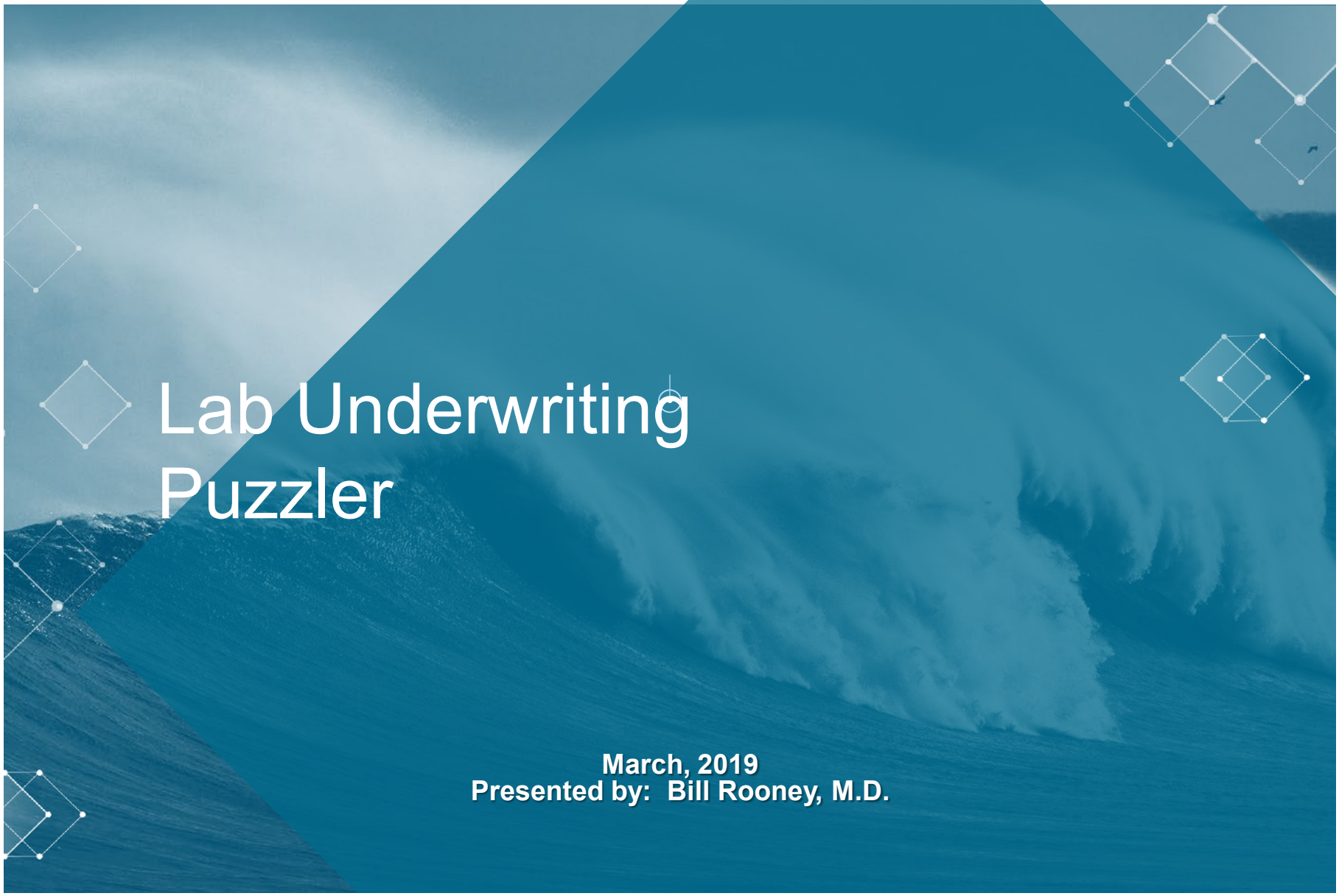


Lab Underwriting Puzzler

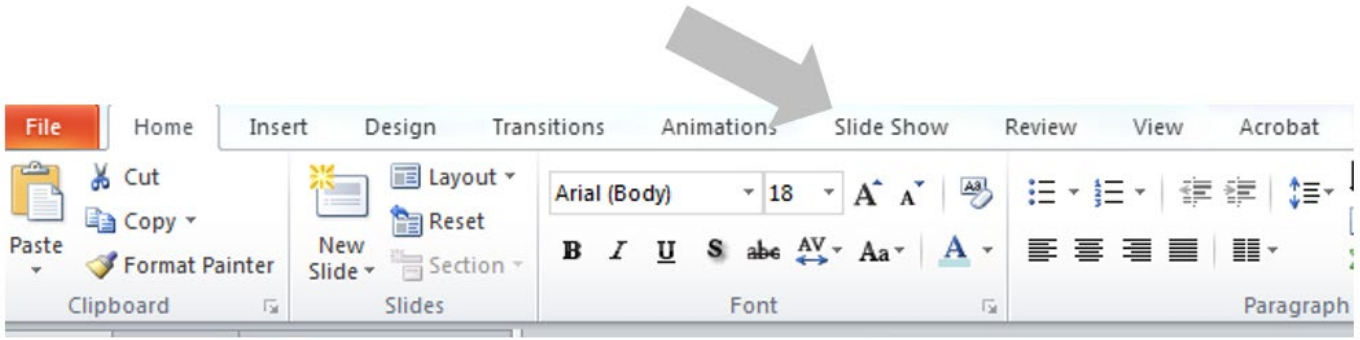
March, 2019
Presented by: Bill Rooney, M.D.

SCOR
The Art & Science of Risk

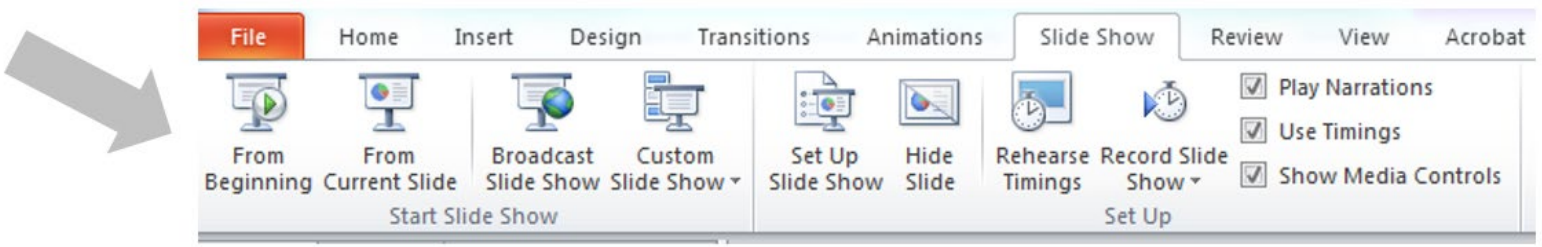
Obtaining Best Results from this presentation

For best results—please do the following:

- Select “Slide Show” from the menu option on top



- Select “From the beginning”



- Slowly click through the presentation
- Have fun!---Good luck

A genetic test has been done and is normal. Does that rule out the presence of the specific disease they are looking for?

Today we will explore why a clinician is watching a patient closely for hypertrophic cardiomyopathy (HCM) despite the patient having a “negative” genetic test. Why would that occur?

Proceed to the next slide for the details of this case.

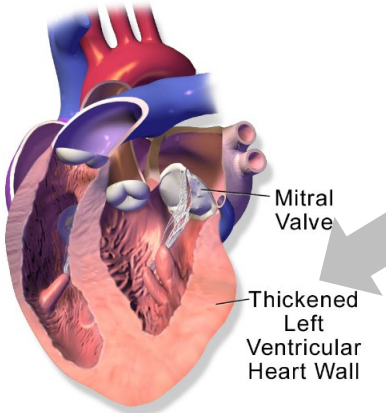
A 33 year old male applies for $750,000.00 of life insurance. He reports having a strong family history (FH) of cardiac problems. He himself has had no cardiac complaints in the past. He has seen a cardiologist because of the FH.

Family History Concern		
Father	Died age 44	Sudden death
Paternal GF	Died "in his 50's"	Sudden death
Paternal aunt	Died recently (? age)	Diagnosed with hypertrophic cardiomyopathy (HCM). HCM discovered after developing atrial fibrillation which was followed by a stroke

APS information		
10/2017	Cardiology evaluation	• EKG: "Nonspecific ST/T wave changes" • Echocardiogram: WNL • Genetic testing: "Negative" • Plans to follow up in 1 year with echocardiogram
11/2018	Cardiology evaluation	• EKG: "Nonspecific ST/T wave changes" • Echocardiogram: WNL • Plans to follow up in 1 year with echocardiogram

Why is the cardiologist following this patient so closely with echocardiograms? The genetic test for HCM was negative.

A Quick Review of Hypertrophic Cardiomyopathy



Hypertrophic Cardiomyopathy

What is HCM?

You will recall that hypertrophic cardiomyopathy is a disorder affecting approximately one out of every 500 adults. It is characterized by abnormal enlargement of the heart muscle.

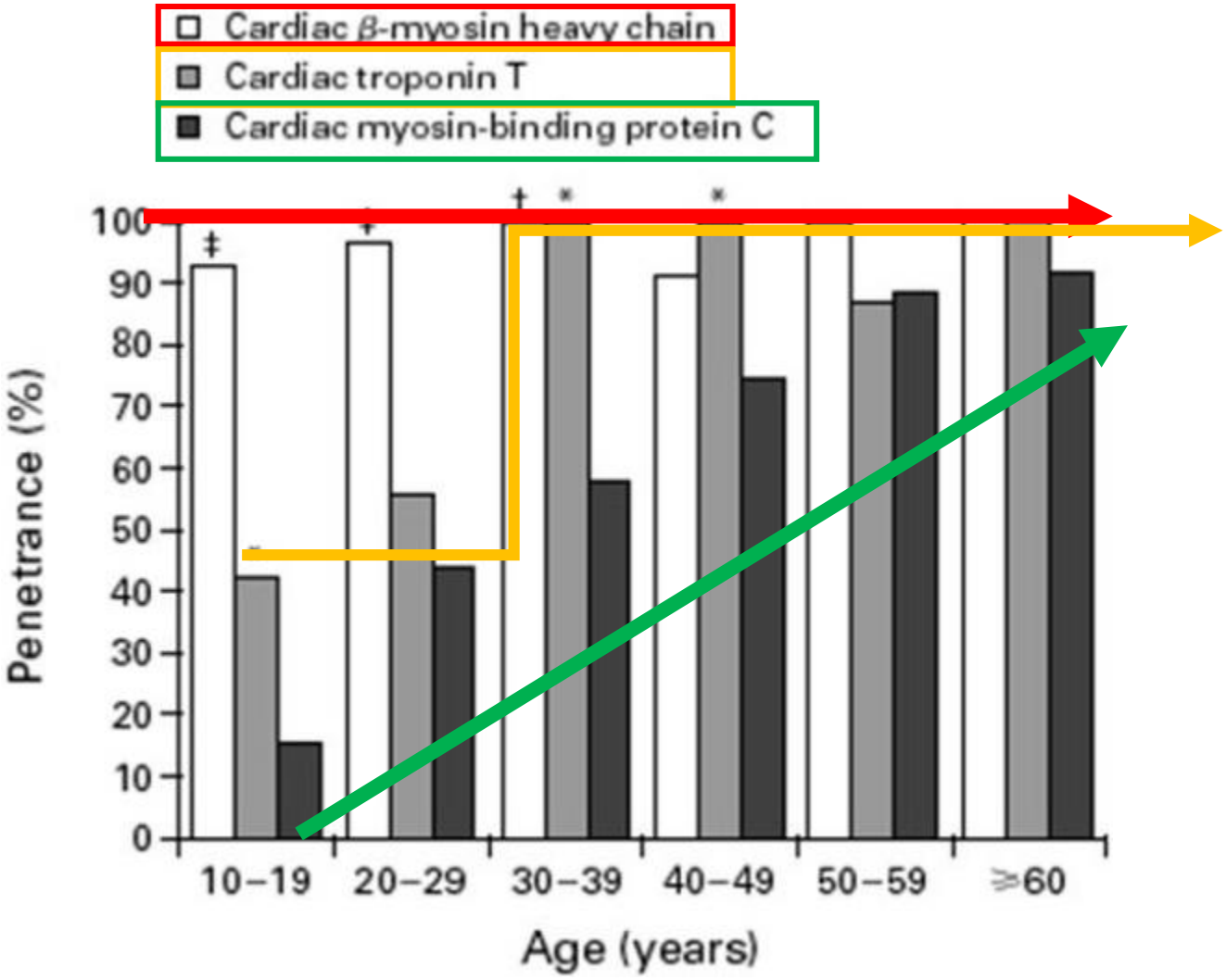
Why are clinicians concerned about HCM?

