Incontro regionale Trentino Alto Adige AIAC – FMSI 2019
Gli esami strumentali cardiologici
per il Medico dello Sport

Utilità del test genetico e quando chiederlo nello sportivo con problemi aritmici

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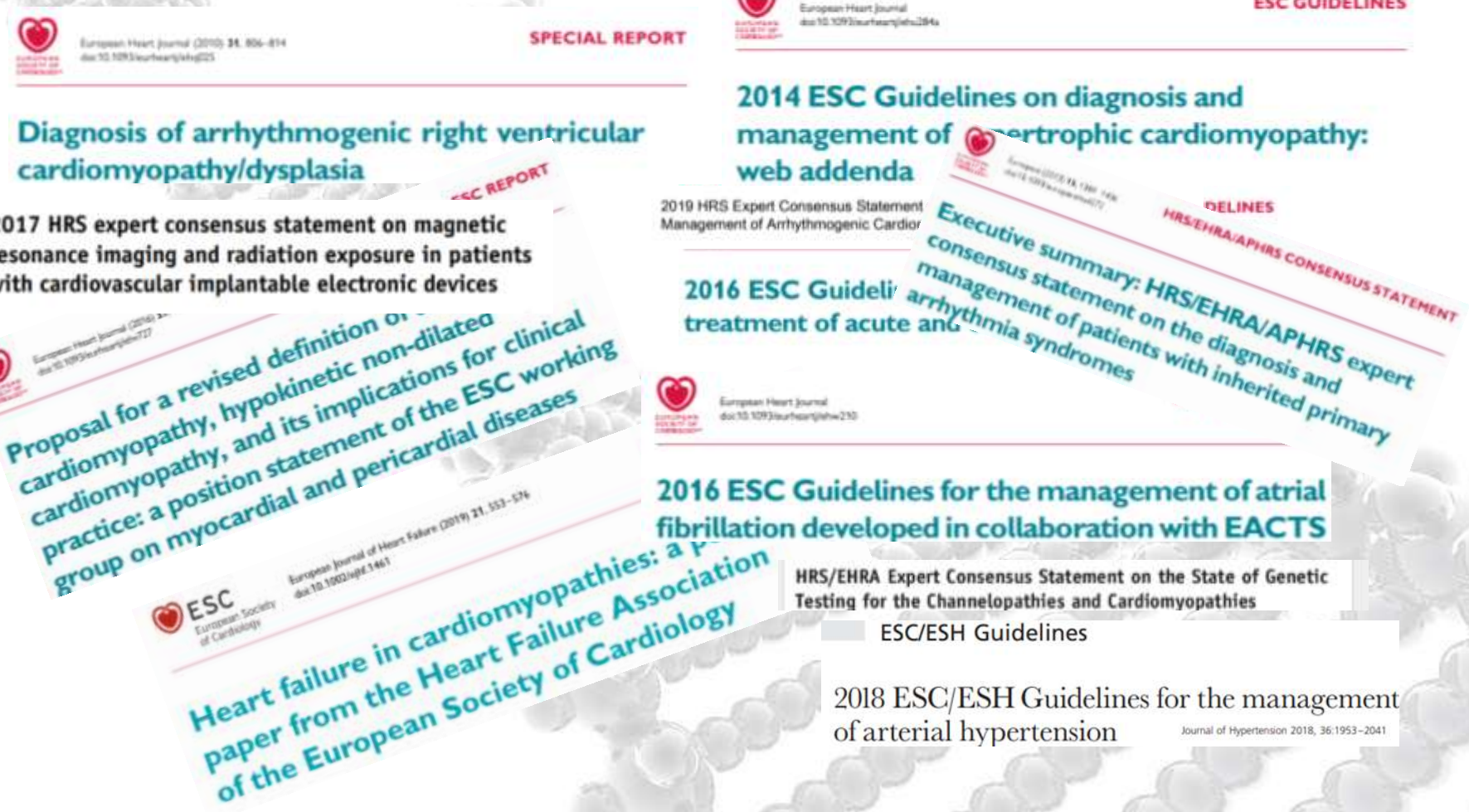
UNIVERSITÀ DEGLI STUDI DI PADOVA

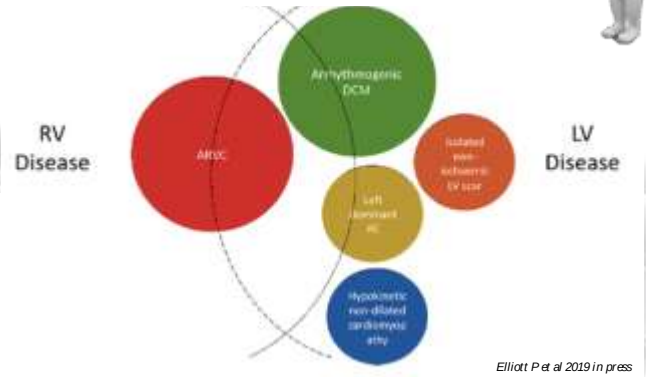
Rovereto, 01 giugno 2019
Aula Magna Dipartimento di Psicologia e Scienze Cognitive
Palazzo Istruzione - Corso Bettini, 84

