

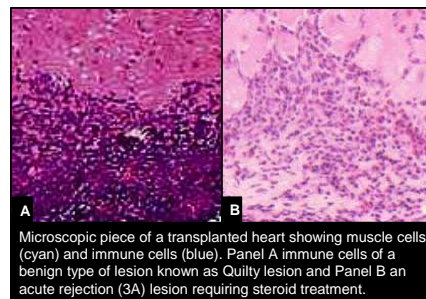
## A GENE EXPRESSION TEST TO DETECT REJECTION OF THE TRANSPLANTED HEART

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### THE CARGO-STUDY

The heart muscle biopsy has for decades been the most reliable method for detecting rejection of the transplanted heart, by placing 4-6 tiny (1x 1x 1 mm) muscle pieces under the microscope and looking for the cells of the immune system which recognize your heart as non-self and destroy it. Unfortunately biopsies are not free of complications and can cause pain, even in the most experienced hands. Also there is a discrepancy in the interpretation of biopsies among different expert pathologists in that 2 out of 10 biopsies are not interpreted in the same way.

These, briefly are some of the reasons why patient and physicians wanted to have a new method for allograft surveillance after heart transplantation.



### Is it possible to watch for rejection of the heart - without looking at the heart?

This question was asked by scientists since the very beginning of heart transplantation. Physicians always look for many signs and symptoms to find out if the heart is being rejected or accepted. But it has been impossible to recognize rejection without biopsy. Things changed during the last decade through increased understanding of how genes work in the cells of our body.

**What are the genes?** The genes are very tiny molecules of our body, located in the nucleus of the cells and telling the cells what they should do. For example if there is an infection certain genes related to defense of our body against infection will “turn-on” to produce specific protein molecules. The protein molecules tell the cells of the immune (defense) system “go, recruit your buddies and fight the infection”. The genes contain the “genetic code” which is now known to mankind after the “Human Genome Project” was completed in 2001.

So basically the next question was: if the immune system (i.e. white blood cells) is controlling what is going on in the body, including the heart, then the genes turned on or off in the white blood cells should carry highly valuable information about the presence or absence of rejection (quiescence) in the transplanted donor heart. This was the hypothesis and starting point for the “CARGO” study in 2000.

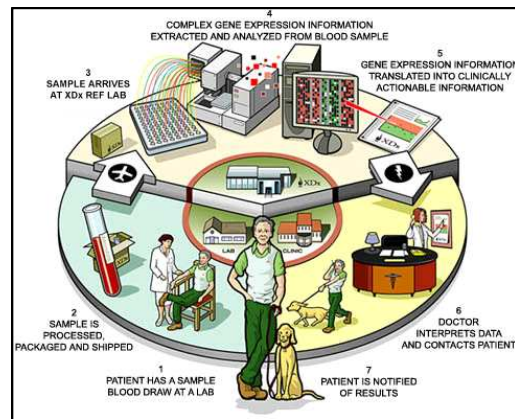
**What is the CARGO study?** The CARGO study is a large clinical research project designed to develop a blood test that measures the activity of genes related to allograft rejection. Researchers hoped that the study would help heart-transplant patients avoid some endomyocardial biopsies and improve their clinicians' ability to make management decisions. The study led to the development of AlloMap™ molecular expression testing. ([www.allomap.com](http://www.allomap.com)) AlloMap testing was developed in collaboration between major US

transplant centers and XDX, a molecular diagnostics company, in South San Francisco, California ([www.xdx.com](http://www.xdx.com)). The results of this research showed a high correlation between results of the test and moderate/severe rejection based on the endomyocardial biopsy. CARGO stands for “**C**ardiac **A**llograft **R**ejection **G**ene Expression **O**bservational Study and the study collected information from 5000 biopsies of more than 650 transplant recipients at the eight major US centers. This study showed that this test was able to differentiate the presence of advanced rejection from quiescence (absence of rejection) by studying the expression of genes in the white blood cells.

### How does AlloMap testing work?

The AlloMap test looks at 20 genes to monitor your immune status. It yields an AlloMap score that reflects the degree to which the heart transplant recipient has mobilized an immune response that causes allograft rejection.

The test is very simple and consists of a normal peripheral blood sample, which is sent to the XDX Reference Laboratory where it is processed and the results mailed back to the medical center within 3 to 5 days. When the test is below a certain number the likelihood of having moderate/severe (grade 3A or higher) rejection is less than 1%. Based on this result your physician can decide whether or not to pursue the biopsy.



**Future Perspectives** After completion of this multicenter study, the international CARGO study consortium is now conducting three follow-up studies, 1) the **IMAGE** (Invasive Monitoring Attenuation Gene Expression) study in the United States will compare the safety of monitoring the allograft with Allomap™ test and biopsy, 2) the **ARGO** (Allograft Rejection Gene expression Observation) study in Columbia will examine details on the relationship between gene expression occurring in the transplanted organ and in the cells of the immune system, and 3) the **CARGO II** study started to recruit patients in major centers in Europe, US and Canada reproducing the findings of the original CARGO study in a broader population.

**IMAGE-STUDY (Columbia IRB # AAAA8832)**

**CARGOII (Columbia IRB # AAAA5465)**

**ARGO-STUDY (Columbia IRB # AAAA5465)**

### More information

<http://www.cardiactransplantresearch.cumc.columbia.edu>

<http://www.xdx.com>

<http://www.allomap.com>

[http://www.ornl.gov/sci/techresources/Human\\_Genome](http://www.ornl.gov/sci/techresources/Human_Genome)