HCM has been associated with an increased risk of heart failure, arrhythmias, chest pain and early death. In the majority of cases it is felt to be secondary to a genetic alteration. In fact, there have been over 1500 mutations involving 11 different genes implicated as being associated with HCM . Unfortunately, in ~50 percent of people who have HCM there is no identifiable mutation found upon genetic testing.

When does it impact a person?

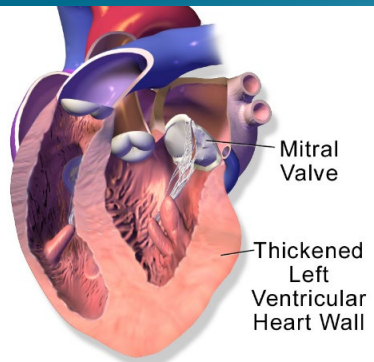
Age of presentation: HCM can present at almost any age. It has been discovered in infants, adolescents, and early adulthood but at times the heart exam is normal until a much older age, including those over age 65. The following slide describes 3 of the genes frequently involved in HCM and the typical age of presentation.

HCM penetrance related to defect



Heart Fail Clin. 2010 April 1; 6(2): 141–159

A Quick Review of Hypertrophic Cardiomyopathy



Hypertrophic Cardiomyopathy

How is HCM diagnosed?

Diagnosis: HCM can cause abnormalities in many cardiac tests and evaluation of patients suspected or found to have HCM because of family history or because of symptoms frequently involves a battery of tests. These tests can include an EKG, an echocardiogram, ambulatory EKG monitoring, cardiac stress testing, cardiovascular magnetic resonance imaging, electrophysiology studies, genetic testing and at times cardiac catherization. An EKG and echocardiogram are common tests performed on individuals as they monitor for the development of HCM, much like this case we are discussing today.

What is the prognosis of those with HCM?

Prognosis: Those with HCM can be completely asymptomatic throughout their entire lives. However, at times, those with the condition can develop complications such as serious arrhythmias, congestive heart failure, stroke, or die from sudden death.

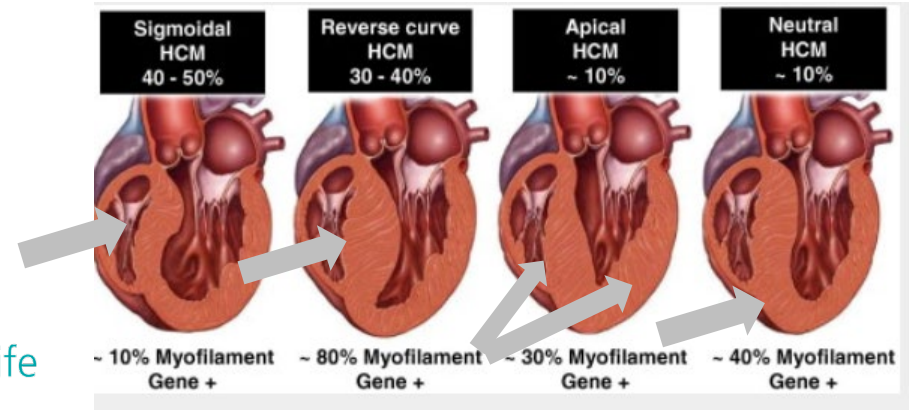
The role of genetic testing for clinicians

HCM is an autosomal dominant disorder. This means that a child born to a parent with HCM has ~ a 50% chance of inheriting the mutation.

HCM has a high degree of penetrance. This means that a person with the genetic mutation has a high probability of developing the abnormal changes in the heart.

HCM has a high degree of heterogeneity. This means that two individuals in the same family with the same genetic mutation can have two completely different cardiac and clinical outcomes. One can be symptomatic and die at a much younger age, the other being completely asymptomatic and have a normal life span.

The abnormal enlargement of the heart can impact different parts of the heart. See the diagram below.



Picture from J Am Coll Cardiol.. 2009;54:201-211; Bos, J. Martin et al.