Guidelines & RED flags in cardiomyopathies



Standard cardiologic workup

- Personal and family history
- Baseline ECG (12/24 leads)
- SAECG
- Echo (2D/3D)
- Holter
- Stress test
- (LE)-CMR
- EPS
- …



Elliott P et al 2019 in press

When Do I Suspect a Genetic Condition?

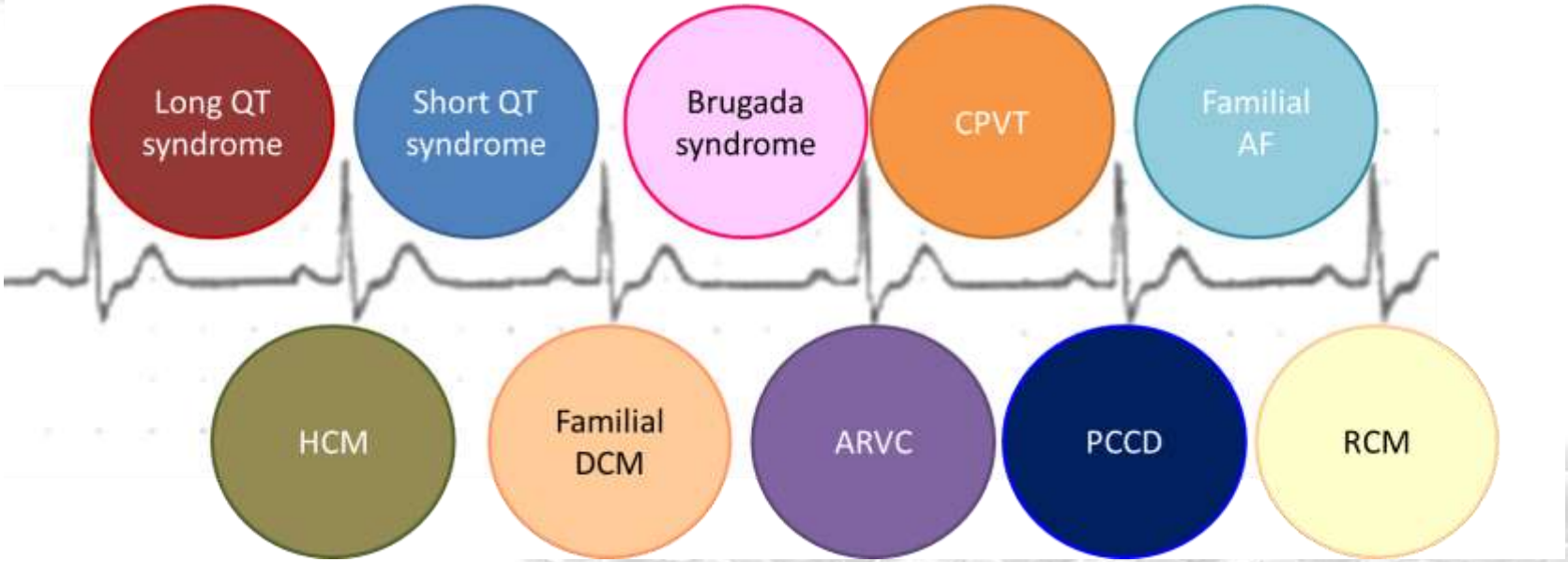
Clinical Findings Suggestive of a Cardiovascular Genetic Disorder
Cardiac disorder with associated developmental delay/intellectual disability
Congenital heart defect with additional birth anomalies
Congenital heart defect with dysmorphic facies
Positive family history of multiple closely related individuals affected with the same condition
Affected offspring of a couple with ≥3 pregnancy losses
Conotruncal heart defects, supravalvular aortic stenosis, bicuspid aortic valve
Thoracic aortic aneurysm or dissection
Unexplained cardiomyopathy
Family history of sudden cardiac death in a previously healthy person
Abnormal ECG findings consistent with inherited arrhythmia

Clinical screening must always preceed genetic testing request!!

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

Ackerman MJ[1], Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP.

Heart Rhythm. 2011 Aug;8(8):1308-39. doi: 10.1016/j.hrthm.2011.05.020.



