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REVIEW

Peripheral blood gene expression profiling for cardiovascular disease assessment

Hamza Aziz · Aimee Zaas · Geoffrey S. