Introduction

Hypertrophic cardiomyopathy (HCM) is a disease of the heart muscle characterized by left ventricular hypertrophy not solely explained by abnormal loading conditions (1-3). In more than half of cases the disease is inherited as an autosomal dominant genetic trait caused by mutations in genes encoding sarcomeric proteins (4-6). A subgroup of cases is caused by mutations in non-sarcomeric genes or systemic disorders causing cardiac hypertrophy, many of which have peculiar clinical features and require targeted therapies and management (7-12). In order to orient and interpret specialized diagnostic testing including molecular genetic analysis, the 2014 European Society of Cardiology consensus guidelines on HCM recommend a systematic search for diagnostic clues or 'red flags' (RF), including cardiac and non-cardiac parameters obtained from pedigree analysis, clinical examination, ECG, cardiac imaging, and standard laboratory tests (1, 13,14). To date, a systematic evaluation of this recommendation has not been performed. The aim of this study was to determine the prevalence and predictive accuracy of a series of predefined diagnostic markers in a consecutive cohort of children and adults with HCM referred to a tertiary cardiomyopathy clinic.

Material and Methods

Study population and definitions

This cross sectional cohort study enrolled patients with HCM referred to the specialist cardiomyopathy and heart failure clinic at the Monaldi Hospital, Naples, Italy between September 2013 and December 2017.

HCM was defined as left ventricular hypertrophy not solely explained by abnormal loading conditions. (in adults: wall thickness of >15mm, or >13mm in patients with family history of HCM; in children: z-score value >3 standard deviations, considering 2-to-3 as a "grey zone" for childhood HCM) (15).

HCM was diagnosed as "sarcomeric HCM" when a disease causing mutation was found in a sarcomeric protein gene. Syndromic, metabolic, infiltrative and neuromuscular disorders associated with HCM were defined as "specific causes of HCM" (including both HCM genocopies and phenocopies, according to the ESC definition) (ESC 2014) (1) and diagnosed using a standardized protocol comprising non-invasive/invasive investigations including tissue biopsy (if necessary). HCM was defined as "idiopathic" when, after a comprehensive clinical and genetic evaluation, an etiological diagnosis was not achieved.

Study protocol

A flow-chart of the study protocol and diagnostic work up is reported in Figure 1 (1,16). Patients were enrolled after informed consent was obtained, according to the procedure established by the Ethics Committee of our institution. They underwent cardiovascular evaluation, including family and personal history, physical examination, blood tests, standard ECG at rest, conventional M-mode, two-dimensional and Doppler echocardiography with Doppler tissue imaging and deformation imaging, 24 hour ambulatory ECG monitoring, exercise stress test, cardiac magnetic resonance imaging, and genetic analysis. Clinical evaluation including standard ECG and echocardiography was repeated every 6 months and laboratory evaluation, ECG monitoring and an exercise test were performed at least once a year. Genetic analysis was performed after obtaining informed written consent, according to the procedure established by the local ethics committee. Molecular genetic testing was guided by the clinical phenotype and performed using direct Sanger sequencing (8 sarcomeric genes: MYH7, MYBPC3, TNNT2, TNNI3, ACTC, TPM1, MYL2, MYL3).
If the genetic test was negative for the genes investigated, molecular genetic testing was extended using next generation sequencing (NGS) panel containing 202 genes, including sarcomeric and non-sarcomeric genes (i.e. metabolic genes, MAP kinases genes, etc.), as previously described (17,18). Testing for specific genetic non-sarcomeric causes of HCM was performed according to the clinical indication (13, 14).

Diagnostic markers

A panel of diagnostic markers was defined using recommendations from the ESC position statement on diagnosis of cardiomyopathies and the 2014 ESC HCM guideline (1,13). Individual markers, or diagnostic red flags (RF) were organized into five groups: family history; signs and symptoms; electrocardiography; cardiac imaging, and laboratory testing (Supplemental Table 1) (13).

Family histories were obtained from patients or, in the case of children, their parents and relatives. Pedigree analysis and a retrospective analysis of medical records, and when required, a further contact with the proband and/or family members, were used to determine patterns of inheritance. Speci-

fic enquiries were made to elicit symptoms, including abdominal pain, carpal tunnel syndrome, deafness and learning difficulties. Physical examination was performed to elicit facial and somatic dysmorphism, cutaneous anomalies, macroglossia, retarded growth. A neuromuscular evaluation was performed to determine cognitive impairment, skeletal muscle weakness, sensorineural hearing loss, carpal tunnel and/or sensitive neuropathy, and other clinical markers suggestive of systemic diseases.

