentation of 15%.
11 damaging or disease associated mutations in 10 genes. Damaging cardiac gene mutations were present in 9/10 patients.

N – Polymorphism, D – Disease causing, F- Frameshift, S – Splice, NA – No prediction

ARVC

- ***ARVC***
- **PKP2** **11-43%**
- **DSG2** **12-40%**
- **DSP** **6-16%**
- Rare/Less than 1%:
- DES DSC2
- LMNA PLN
- RYR2 TGFB3
- JUP TMEM43
- TTN
- *EJHG 2013 e1-e4*
- *Gene Reviews*



Watkins et al NEJM 2011

Other Cardiomyopathies

- ***LVNC***
- (% unclear)
- ACTC1 CASQ2
- DTNA LDB3(ZASP)
- LMNA MYBPC3
- MYH7 TAZ
- TNNT2 VCL
- *J Mol Diagn 2013, 15:158-170*

- ***Restrictive Cardiomyopathy***
- (Rare, % unclear)
- ACTC1 DES
- MYPBC3 MYH7
- MYL2 MYL3
- MYPN TNNI3
- TNNT2 TPM1
- *J Mol Diagn 2013, 15:158-170*
- *AJMG 2011, 155(9):2229-2235*

Next Generation Sequencing Cardiomyopathy Panel

ABCC9	*DSG2*	*LAMP2*	*RYR2*
ACTC1	*DSP*	*LDB3 (ZASP)*	*SCN1B*
ACTN2	*DTNA*	*LMNA*	*SCN4B6*
AKAP9	*EYA4*	*MYBPC3*	*SCN5A*
ANK2	*FHL1*	*MYH6*	*SGCD*
ANKRD1	*FHL2*	*MYH7*	*SNTA1*
BAG3	*FKTN*	*MYL2*	*TAZ*
CACNA1C	*GLA*	*MYL3*	*TCAP*
CACNB2	*GPD1L*	*MYLK2*	*TGFB3*
CALR3	*JPH2*	*MYOZ2*	*TMEM43*
CASQ2	*JUP*	*MYPN*	*TNNC1*
CAV3	*KCNE1*	*NEXN*	*TNNI3*
CRYAB	*KCNE2*	*PKP2*	*TNNT2*
CSRP3	*KCNE3*	*PLN*	*TPM1*
CTF1	*KCNH2*	*PRKAG2*	*TTN*
DES	*KCNJ2*	*PSEN1*	*TTR*
DMD	*KCNQ1*	*PSEN2*	*VCL*
DSC2	*LAMA4*	*RBM20*	

Nebraska NGS Panel
Covered Cardiac Disorders

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- LV non-compaction
- Restrictive cardiomyopathies
- Arrhythmogenic RV dysplasia
- Long-QT syndromes, Brugada syndrome, catacholminergic polymorphic ventricular tachycardia, familial amyloidosis…

Case: Event Free Survival in Lamin A/C Carriers

- Cohort of 269 patients who carry Lamin mutations
- Risk factors for malignant arrhythmias:
  - Male
  - LVEF < 45%
  - Nonsense mutations
  - Nonsustained ventricular tachycardia

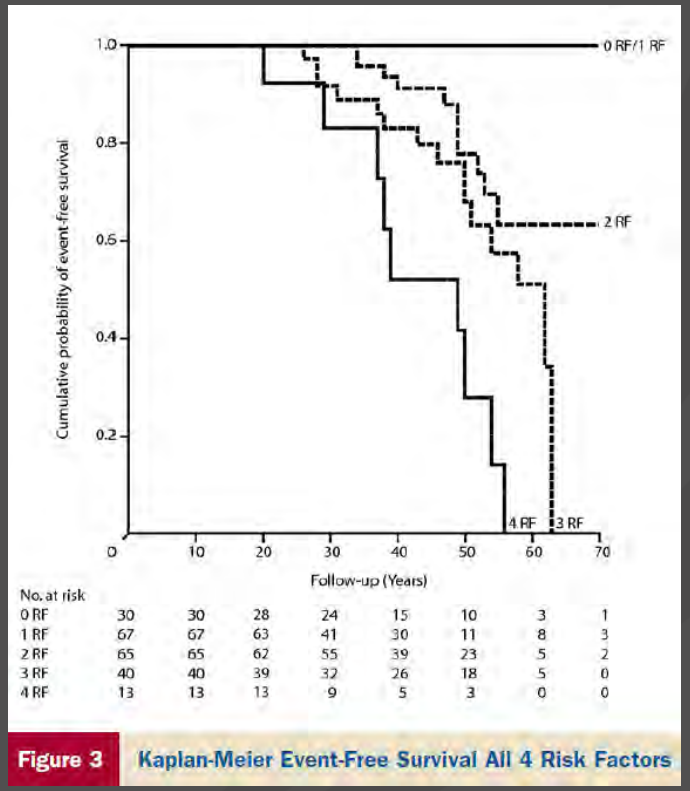


Figure 3 Kaplan-Meier Event-Free Survival All 4 Risk Factors

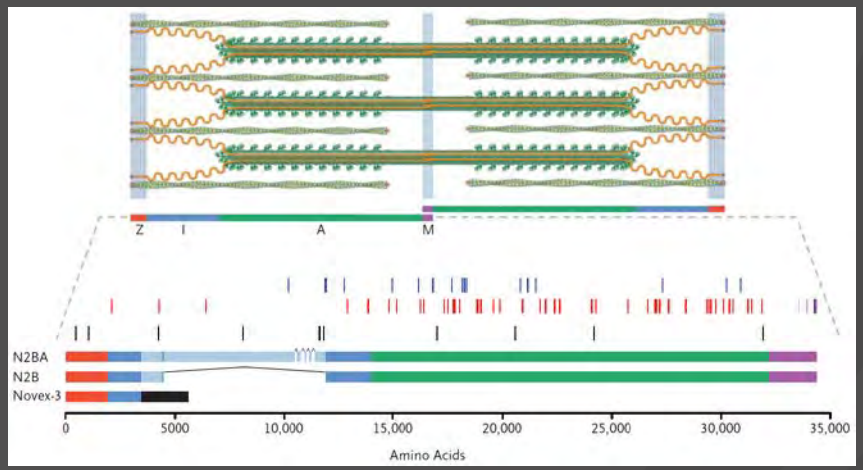
Rijsingen et al JACC 2013

Clinical Case 2

- 36 y/o with a dilated cardiomyopathy referred for heart transplantation
- Mom, uncle and a cousin all have a dilated cardiomyopathies
- Just married, wants to have kids…
- Titan mutation of “unknown clinical significance”

Limitation: Uncertainty

- " the c.7501C>T mutation has not been previously reported but is predicted to cause premature truncation of the protein product." (A nonsense mutation)
- Mutations are often "private", only exist within a family