Genetic test

- Diagnostic	R	R	U	R	U	U	R	U	N.R.	U
- Cascade	R	R	R	R	R	R	R	R		R

R: recommended
U: useful
N.R.:not recommended

Test	Format	Strengths	Limitations	Used for
Chromosome analysis	Examines chromosome structure	Detects trisomies, sex chromosome abnormalities, chromosomal translocations	Only detects major chromosomal abnormalities involving large DNA segments	Patients with multiple congenital anomalies
Fluorescent In-Situ Hybridization (FISH)	Fluorescent probes detect presence or absence of a specific chromosome region	Detects small chromosomal deletions not detectable by karyotype analysis	Only evaluates a specific genetic region	22q11.2 syndrome; 7q11.23 syndrome
Targeted deletion/duplication	Multiple platforms including multiplex	Detects very small chromosomal	Only detects deletions/duplications	Used when DNA sequencing doesn't

Understanding of genetic testing technology and diagnostic yield of genetic tests is mandatory because this affects both test choice and interpretation

Sequencing (single gene/multiple gene panel)	DNA sequencing of specific gene(s)	Can detect single base pair genetic variants within coding sequence of a defined set of genes	Only tests a specific set of genes; test needs to be updated/repeated as additional causative genes are identified	Patients with identified or suspected cardiovascular conditions with defined genetic etiologies (e.g., HCM, ARVC, LQTS, CPVT, Marfan Syndrome, Loeys-Dietz Syndrome, Noonan Syndrome).
Sequencing (Whole exome) (WES)	Next generation sequencing of all coding DNA (1% of genome)	Can detect single base pair genetic variants within coding sequence of any gene	Identifies variants of uncertain significance. Insertions-deletions difficult to detect. Can lead to incidental findings that require further follow-up and evaluation	Patients in whom targeted genetic testing has not identified a causative variant
Sequencing (Whole genome) (WGS)	Next generation sequencing of all genomic DNA	Can detect single base pair genetic variants in coding and non-coding DNA	Identifies variants of uncertain significance. Can lead to incidental findings that require further follow-up and evaluation	Patients in whom targeted genetic testing (and possibly WES) has not identified a causative variant

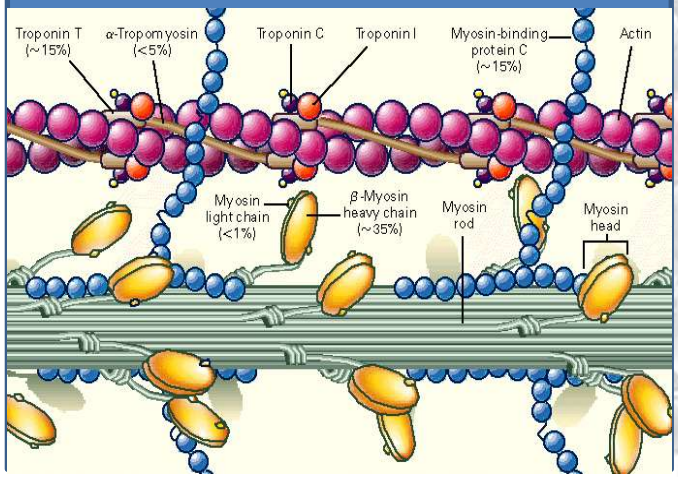
HCM, Hypertrophic cardiomyopathy; ARVC, arrhythmogenic RV cardiomyopathy; LQTS, long QT syndrome; CPVT,

'COMMON' AORTA DISORDERS

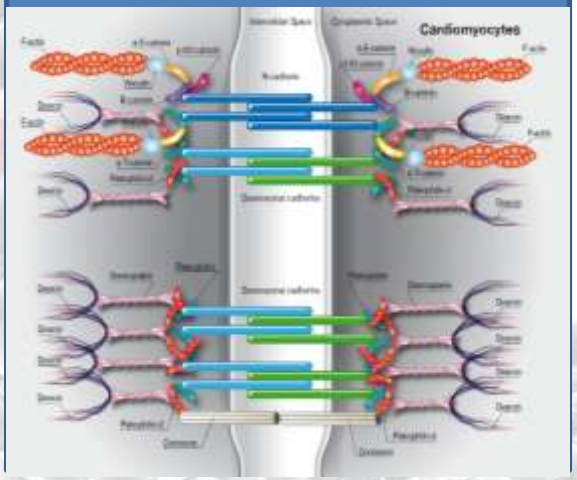
	MARFAN SYNDROME – *elastic fiber network*	LOYES-DIETZ SYNDROME– *elastic fiber network*	EHLERS-DANLOS SYNDROME – *collagenous network*
Gene	FBN1	TGFBR1 & 2, TGFB2 & 3, SMAD3, SKI	COL1A1, COL1A2, **COL3A1**, COL5A1, COL5A2.
Inheritance	Autosomal Dominant Sporadic:25%	Autosomal Dominant Sporadic: 75%	Autosomal Dominant
Prevalence	1:5.000-10.000	N/A	1:5.000 → vascular type 1:250.000
Penetrance	Complete	N/A	Incomplete
Yield of GT	100%	40-60%	15-25%
Clinical features	MVP, tall stature, arachnodactyly, pectus abnormality, scoliosis, ectopia lentis, dural ectasia, spontaneous pneumothorax, striae	Bifid uvula/cleft palate, skeletal feature s similar to MFS, craniosynostosis	Thin translucent skin, gastrointestinal rupture **Vascular EDS** patients can present as early as the first 2 weeks of life with aneurysm or rupture of large blood vessels, or sudden spontaneous rupture of the bowel or other intra-abdominal organs.