Laboratory analysis included measurement of blood glucose, proteinuria, blood urea nitrogen, creatinine, electrolytes, lactate, ammonia, creatine phosphokinase, transaminases, and lactate dehydrogenase according to a standard clinical protocol. Second line parameters (e.g. insulin; carnitine, acylcarnitine; organic acids; ketones; coagulation factors, etc.) were evaluated according to the clinical picture.

Standard 12 lead ECG was used to record PR interval, QRS voltage, QT interval and repolarization abnormalities. Cardiac imaging with transthoracic echocardiography and cardiac magnetic resonance imaging was used to evaluate the severity and distribution of left ventricular hypertrophy (LVH), the presence of LV non-compaction, LV systolic and diastolic function and tissue characteristics.

We defined 3 phenotype clusters: 1) syndromic phenotype: biventricular, obstructive HCM + pulmonary stenosis; myopathy phenotype: concentric hypertrophy + muscle myopathy + lab abnormalities (CK and/or transaminases increase); infiltrative phenotype: ground-glass appearance of ventricular myocardium + lab abnormalities (gamma peak and/or proteinuria).

Statistical analysis

Statistical analysis was performed using a commercially available package (SPSS, version 15.0, 2002, SPSS Inc., Chicago, Illinois, USA). Data are presented as percentages, means and standard deviations. Categorical variables were compared using the Fisher exact test. Normally distributed variables were compared using the Student t-test. Skewed data were analyzed using the Mann–Whitney U test, the Wilcoxon rank-sum test and the Kruskal Wallis test, as appropriate. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and predictive accuracy (PA) of RF for specific causes of HCM were analyzed. In brief: a) for overall RF, we have calculated the accuracy of any RF to detect the presence of any specific aetiology (non sarco-

meric form) of HCM (i.e. Se, Sp, PPV, NPV, PA of lentigines was calculated not only for raropathies, but for all the non-sarcomeric aetiologies); b) for single RF and clusters, we have calculated the accuracy of RF to detect the specific aetiology (i.e. lentigines for rasopathies). Statistical significance was defined as two-sided p-value <0.05.

Results

Prevalence of RF in the overall study population

A total of 129 consecutive patients with HCM (23.7±20.9 years, range 0-74 years; male/female 68%/32%) were evaluated between September 2013 and December 2017 (Figure 1) (1,16) Following diagnostic work-up, 94 patients (74%) had a definite diagnosis (sarcomeric HCM or specific causes of HCM). Sixty-one patients (47%) were positive for sarcomeric gene disease (sarcomeric group: including 30 [49%] with MYH7; 19 [31%] with MYBPC3; 6 [10%] with TNNT2; 4 [7%] with TPM1; 1 patient [2%] with MYL2; 1 [2%] with TNNC1). Thirty-five patients (27%) were diagnosed with systemic disorders (specific causes of HCM group): 17 malformation syndromes (9 patients [26%] with Noonan syndrome, 5 patients [14%] with LEOPARD syndrome; 1 patient [3%] with cardiofaciocutaneous syndrome; 1 patient [3%] with Costello syndrome; 1 patient [3%] with Cornelia de Lange syndrome); 2 glycogen storage disease (1 patient [3%] with Pompe disease; 1 patient [3%] with type III glycogenosis); 3 lysosomal storage disease (3 patients [9%] with Anderson Fabry disease); 4 neuromuscular diseases (4 patients [11%] with Friedreich's ataxia); 4 patients [11%] with mitochondrial disease; 5 amyloidosis (3 patients [9%] with AL amyloidosis, 2 patients [6%] patients with wild type TTR amyloidosis). Thirty-three patients (26%) were diagnosed as idiopathic HCM (Supplemental Figure 1a).

Patients with specific causes of HCM were most prevalent in infants and in adults >55 years old. Sarcomeric gene disease was more prevalent in the age range between 11 and 55 years old. Idiopathic HCM was more frequent between 19 and 55 years old (Supplemental Table 2, Supplemental Figure 1b-1e and Figure 2).