Titan: Largest protein
72 unique mutations described

Herman et al NEJM 2012

Mutation Classification

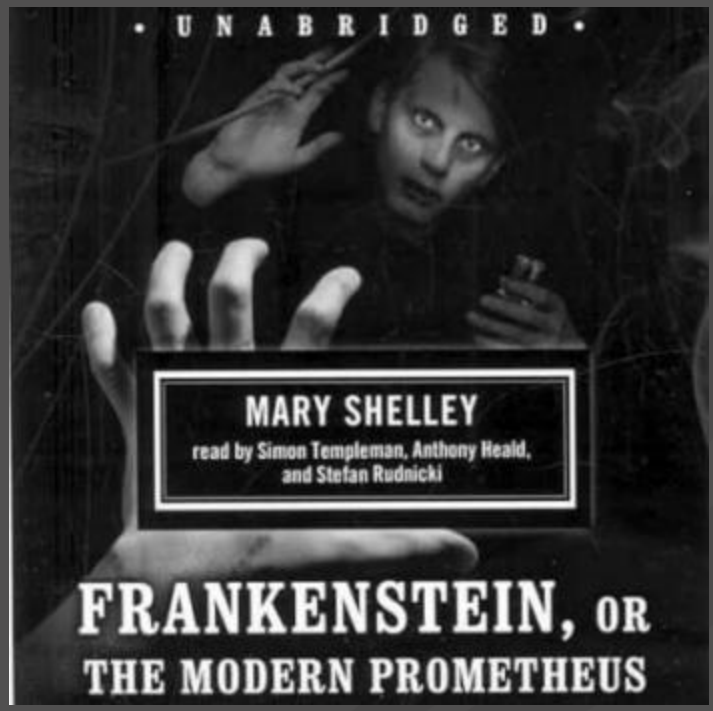
- American College of Medical Genetics
- Reporting: Pathogenic, UCS-likely pathogenic, UCS, UCS-likely benign, Benign
  - minor allele frequencies (MAF)obtained from ~7,500 genomes(1000 from the 1000 Genome Project and 6,500 from the Exome Sequencing Project)
  - in silico prediction models (“SIFT” and “Polyphen”)
  - database searches (LOVD, Emory, HGMD, UniProt (Universal Protein Resource) Knowledgebase…some genes have their own database as well)
  - literature searches
  - amino acid change effects
  - clinical correlation

Computing and Informatics

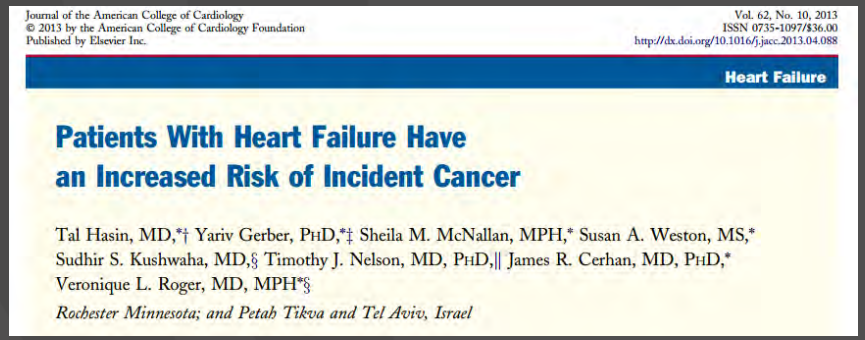
- Tianhe-2
  - 34,000 trillion calculations/second
  - World's fastest computer

Limitations: Too Much Information

- PSEN1 and PSEN2 mutations account for about 1% of dilated cardiomyopathy patients
- Mutations in these genes can also give you early onset Alzheimer's disease
- Familial testing and questions of parentage



Cardio-Oncology



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Heart Failure

Patients With Heart Failure Have an Increased Risk of Incident Cancer

Tal Hasin, MD,*† Yariv Gerber, PHD,*‡ Sheila M. McNallan, MPH,* Susan A. Weston, MS,* Sudhir S. Kushwaha, MD,§ Timothy J. Nelson, MD, PHD,‖ James R. Cerhan, MD, PHD,* Veronique L. Roger, MD, MPH*§

Rochester Minnesota; and Petah Tikva and Tel Aviv, Israel

- 9,203 patient years of f/u
- 244 new cancer cases
- Heart failure patients have 68% higher incidence of cancer

Oncogene Variants in Advanced Heart Failure

Damaging oncogene variants are common in the advanced heart failure population

Cancer Gene	Prevalence	Sample – Mutation
NSD1	1/8	N
BTK	1/8	F
WRN	2/8	2 NA
MLH1	1/8	D
FANCG	1/8	F
MYH11	1/8	D
NF1	1/8	F
RET	1/8	D
APC	1/8	D
FANCA	1/8	N

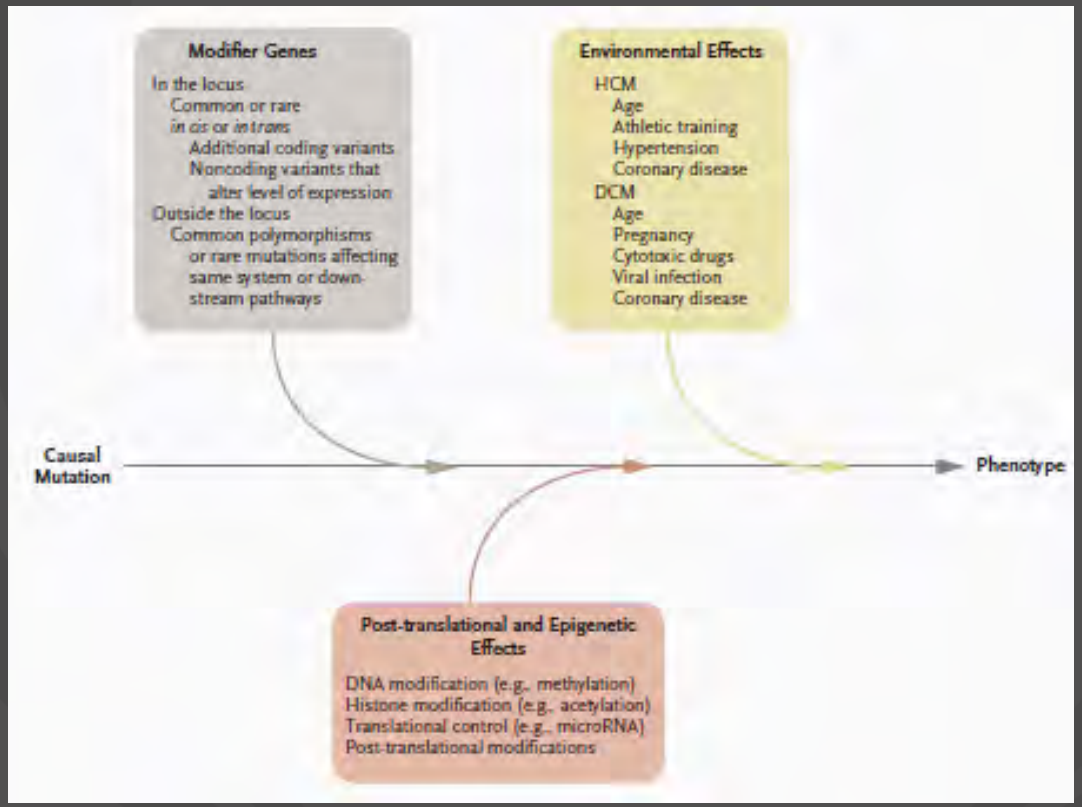
N – Polymorphism, D – Disease causing, F- Frameshift, NA – No prediction