‘COMMON’ INHERITED ARRHYTHMIC CARDIOMYOPATHIES WITH STRUCTURAL DEFECT

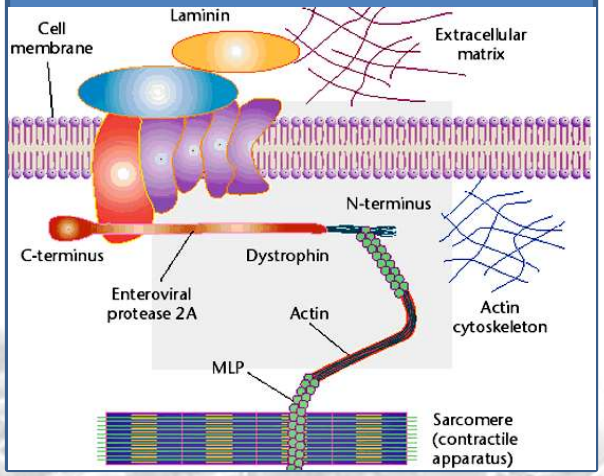
HCM – *SARCOMERE*



AC – *DESMOSOME*



DCM* - *CYTOSKELETON*

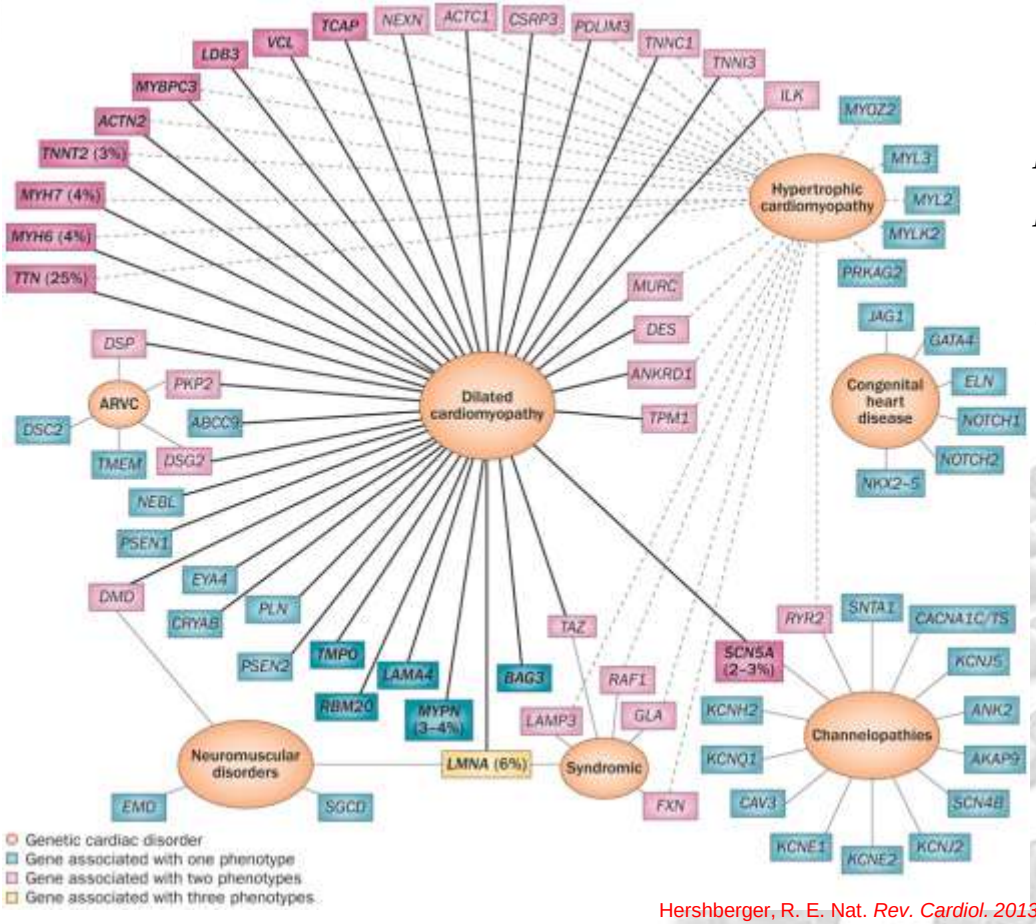


Inheritance	Autosomal Dominant/ Recessive	Autosomal Dominant/Recessive linked to cardiocutaneous syndromes	Autosomal Dominant/ Recessive, mitochondrial, X-linked
Prevalence	1:500	1:2500-1:5000	1:2500
Penetrance	Incomplete, age-dependent	Incomplete, age-dependent	Incomplete, age-dependent
Yield of GT	50-70%	40-60%	15-25%

'COMMON' CHANNELOPATHIES

	LQT	SQT	BrS	CPVT	PCCD
Genes	LQT1-KCNQ1, LQT2-KCNH2, LQT3-SCN5A	SQT1-KCNH2 , SQT2-KCNQ1, SQT3-KCNJ2	BrS1-SCN5A	CPVT1-RYR2, CPVT2-CASQ2	SCN5A, TRPM4, SCN1B, SCN10A
Inheritance	Autosomal Dominant (Romano- Ward syndrome)/ Recessive linked to congenital deafness (Jervell & Lange Nielsen syndrome), dysmorphic faces (Andersen- Tawil syndrome), autism (Timothy syndrome)	Autosomal Dominant	Autosomal Dominant	Autosomal Dominant/ Recessive	Autosomal Dominant
Prevalence	1:2.500 (AR 1:1.000.00)	Only 70 cases worldwide reported	1:1.000-10.000	1:10.000	1:20.000
Penetrance	Incomplete	Incomplete	Incomplete	Incomplete	Incomplete
Yield of GT	Up to 80%	20%	25%	60-70%	5-10%

The complexity of a diverse genetic architecture



The human genome comprise 20,000 protein-coding genes of which in the past 10 years, about 3,000 have been linked to at least one Mendelian disease.

Hershberger, R. E. Nat. *Rev. Cardiol. 2013;* 10:531-47

Mind that NOT all rare variants (missense/truncating) are Pathogenic and likely pathogenic…

Genetic noise

J Am Coll Cardiol. 2011 Jun 7;57(23):2317-27. doi: 10.1016/j.jacc.2010.12.036.

Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise.