In the overall cohort of 129 patients, 169 RF were identified in 62 patients (48%). Fourteen RF were present in 13 patients (21%) with sarcomeric gene disease, 129 RF in 34 patients (97%) with

specific causes of HCM, 26 RF in 15 patients (45%) with idiopathic HCM ($p<0.0001$) (Table 1). Mean number of RF per patient was significantly higher in patients with specific causes of HCM compared to idiopathic or sarcomeric HCM (3.7 [±1.6], 0.8 [±0.9], 0.2 [±0.4] respectively) ($p<0.0001$).

The prevalence of RF was higher in infants and in adults >55 years old. In Supplemental Table 3 are reported the total number of RF and the number and the percentages of patients with RF subdivided by age groups.

Diagnostic accuracy of RF in patients with HCM

Overall, RF showed a high negative predictive value to exclude any specific (non sarcomeric) HCM disease (98% [95%CI 94-99%]) (Table 2a). Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and predictive accuracy (PA) of single RF and combination of RF (clusters) for specific HCM disease are reported in Table 2b-c.

Discussion

HCM is an unexplained left ventricular hypertrophy, unrelated to loading condition, due to sarcomeric gene protein disease in up to 50-60% of the cases (1,2). An overlapping phenotype is a consequence of different disorders mimicking sarcomeric HCM, with an estimated overall prevalence of about 15% of the cases (1, 4, 13,14). RF have been defined as diagnostic clues that help clinical diagnosis of specific disorders. Cardiac and systemic RF can be obtained from a comprehensive clinical evaluation, including family history, clinical examination, ECG, and imaging (1,13,14).

To date, few studies have examined clinical diagnostic markers in children and adults with different cardiomyopathies. In a multicenter (London-Bologna) study in adults with HCM, reduced LV systolic function (combined with age at presentation) was suggested as a marker of specific aetiologies (infiltrative and/or metabolic disorders) and was associated with poorer long-term survival (19). In children, female sex, small size, presentation with congestive heart failure and an increased left ventricular posterior wall thickness have been reported as highly suggestive of secondary causes of heart muscle disease but are not highly specific or prevalent in HCM (20).

In our study, after an extensive diagnostic work up, we identified 96 patients (74% of the investigated cohort) with a definite diagnosis of sarcomeric or specific causes of HCM. These data contrast with the published literature, which describing a lower prevalence of specific causes of HCM (1, 4, 21). Indeed, previous studies have examined predominantly adult HCM cohorts. Nevertheless, if we focus on the adult cohort, our data are comparable with previous studies in literature (Supplemental Table 2; Supplemental Figure 1d)

To our knowledge, this is the first systematic investigation of RF in HCM across the entire age spectrum. As reported in Figure 2, specific causes of HCM were the most prevalent in ages <1yo (74%) and >55yo (50%) and there was a correlation between age and specific etiology: in infants there was a prevalence of rasopathies and glycogen/lysosomal storage diseases, while in adults >55yo there was an increased prevalence of infiltrative (amyloidosis) and lysosomal storage (Anderson-Fabry) disease consistent with the known natural history of these disorders. Sarcomeric HCM was most prevalent in the age range between 11 and 55yo (particularly in the age range between 11 and 18yo, which is the most common age of onset for sarcomeric HCM).

Interestingly, the prevalence of sarcomeric HCM diagnosed in infants was very low, suggesting that when present, RF may have a major clinical role to suggest etiological diagnosis. This is in line with the data coming from the Pediatric Cardiomyopathy Registry, showing that HCM patients presenting before 1 year of age have the broadest spectrum of causes and the poorest outcome (particularly for syndromic and metabolic HCM) (22).

An important finding of our study was that the presence of RF in the clinical setting had a high NPV in our HCM cohort (98%). According to practical experience, single RF showed an high specificity, NPV and predictive accuracy for specific HCM aetiologies. Moreover, matching together selected cardiac and non cardiac RF may help to design specific clinical picture (i.e. the presence of biventricular, obstructive HCM and pulmonary valve dysplasia for rasopathies). These findings have a high impact in the clinical practice, since investigation of RF is clinically relevant to exclude or suggest a specific HCM etiology.

Clinical Implications

RF showed a high specificity, NPV and predictive accuracy for the differential diagnosis between sarcomeric HCM and specific causes of HCM. An early and etiological diagnosis in HCM patients is indubitably important for cascade family screening, but also for present (23-26) and future perso-

nalized therapies (27) to treat different cardiomyopathies. Nevertheless, the present study was not conceived to analyzed the impact of RF on clinical outcome and management of HCM patients. This will require a larger, longitudinal, long term study.