Caballero A et al JCF 2013

Limitation: Phenotypic Variation in Genetic Mutations

KCNJ2	Long QT (LQT7), Andersen-Tawil syndrome, Short QT, CPVT	Dominant
KCNQ1	Long QT (LQT1), Short QT	Dominant
LAMA4	DCM	Dominant (uncertain)
LAMP2	Danon disease*, HCM, DCM	X-linked
LDB3(ZASP)	*DCM, LVNC, HCM, myofibrillar myopathy	Dominant
LMNA	DCM with and without conduction disease*, LVNC, ARVC, myopathies, muscular/lipodystrophies	Dominant
MYBPC3	HCM*, DCM, LVNC	Dominant
MYH6	HCM, DCM, congenital heart defects	Dominant
MYH7	HCM*, DCM, RCM, LVNC, myopathies	Dominant
MYL2	HCM	Dominant
MYL3	HCM	Dominant

Autosomal Dominance & Variable Penetrance



Changes in Gene Expression and Phenotype

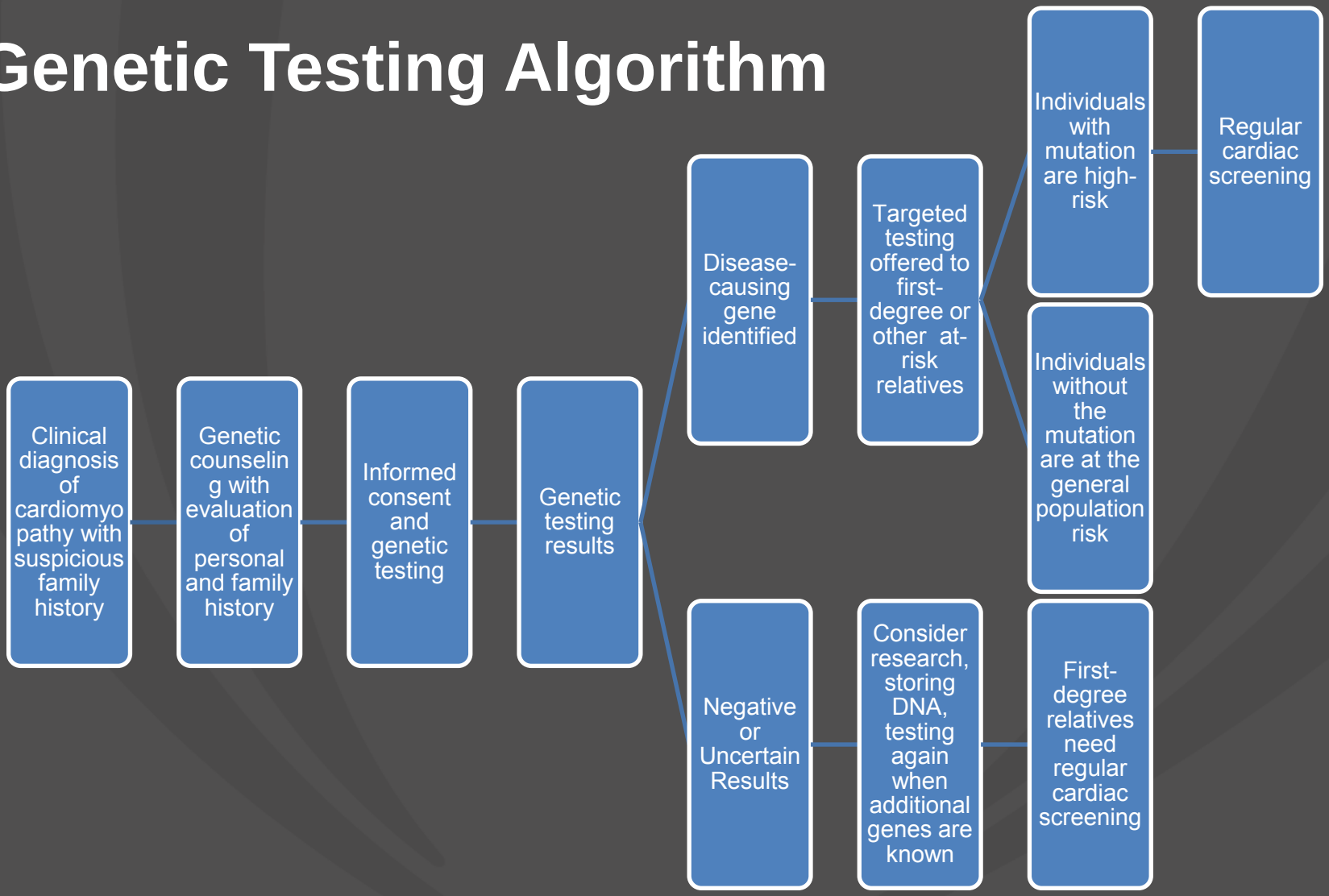
Pre-Test Genetic Counseling

- Three generation family history
- Discuss with patient
  - Genes included in test
  - What kind of information we might find
  - Limitations of test
  - Possibility of finding carrier status for recessive conditions
  - Benefit of finding a mutation
  - Risk of finding an uncertain variant
  - Insurance discrimination (health insurance is protected by law, while life insurance, long-term care, etc, is not protected)
- Patient gives informed consent
- Pre-authorization requested from patient's insurer

Post-Test Genetic Counseling

- Discuss results
  - Pathogenic mutation found
  - No mutation found
  - Variant(s) of uncertain clinical significance found
- Follow-up for patient
  - Pathogenic mutation: may offer risk stratification, eligibility for research studies
  - No mutation identified *or* uncertain variant(s) found: return in approximately 1 year to follow-up on variants and determine if new testing is recommended
- Follow-up for family members
  - Pathogenic mutation found: targeted testing available to family members
  - No mutation found: first-degree relatives regular cardiac screening
  - Uncertain variant(s) found:
    - Affected family members: it may be useful to test other *affected* family members to lend strength to whether a variant is tracking with disease in the family
    - Unaffected family members: it is dangerous to test unaffected family members unless it is part of a research protocol, as a normal result would not be informative without knowing a variant is definitely the cause of cardiomyopathy in that family.
- Genetic counseling letter sent to patient explaining the results, risks for family members, follow-up. Cover letter for patient to give family members also provided.

Genetic Testing Algorithm



Clinical Pathway

Table 2 Clinical family screening indicated in first-degree relatives of a patient with cardiomyopathy (situation in which genetic results are not available within the family)

	HCM	DCM	ARVC	RCM	LVNC
Cardiac evaluation	ECG, echocardiography	ECG, echocardiography (*and Holter-ECG if CD in the proband*)	ECG, echography, Holter-ECG, signal-averaged ECG	ECG, echocardiography (*and Holter-ECG if CD in the proband*)	ECG, echocardiography
Start of the cardiac evaluation	10–12 years	Childhood (*except laminopathies: 10–12 years*)	10–12 years	10–12 years	New-born
Repeated cardiac evaluation	[Every 3–5 years if performed before 10 years]	Every 1–3 years before 10 years[a]	[Every 3–5 years if performed before 10 years][b]	[Every 3–5 years if performed before 10 years]	Every 1–3 years before 20 years[a,c]
	Every 1–2 years between 10 and 20 years	Every 1–2 years between 10 and 20 years[a]	Every 1–2 years between 10 and 20 years	Every 1–2 years between 10 and 20 years	Every 2–5 years after 20 years[a,c]
	Every 2–5 years after 20 years	Every 2–5 years after 20 years[a]	Every 2–5 years after 20 years	Every 2–5 years after 20 years	
Screening can be stopped at:[d]	50–60 years	50–60 years	50–60 years	50–60 years	50–60 years[c]