Kapplinger JD[1], Landstrom AP, Salisbury BA, Callis TE, Pollevick GD, Tester DJ, Cox MG, Bhuiyan Z, Bikker H, Wiesfeld AC, Hauer RN, van Tintelen JP, Jongbloed JD, Calkins H, Judge DP, Wilde AA, Ackerman MJ.

«Radical mutations are high probability AC-associated whereas rare missense variants should be interpreted in the context of race, ethnicity, mutation location and sequence conservation.»

Genet Med. 2017 May 4. doi: 10.1038/gim.2017.40. [Epub ahead of print]

Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing.

Haggerty CM[1], James CA[2], Calkins H[2], Tichnell C[2], Leader JB[3], Hartzel DN[3], Nevius CD[1], Pendergrass SA[3], Person TN[3], Schwartz M[4], Ritchie MD[3], Carey DJ[5], Ledbetter DH[4], Williams MS[4], Dewey FE[6], Lopez A[6], Penn J[6], Overton JD[6], Reid JG[6], Lebo M[7,8], Mason-Suares H[7,8], Austin-Tse C[7], Rehm HL[7,8], Delisle BP[9], Makowski DJ[10], Mehra VC[10], Murray MF[4], Fornwalt BK[1].

Identification of radical variants alone does not provide a genome-first solution to the identification of AC

1 in 200 controls actually have a positive genetic test ; 1 in 6 controls would potentially meet criteria for a positive genetic test result.

Genetics standards and guidelines

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Genet Med. 2015 May ; 17(5): 405–424. doi:10.1038/gim.2015.30.

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Comm

Novel missense or nonsense variants by current ACMG rules cannot be classified as likely pathogenic (or pathogenic), and thus actionable, unless data regarding the same variant is available from multiple probands and/or affected family members.

A variant classified as a VUS by a laboratory report seldom impacts the clinician's decision.