Conclusions

An extensive diagnostic work-up in patients with HCM is able to define a clinical diagnosis in more than 2/3 of patients. RF were more frequent in the specific causes of HCM group, particularly in infancy and in adults >55yo. Overall, RF had an high NPV, while single RF and clinical combination of RF had a high predictive accuracy for specific etiologies.

Limitations

Potential biases of our study protocol may be related to the age at patient diagnosis and the diagnostic work-up performed. Indeed, the percentages of risk factors, specific diseases and RF predictive values are possibly influenced by the relatively low mean age of the study cohort (23.7±20.9 years). Some RF are age-related. This is particularly frequent in patients with mitochondrial disease, where the clinical phenotype is highly dependent from the genetic background (nuclear or mithocondrial DNA mutations; deletion, point mutation; mutation load effect), but also in Rasopathies, where some of the typical features may be absent at disease onset (e.g. lentigines in LEOPARD syndrome). Moreover, the second step of diagnostic work-up process (Figure 1) was driven by the presence of RF and phenotype of the patients, as generally recommended in the cardiomyopathy and rare disease clinics. It is possibile that predictive value of RF has been influenced by specific methods used to define aetiological diagnosis." An important difference between our study and the multicenter (London/Bologna) study (19) is the age range of the study cohort. Indeed, we included HCM patients diagnosed at any age, which we think is more a strength than a limitation of our study. This can probably explain the different percentage of specific causes of HCM between the 2 studies.

REFERENCES

1. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014 Oct 14;35(39):2733-79.
2. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011 Dec 13;124(24):e783-831.
3. Maron BJ. Clinical Course and Management of Hypertrophic Cardiomyopathy. N Engl J Med. 2018 Aug 16;379(7):655-668.
4. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P, Jurcut R, Calò L, Heliö TM, Sinagra G, Zdravkovic M, Kavoliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, García-Pinilla JM, Salazar-Mendigu-

chia J, Mizia-Stec K, Maggioni AP; EORP Cardiomyopathy Registry Investigators. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J. 2018 May 21;39(20):1784-1793.

5. Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. Heart. 2013 Dec;99(24):1800-11.
6. Girolami F, Frisso G, Benelli M, Crotti L, Iascone M, Mango R, Mazzaccara C, Pilichou K, Arbustini E, Tomberli B, Limongelli G, Basso C, Olivotto I. Contemporary genetic testing in inherited cardiac disease: tools, ethical issues, and clinical applications. J Cardiovasc Med (Hagerstown). 2018 Jan;19(1):1-11.
7. Kaski JP, Syrris P, Shaw A, Alapi KZ, Cordeddu V, Esteban MT, Jenkins S, Ashworth M, Hammond P, Tartaglia M, McKenna WJ, Elliott PM. Prevalence of sequence variants in the RAS-mitogen activated protein kinase signaling pathway in pre-adolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2012 Jun;5(3):317–326.
8. Calcagni G, Limongelli G, D'Ambrosio A, Gesualdo F, Digilio MC, Baban A, Albanese SB, Versacci P, De Luca E, Ferrero GB, Baldassarre G, Agnoletti G, Banaudi E, Marek J, Kaski JP, Tuo G, Russo MG, Pacileo G, Milanesi O, Messina D, Marasini M, Cairello F, Formigari R, Brighenti M, Dallapiccola B, Tartaglia M, Marino B. Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. Int J Cardiol. 2017 Oct 15;245:92-98.
9. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. Heart 2007 Apr;93(4):528-535.