Charron et al EHJ 2010

Genetic Pathway

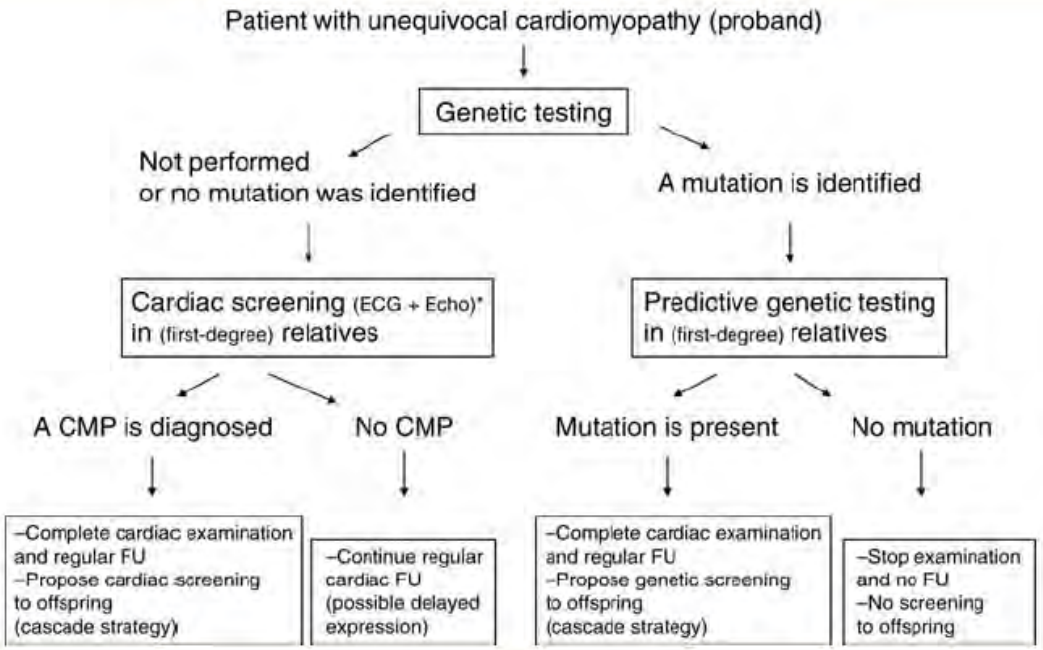


Figure 2 Organization of family screening. Asterisk (*) indicates additional cardiac examination in selected cardiomyopathies (i.e. Holter-ECG, SAECG, MRI, etc.). FU, follow-up.

Charron et al EHJ 2010

Outcomes

Table 3 Main outcomes associated with predictive diagnosis in cardiomyopathies

	If the mutation is present	If the mutation is absent
Positive outcome	Removal of uncertainty	Removal of uncertainty, and relief
	Regular medical follow-up is organized which will improve the prognosis	No future development of the disease, and medical follow-up is no more required
		No risk of transmission to offspring
Negative outcome	Anxiety because of future cardiac expression (risk of premature death)	Possible 'survivor' guilt
	No treatment to begin at this stage in most disorders	
	Risk of transmission to offspring	
Uncertainties remaining	Recommend environmental modifications? (exercise or alcohol restriction)	Not always easy to affirm that the mutation identified in the proband is the cause of the disorder in the family, especially if missense mutation
	Medical costs?	
	Insurability or professional concerns?	

Charron et al EHJ 2010

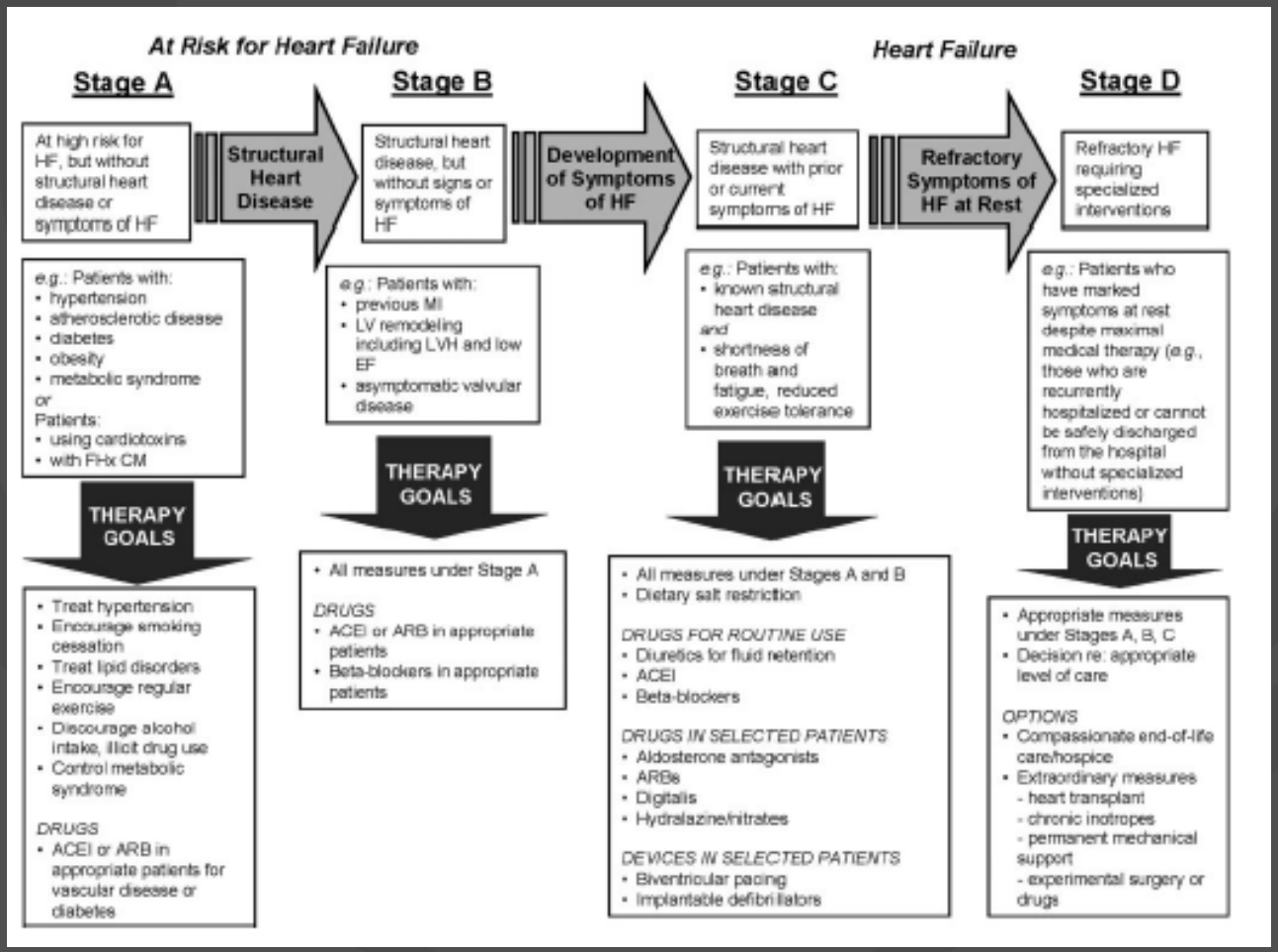
Medical Therapy is Effective in Asymptomatic LV Dysfunction

- Framingham Study: 40% people with asymptomatic LV dysfunction die within 5 years