Clinical guidelines and position article

FIC Federazione Italiana di Cardiologia Italian Federation of Cardiology

OPEN

Contemporary genetic testing in inherited cardiac disease: tools, ethical issues, and clinical applications

Francesca Girolami[a], Giulia Frisso[b], Matteo Benelli[c], Lia Crotti[d], Maria Iascone[e], Ruggiero Mango[f], Cristina Mazzaccara[b], Kalliope Pilichou[g], Eloisa Arbustini[h], Benedetta Tomberli[i], Giuseppe Limongelli[j], Cristina Basso[g] and Iacopo Olivotto[i]

J Cardiovasc Med 2018, 19:1–11

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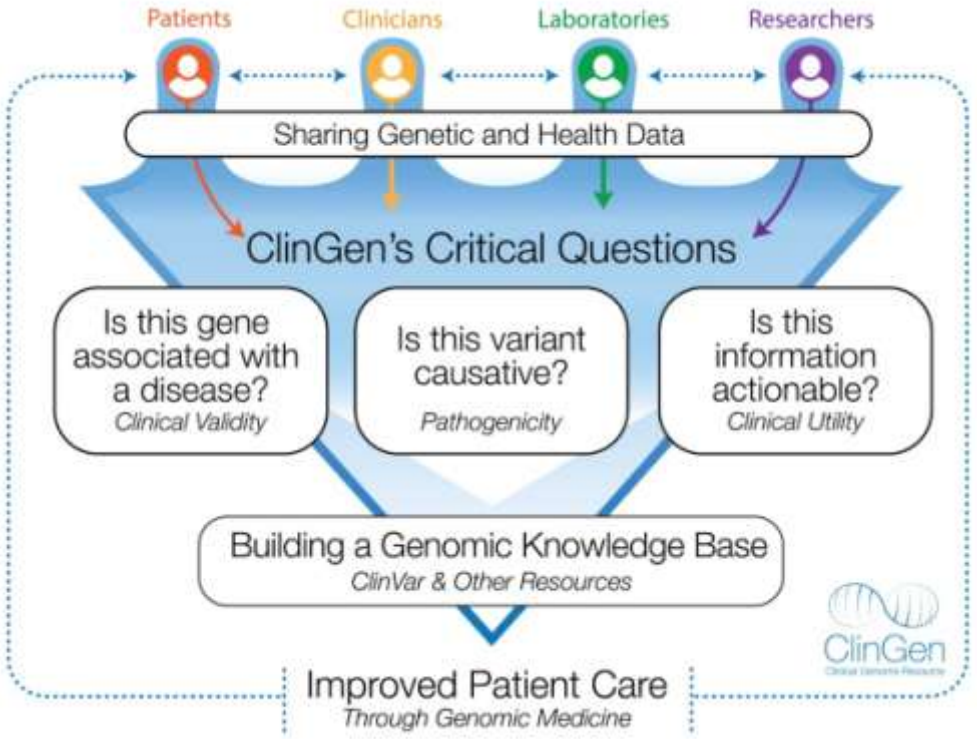
Genetics in Medicine (2018) 20:899–909; https://doi.org/10.1038/s41436-018-0039-z

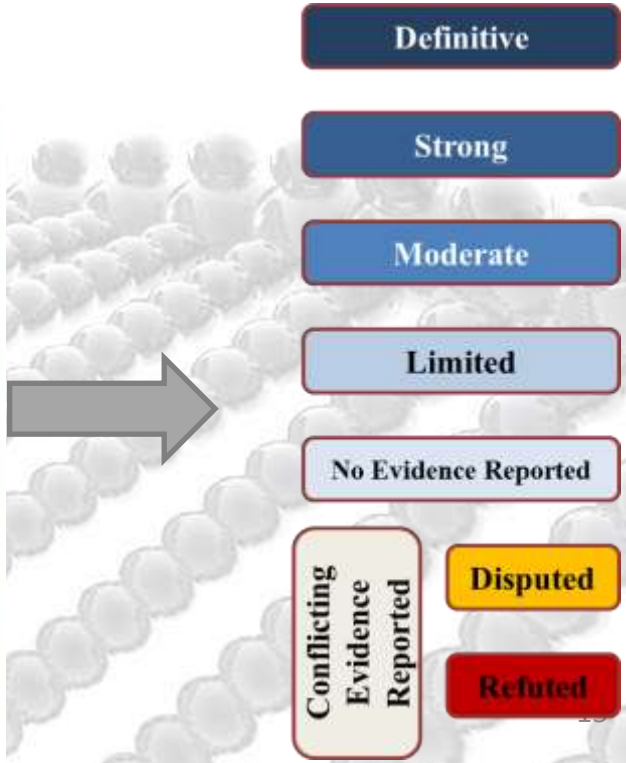
Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG)

Ray E. Hershberger, MD[1], Michael M. Givertz, MD[2], Carolyn Y Ho, MD[3], Daniel P. Judge, MD[4], Paul F. Kantor, MD[5], Kim L. McBride, MD[6], Ana Morales, MS, LGC[1], Matthew R. G. Taylor, MD[7], Matteo Vatta, PhD[8,9,10] and Stephanie M. Ware, MD, PhD[9,11] on behalf of the ACMG Professional Practice and Guidelines Committee

Which genes have sufficient evidence to be considered disease related?