10. Limongelli G, Masarone D, Pacileo G. Mitochondrial disease and the heart. Heart 2017 Mar;103(5):390-398.
11. Limongelli G, D'Alessandro R, Maddaloni V, Rea A, Sarkozy A, McKenna WJ. Skeletal muscle involvement in cardiomyopathies. J. Cardiovasc. Med. (Hagerstown). 2013 Dec;14 (12):837-861.
12. Maurer MS, Elliott P, Merlini G, Shah SJ, Cruz MW, Flynn A, Gundapaneni B, Hahn C, Riley S, Schwartz J, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Design and Rationale of the Phase 3 ATTR-ACT Clinical Trial (Tafamidis in Transthyretin Cardiomyopathy Clinical Trial). Circ Heart Fail. 2017 Jun;10(6).
13. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Heliö T, Linhart A, Mogensen J, Pinto Y, Ristic A, Seggewiss H, Sinagra G, Tavazzi L, Elliott PM. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013 May;34(19):1448-1158.
14. Limongelli G, Masarone D, Verrengia M, Gravino R, Salerno G, Castelletti S, Rubino M, Marrazzo T, Pisani A, Cecchi F, Elliott PM, Pacileo G. Diagnostic Clues for the Diagnosis of Nonsarcomeric Hypertrophic Cardiomyopathy (Phenocopies): Amyloidosis, Fabry Disease, and Mitochondrial Disease. J Cardiovasc Echogr. 2018 Apr-Jun;28(2):120-123.
15. Colan SD. Hypertrophic cardiomyopathy in childhood. *Heart Fail Clin*. 2010 Oct;6(4):433-444.
16. Limongelli, Giuseppe; Perry, M. Elliott. "The genetics of heart failure." *Oxford Textbook of Heart Failure.* Ed. Teresa A. McDonagh. Oxford, 2011; 39-54.
17. Frisso G, Limongelli G, Pacileo G, Del Giudice A, Forgione L, Calabrò P, Iacomino M, Detta N, Di Fonzo LM, Maddaloni V, Calabrò R, Salvatore F. A child cohort study from sou-

thern Italy enlarges the genetic spectrum of hypertrophic cardiomyopathy. Clin Genet. 2009 Jul;76(1):91-101.

18. D'Argenio V, Frisso G, Precone V, Boccia A, Fienga A, Pacileo G, Limongelli G, Paolella G, Calabrò R, Salvatore F. DNA sequence capture and next-generation sequencing for the molecular diagnosis of genetic cardiomyopathies. J Mol Diagn. 2014 Jan;16(1):32-44.
19. Rosmini S, Biagini E, O'Mahony C, Bulluck H, Ruozi N, Lopes LR, Guttmann O, Reant P, Quarta CC, Pantazis A, Tome-Esteban M, Mckenna WJ, Rapezzi C, Elliott PM. Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy. Heart. 2017 Feb 15;103(4):300-306.
20. Cox GF, Sleeper LA, Lowe AM, Towbin JA, Colan SD, Orav EJ, Lurie PR, Messere JE, Wilkinson JD, Lipshultz SE. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. Pediatrics. 2006 Oct;118(4):1519-31.
21. Elliott P, Charron P, Blanes JR, Tavazzi L, Tendera M, Konté M, Laroche C, Maggioni AP; EORP Cardiomyopathy Registry Pilot Investigators. European Cardiomyopathy Pilot Registry: EURObservational Research Programme of the European Society of Cardiology. Eur Heart J. 2016 Jan 7;37(2):164-73.
22. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation. 2007 Feb 13;115(6):773-81.
23. Van Capelle CI, Poelman E, Frohn-Mulder IM, Koopman LP, van den Hout JMP, Régal L, Cools B, Helbing WA, van der Ploeg AT. Cardiac outcome in classic infantile Pompe disease after 13 years of treatment with recombinant human acid alpha-glucosidase. Int J Cardiol. 2018 Oct 15;269;104-110.

24. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, Scheinberg M, Brannagan TH 3rd, Litchy WJ, Whelan C, Drachman BM, Adams D, Heitner SB, Conceição I, Schmidt HH, Vita G, Campistol JM, Gamez J, Gorevic PD, Gane E, Shah AM, Solomon SD, Monia BP, Hughes SG, Kwoh TJ, McEvoy BW, Jung SW, Baker BF, Ackermann EJ, Gertz MA, Coelho T. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):22-31.
25. Spada M, Baron R, Elliott PM, Falissard B, Hilz MJ, Monserrat L, Tøndel C, Tylki-Szymańska A, Wanner C, Germain DP. The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease - A systematic literature review by a European panel of experts. Mol Genet Metab. 2019 Mar;126(3):212-223.
26. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-1016.
27. Limongelli G, Bossone E, Elliott PM, Day SM. On the Road from Gene to Therapy in Inherited Cardiomyopathies. Heart Fail Clin. 2018 Apr;14(2):xi-xv.