



Pennsylvania

CHAPTER

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Dear Ms Lamens:

The Pennsylvania Chapter of the American College of Cardiology appreciates the opportunity to offer an opinion on the role of Allomap (gene expression profile) testing in the care of patients post heart transplantation.

I write this letter as the Governor-elect of the Pennsylvania Chapter of the American College of Cardiology (PaACC)-western. This opinion will be derived from clinical experience and the medical literature as well as from opinions of colleagues from transplant centers around the country. I will specifically address the role of genetic expression profiling in the care of patients post heart transplantation. No position exists currently that I am aware of in the appropriateness or practice guidelines of the national ACC.

We are quite appreciative of the opportunity to offer this opinion. The Pennsylvania Chapter of the American College of Cardiology represents over 1,000 practicing cardiologists in the state of Pennsylvania as well as cardiac care associates whose main mission is to advocate for quality of cardiovascular care, disseminate continuing medical education, and promote research. It is thus a welcomed opportunity as one of our main missions is to insure quality care for the patients we care for.

Genetic expression testing, Allomap, from XDx Laboratories is an innovative test that uses genomic technology to help physicians care for heart transplant patients. **In particular, it is currently used to determine who is at low risk of acute cellular rejection and in whom a right heart catheterization and endomyocardial biopsy may be safely avoided.**

The Allomap test assesses the expression of 20 genes 11 of which are used to determine the risk of acute cellular rejection and 9 others for normalization and quality control. The Allomap score ranges between 0 and 40. The lower the score the lower the probability of acute cellular rejection at the time of testing. This test is currently used along with other standard clinical assessments like history, physical examination, blood work, and echocardiography to evaluate the patient's probability of rejection and the need for additional diagnostic evaluation. Endomyocardial biopsy currently is the gold standard, and as you are aware this is an invasive test associated with well documented morbidities that patients have to undergo up to 20 times in the first year post transplant alone. The Allomap test has a very high negative predictive value which therefore identifies patients who have a low probability of cellular rejection and can spare patients many if not all of these biopsies. It is a simple blood test that is used when a blood sample obtained during the routine phlebotomy that occurs during a standard post-transplant clinic visit. Quantitative real time polymerase chain reaction is performed at an outside

lab and the differential gene expression is quantitated to a simple actionable score which has been thoroughly validated. This score, in conjunction with clinical and echocardiographic data, can be used to make clinical decisions regarding immunosuppression and the role of biopsy. This is truly a significant innovation in genetic testing and a great advance in our ability to non-invasively detect the absence of clinical rejection.

This test has been clinically validated and the data was published in the Cardiac Allograft Rejection Gene Expression Observational Study (CARGO) in over 5,000 blood samples from patients who have had heart transplants. This test is performed in CLIA certified X Dx Reference Laboratory in Brisbane, CA and has received FDA clearance as an in vitro-diagnostic multi-variate index assay.

There are multiple states throughout the country that do reimburse for this clinically important test. Medicare also has agreed to reimburse for this test. It is being used throughout the country at major transplant centers. We currently use Allomap testing within the context of the IMAGE trial. This technology is innovative, validated and will hopefully replace endomyocardial biopsies in the future. It represents a significant step towards improving our ability to detect clinically significant rejection in heart transplant patients.

Therefore, it is the position of the Pennsylvania Chapter of the American College of Cardiology that Allomap testing is a validated FDA cleared in-vitro assay with a very high negative predictive value to exclude acute cellular rejection. We feel that gene expression profiling is an exciting modality that will continue to expand and play a vital role in the care of patients post heart transplantation. We also feel that eventually a cost-saving benefit will be realized when the number and frequency of endomyocardial biopsies will be decreased sparing patients from adverse complications and invasive procedures.

Therefore, we would recommend coverage of Allomap testing to exclude acute cellular cardiac rejection. This currently is the only FDA-cleared indication for this test.

It has been my privilege and pleasure to be able to offer this opinion on behalf of the Pennsylvania Chapter of the American College of Cardiology. We appreciate the opportunity to do so and thank Highmark for asking us to be involved in this important decision. The PaACC is committed to the goal of appropriate use of technology in the care of cardiovascular patients and appreciate the opportunity to be involved in the evaluation of new and exciting technology.

Most sincerely,

A handwritten signature in black ink, reading "Rene' J. Alvarez, Jr., MD". The signature is written in a cursive style with a small "MD" at the end.

Rene' J. Alvarez, Jr., MD, FACC