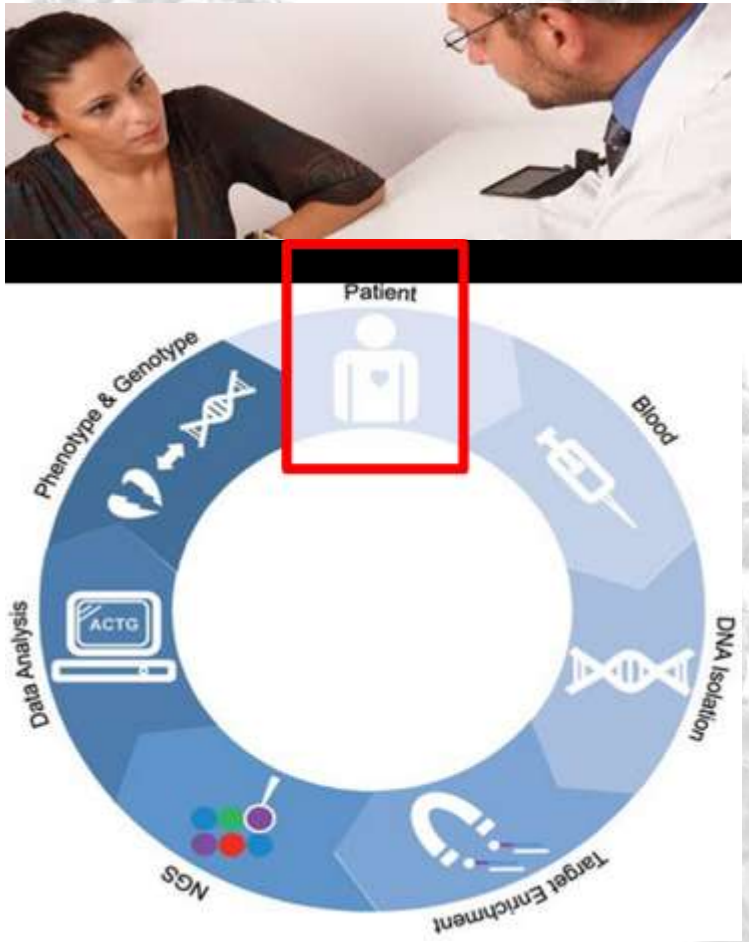
How to demonstrate the pathogenicity in genetic variants?





How Should pts Be Tested?

GENETIC COUNSELING: PRE-TEST



- ✓ *indication for genetic testing: Clinical & familial history*
- ✓ *Choice of genetic test*
- ✓ *Genetic test: limits & benefits*
- ✓ *Informed consent , understand social implications*

How Should Be Tested?

Large gene panels increase likelihood of identifying

- **molecular etiology**, especially in patients with mixed phenotypes (i.e. AC-DCM) or those lacking pathognomonic features
- **individuals who carry disease-causing variants in multiple genes**, extremely important for appropriate targeted testing of family members.

Caveat:

- **VUS** in proportion to the number of genes tested increase complexity of the interpretation → genetic counseling is mandatory given that results drive clinical decision-making!

Copy number variation assays, given that frequency of these variants is high and identification is difficult through target re-sequencing panels.

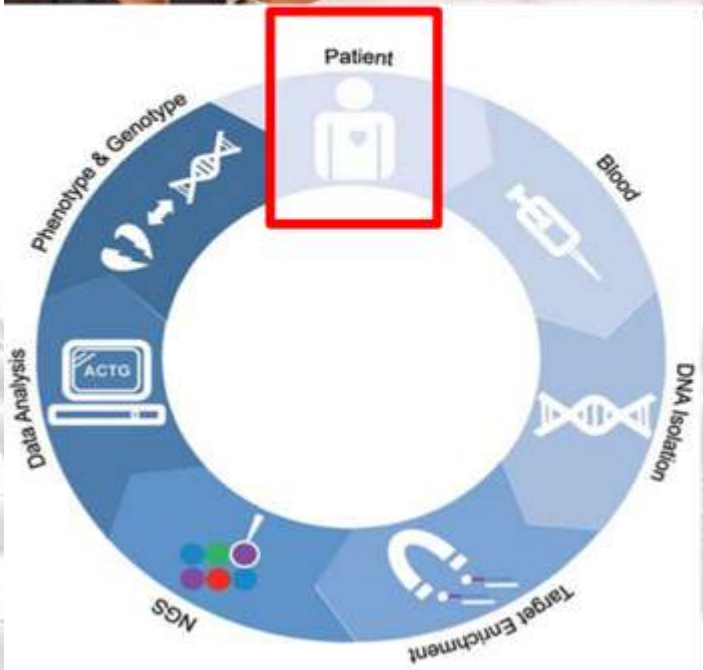
ACMG PRACTICE RESOURCE | Genetics inMedicine

Genetics in Medicine (2018) 20:899–909; https://doi.org/10.1038/s41436-018-0039-z

How Should pts Be Tested?