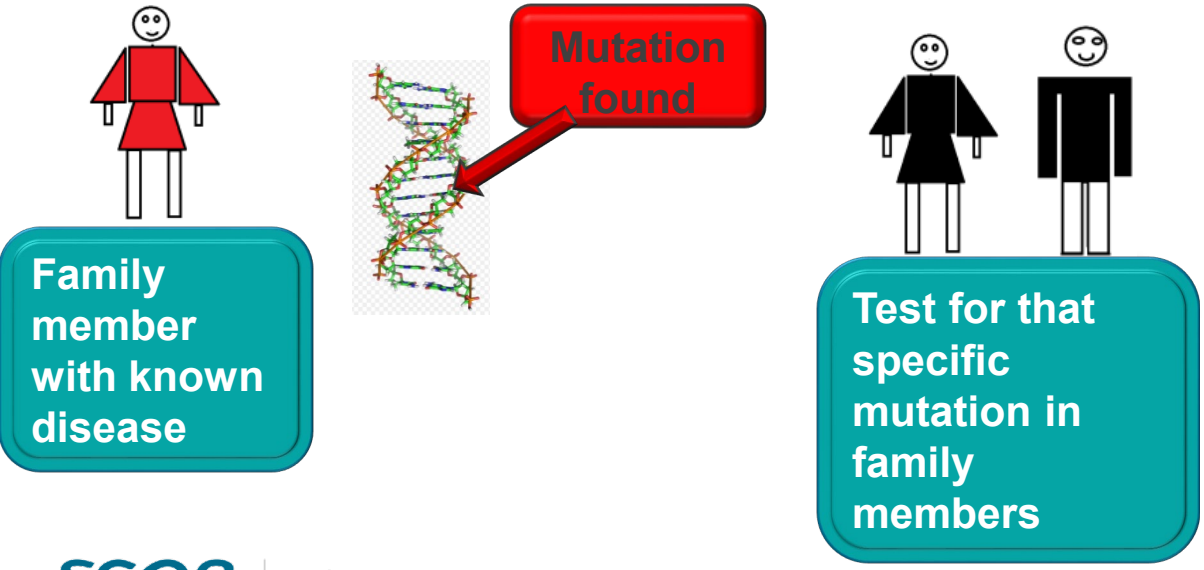
The role of genetic testing for clinicians

How often are genetic tests accurate in HCM?

As previously stated genetic testing can find a specific mutation associated with development of the disease in only ~50 percent of cases. When a specific mutation is found it is very helpful for the family members.

Family members can be tested specifically for this known mutation.

- If positive, they are at risk of developing the disorder.
- If negative, they are at substantially less risk of developing HCM, their risk is probably more close to the general population.



The role of genetic testing for clinicians

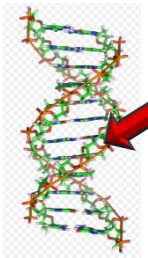
It can be frustrating for patients who don't know what the specific mutation is that has caused the disease in a family member.

When the specific genetic mutation has not been tested for in the family member who had the disease it is difficult for family members.

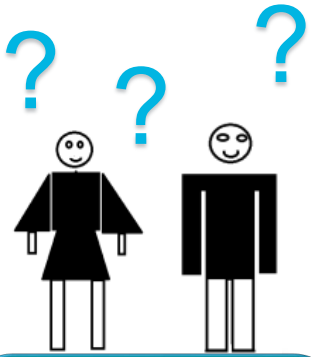
- Was the HCM in the family member from the 50% who have a known mutation and testing would have been helpful?
- Is the mutation in the family in the 50% that testing doesn't find a mutation?

Without this information, the concerned patient doesn't know if a negative test is truly negative.

Family member with known disease—not tested



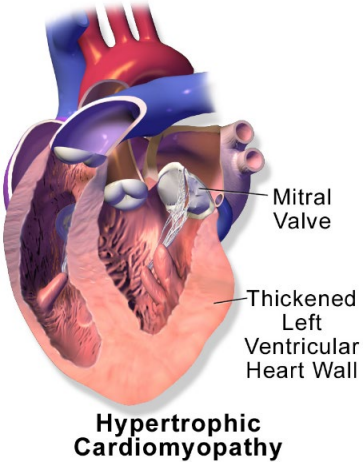
Mutation not known (It might have been there if tested. It might have not been there)



Test for a mutation in family members

Not as helpful.

Returning to the case



Hypertrophic Cardiomyopathy

In summary

In this case, despite negative genetic testing, the clinician is worried her patient might fit into the 50% chance of having negative genetic testing but still having the disease. Since the disease can manifest itself at almost any age, she has documented her recommendation that he be followed closely with an annual history, physical exam, EKG and echocardiogram and to notify her immediately if there is any chest pain, palpitations, or shortness of breath symptoms.

Question answered.