Study	Patient Population (n)	Treatment	Average Duration, mo	Relative Mortality Risk Reduction	Sudden Death Risk Reduction	Death Due to Worsening HF Risk Reduction
ACE Inhibitors						
SAVE[21]	AMI and asymptomatic LVSD (2231)	Captopril vs placebo	42	19% (P=0.019)	No difference (P=NS)	38% (P=0.032)
SOLVD Prevention[17]	Asymptomatic LVSD (4228)	Enalapril vs placebo	37.4	8% (P=NS)	No difference (P=NS)	20%* (P<0.001)
TRACE[22,23]	MI and LVSD (6676; 1749 randomized); Asymptomatic LVSD (542)	Trandolapril vs placebo	24–50	22% (P=0.001)	24% (P=0.03)	29%† (P=0.003)
β-Blockers						
Retrospective analysis of SOLVD Prevention[24]	Asymptomatic LVSD (4228; 1015 patients taking β-blockers)	β-Blockers vs no β-blockers plus enalapril	37.4	23% (P<0.01)	28%‡ (P<0.05)	29% (P<0.05)
Post hoc analysis of SAVE[25]	Asymptomatic LVSD (2231; 789 patients taking β-blockers)	β-Blockers vs no β-blockers plus captopril	42	43% (P<0.001)	NR	32%† (P<0.001)
ANZ[26]	HF (415); asymptomatic LVSD (124)	Carvedilol vs placebo	19	36%* (P=0.02)	10% (P=NS)	8% (P=NS)
CAPRICORN[27]	Post-AMI LVSD (1959); asymptomatic LVSD (1023)	Carvedilol vs placebo (including ACE inhibitor)	15.6	23% (P=0.03)	26% (P=0.098)	40% (P=0.083)

Goldberg et al Circulation 2013

AHA/ACC Guidelines



Ethical Principles

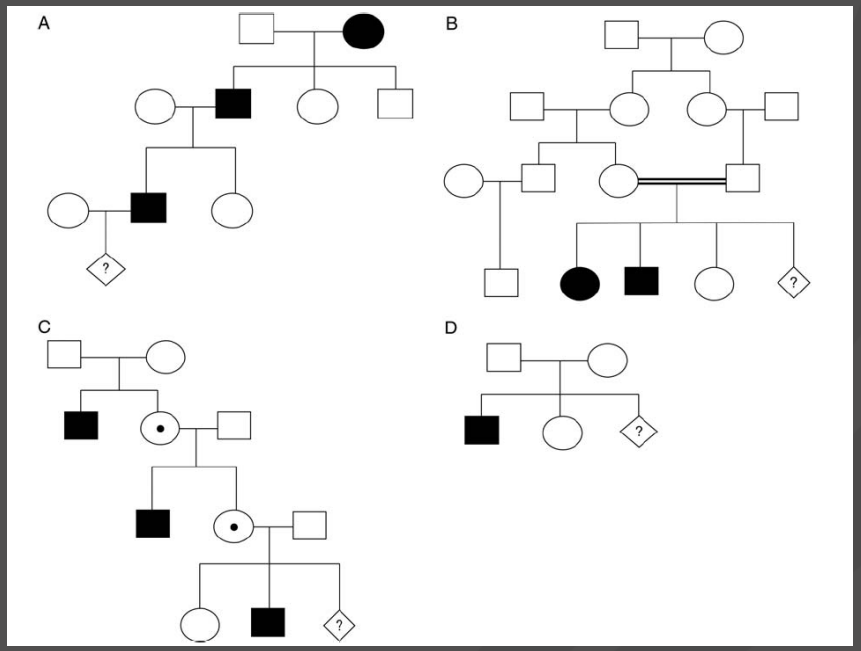
Table 4 Main principles of genetic counselling when genetic testing is discussed (especially predictive testing). Adapted from Cassiman.[69]

Autonomy: decision to make genetic testing is solely the choice of the counsellee. No pressure can be put on the counsellee and every decision should be equally accepted
Non-directiveness: information should be appropriate and honest
Written informed consent: must be provided before blood sampling
Right to know and not to know the genetic result: both should be respected
Confidentiality: should be respected so that the counsellee cannot be discriminated against in any way

Charron et al EHJ 2010

Genetic Counseling Guidelines
HFSA

- "A careful family history for ≥ 3 generations is recommended for all patients with cardiomyopathy"
- "Genetic and family counseling is recommended for all patients and families with cardiomyopathy"



Hershberger et al JCF 2009

Genetic Testing Guidelines

17.4. Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

a. Cardiomyopathy phenotype

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	B
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	C
Restrictive cardiomyopathy (RCM)	C
Cardiomyopathies associated with other extracardiac manifestations	A

Hershberger et al JCF 2009

Clinical Screening Guidelines

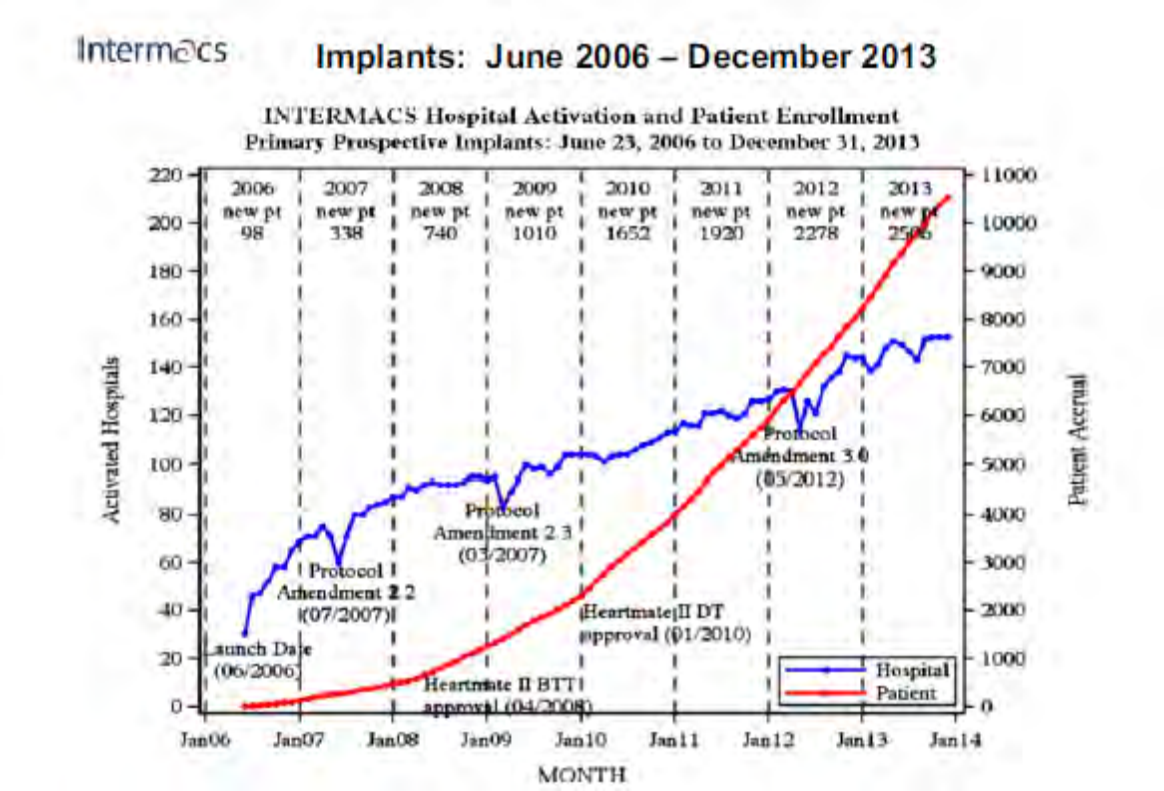
17.2. Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended.

a. Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	B
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with extracardiac manifestations (Table 4)	A

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Level of Evidence
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years, if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter.	B
Dilated	Every 3–5 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	B
ARVD/C	Every 3–5 years after age 10	Yearly after age 10 to 50 years of age.	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	C
Restrictive	Every 3–5 years beginning in adulthood	Yearly in childhood; every 1–3 years in adults.	C

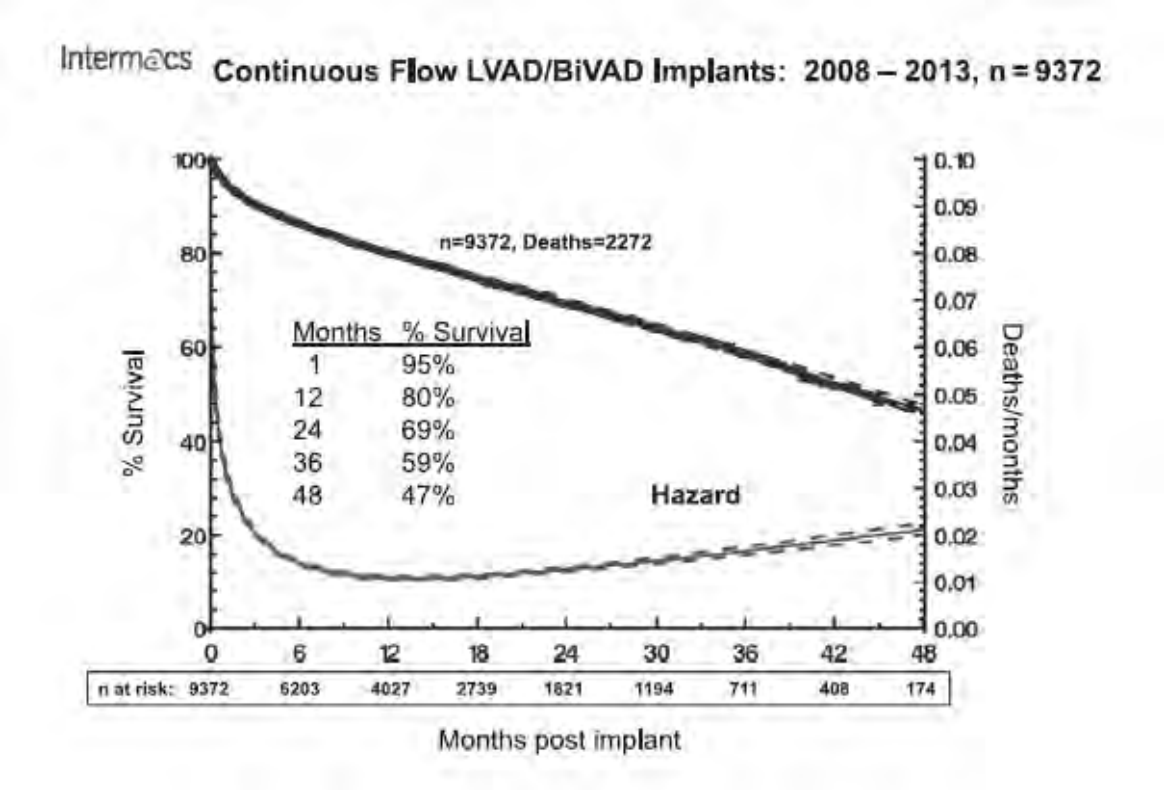