GENETIC COUNSELING: POST-TEST

- *Genetic report should be handed to directly to patient*
- *the results of genetic testing should be provided in the context of the patient's clinical phenotype and family history → multidisciplinary collaborative teams*
- *Many genetic tests inform likelyhood of disease and are not the sole determinants of disease status*



'Genotype +' does not mean 'disease-affected'

Take-home message

- *Genetic testing should be performed after clinical evaluation in probands/athletes*
- *Genetic testing results are probabilistic rather than determinative, relying on strength of evidence, both for and against, of specific variants causing or contributing to disease.*
- *As such must be always interpreted in the context of patient's medical and family history.*
- *Cascade genetic screening is mandatory both for a predictive test (P/LP variants) and for determining variants causality (VUS)*
- *Genetic counseling is crucial given that genetic results drive clinical decision-making.*
- *Referral of cardiomyopathy patients in expert centers*

IL CONVEGNO LA SCOMPARSA DI MOROSINI HA STIMOLATO LA RICERCA PER EVITARE ALTRE TRAGEDIE

14 aprile 2012

Mai più morti in campo, ora c'è il test del dna

E' possibile scoprire prima chi sono gli atleti più a rischio di malattie cardiovascolari

ALEX FROSIO

Mai più morti in campo. La cosiddetta morte improvvisa, il black out del cuore che ha portato a drammi come quello di Piermario Morosini, può essere prevenuta, prima ancora che curata con l'utilizzo - in caso di estremo bisogno - del defibrillatore. In Portogallo è stata messa a punto una nuova tecnologia, la HeartGenetics, che scova a livello genetico le patologie asintomatiche che portano alla morte improvvisa, causata in oltre il 60% dei casi proprio da difetti del dna. Il dna microchip riconosce, anche in soggetti giovani e apparentemente sani, con una accuratezza del 99% le principali anomalie genetiche, tra cui la cardiomiopatia ipertrofica, la cardiomiopatia dilatativa, la cardiomiopatia aritmogena del ventricolo destro, le sindromi congenite del QT lungo e la sindrome di Brugrada. In parole più semplici: Morosini, con questo test, sarebbe stato fermato molto prima della fatale partita di Pescara. E infatti club come Real Madrid e Barcellona, ma anche Milan, Inter e Juventus, si sono dimostrate estremamente interessate al dna microchip, pianificando a partire dal settore giovanile.

Il convegno Di questo e di tanto altro si parlerà oggi a Pavia (alla sala del Broletto) al convegno organizzato dall'Associazione prevenzione malattie genetiche, presieduta dal professor Richichi, già direttore del reparto cardiologia San Matteo. Un luminare della cardiologia, il professor Schwartz, terrà una *lectio magistralis* sulla morte improvvisa, che ogni anno causa la morte di 70mila persone in Italia e che ha un'incidenza di una persona su 500. In una tavola rotonda su genetica e sport, sarà presentato il «Progetto Pavia '93», ovvero la mappatura genetica di tutti i nati a Pavia nel 1993. «Un progetto lodevole e avveniristico, un segnale importante destinato a rivoluzionare l'approccio culturale al fenomeno: non attendere che il problema si manifesti ma anticipare i tempi», ha scritto Giovanni Malagò, presidente del Coni, in una lettera agli organizzatori del convegno. Morosini, Bovolenta, Puerta, Curi. Lo sport ha già pagato un prezzo molto alto. Ora i conti si possono chiudere.

Piermario Morosini ANSA

SPORT - CALCIO

(*28 agosto 2007*)

Il terzino, 22 anni, era stato colpito da un infarto sabato nel match contro il Getafe Nonostante i rapidi soccorsi, le sue condizioni erano apparse subito molto gravi.

Spagna, dramma nella Liga è morto Antonio Puerta

Puerta accompagnato fuori dal campo dal medico sociale

Trovato morto nella stanza dell'hotel capitano della Fiorentina Davide Astori

04 Marzo 2018

Reggio Emilia, la morte di Mattia Dall'Aglio. "Era disteso a terra, pensavano dormisse"

Calista 24enne trovato morto in palestra, lo strazio del padre: "Stava bene, aveva fatto di recente degli esami medici"

Reggio Emilia, 8 agosto 2017 – Un ragazzo abituato ad affrontare la vita a

Genetic test: yes/no ?

Inherited Arrhythmic Cardiomyopathies/Channelopathies Multidisciplinary Team, University of Padua

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