Hershberger et al JCF 2009

LVAD Volumes are Growing

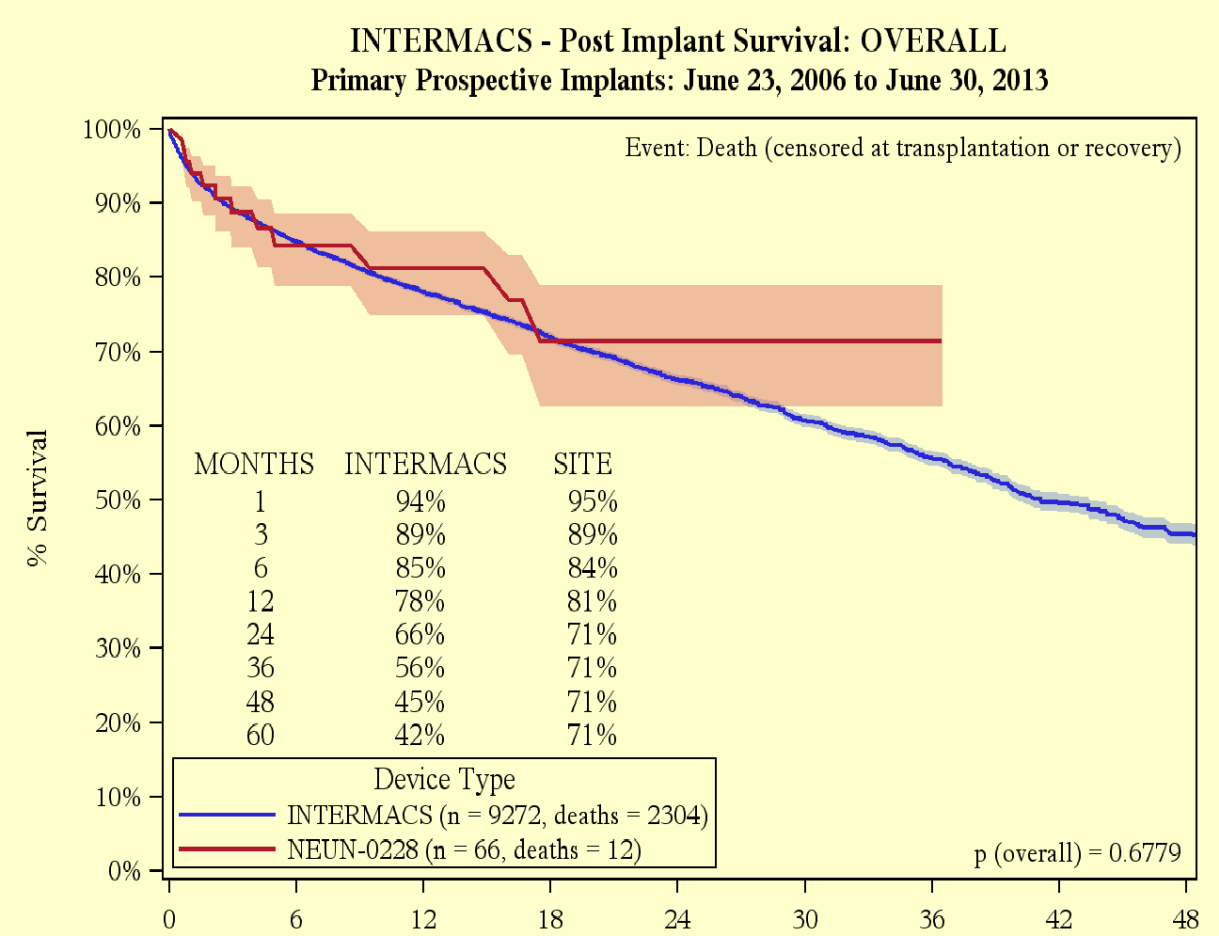


Kirklin et al JHLT 2014

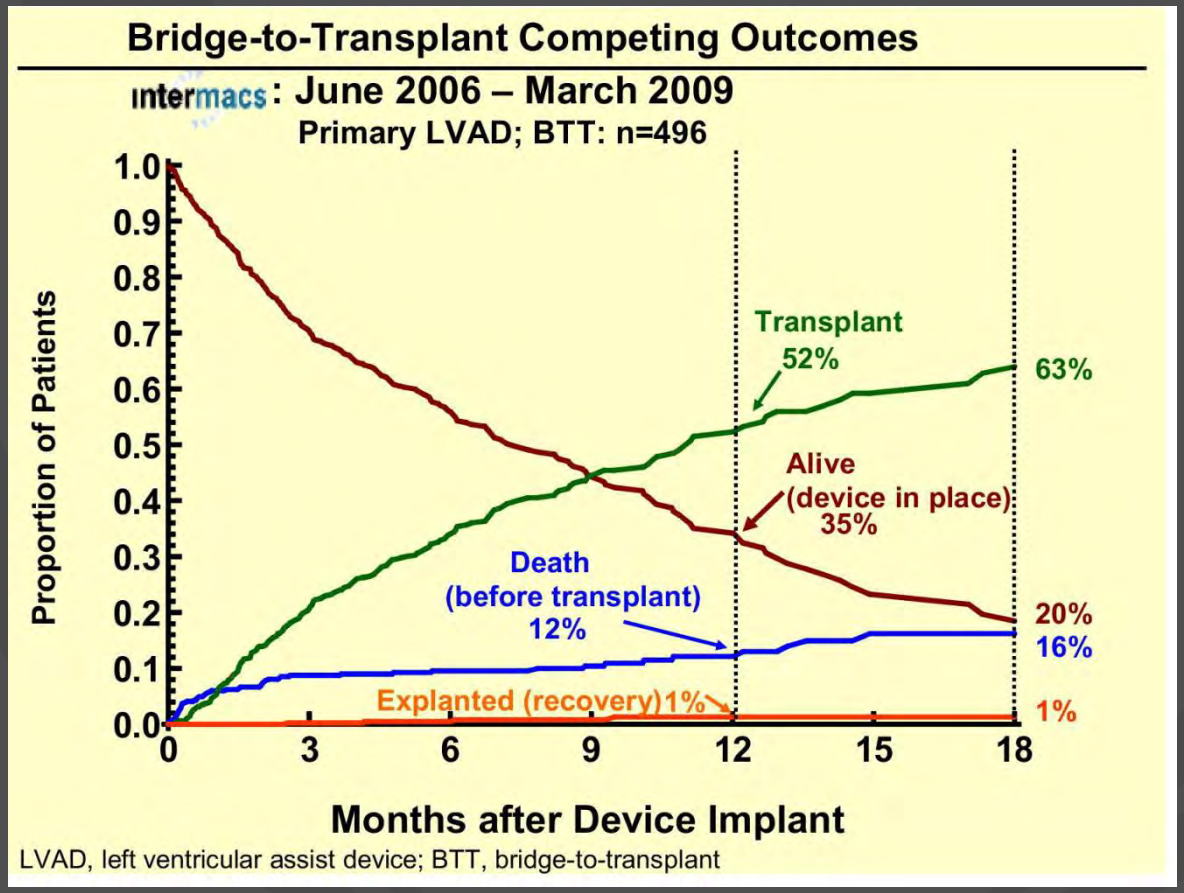
LVAD Survival



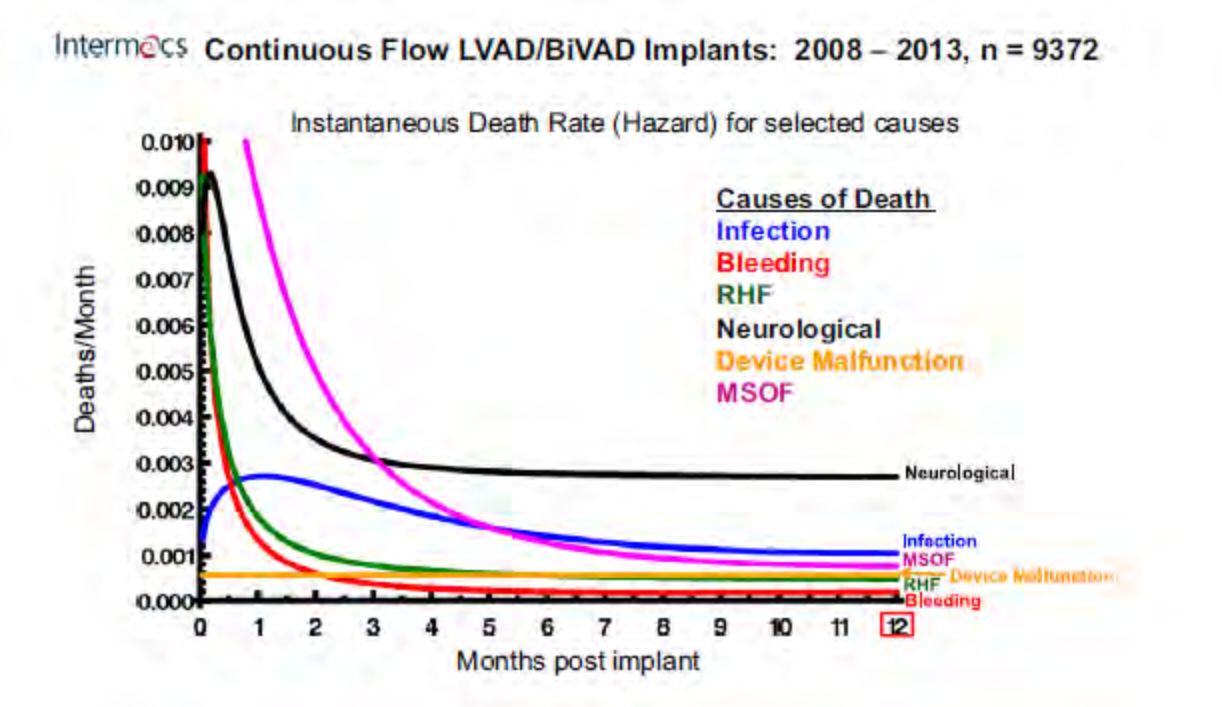
VAD Survival



Background: Recovery is Rare



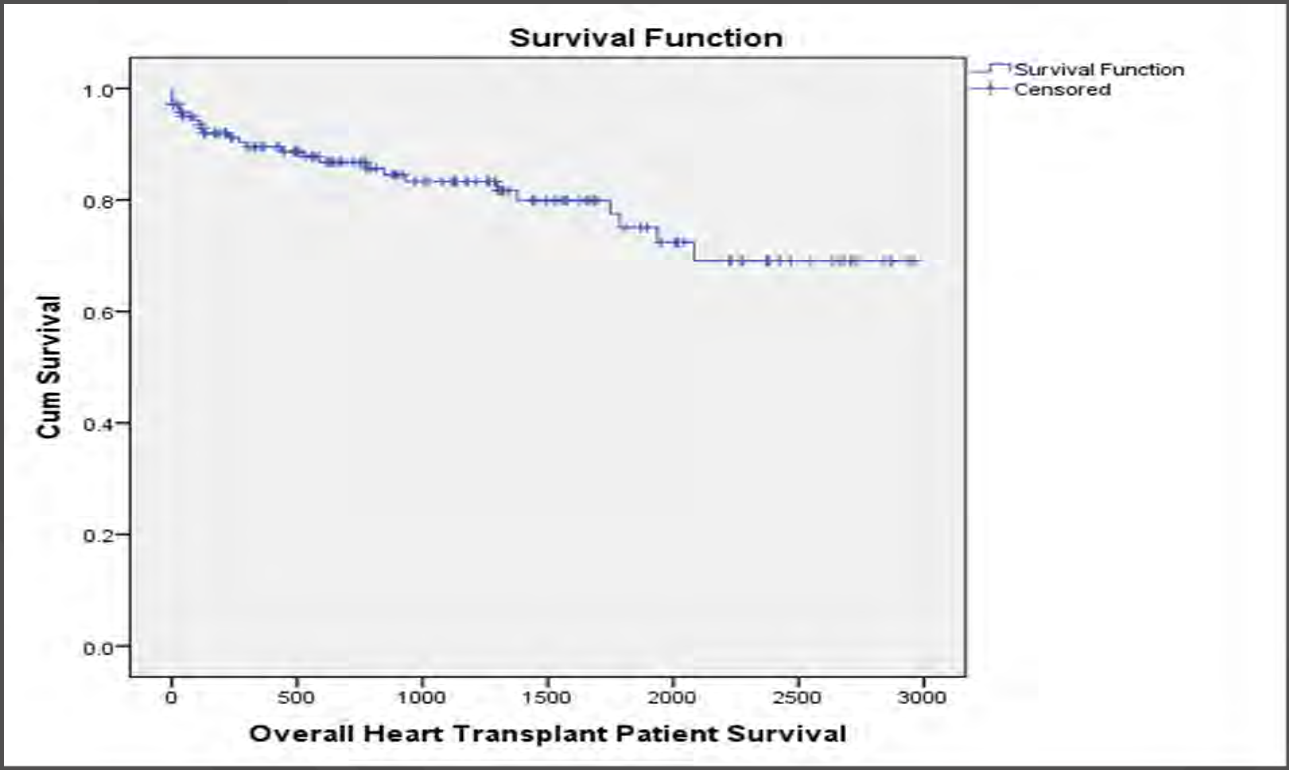
Kirklin JHLT 2010


Intermacs
Continuous Flow LVAD/BiVAD Implants: 2008 – 2013, n = 9372
Instantaneous Death Rate (Hazard) for selected causes
Deaths/Month
0.010
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
0 1 2 3 4 5 6 7 8 9 10 11 12
Months post implant
Causes of Death
Infection
Bleeding
RHF
Neurological
Device Malfunction
MSOF
Neurological
Infection
MSOF
Device Malfunction
RHF
Bleeding

The Overall Heart Transplant Recipient Survival

The period: 09/29/2005 through 10/30/2013

The follow-up stop time: 11/04/2013

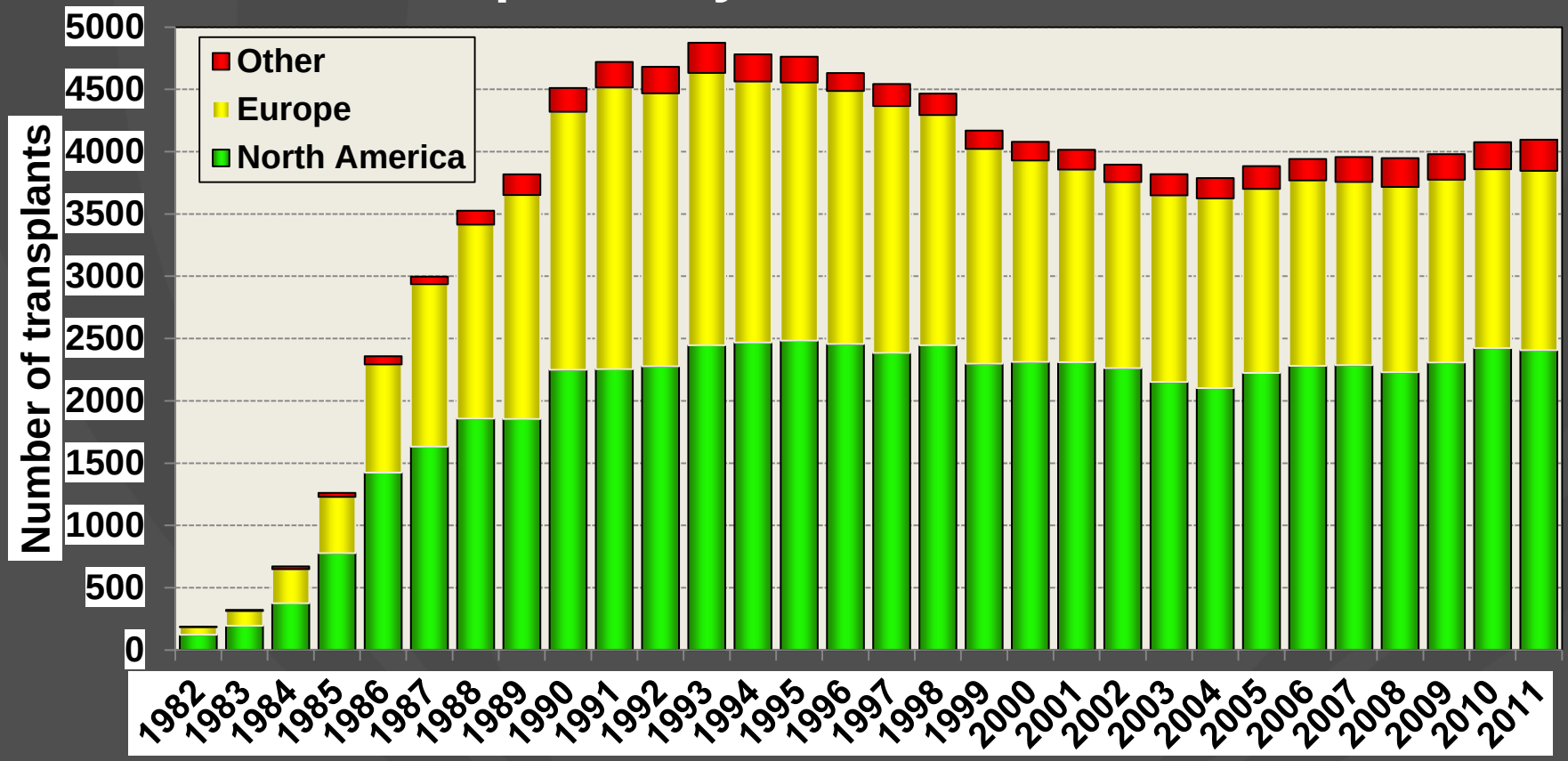


Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
142	26	116	**81.7%**

Adult and Pediatric Heart Transplants

Number of Transplants by Year and Location



Summary

- Many “cardiomyopathies” are genetic
- Broad genetic testing is widely available and applicable to these patients
- Genetic counseling should be done for patients and their families
- We need to identify patients who are at risk and target them for early interventions

University of Nebraska Medical Center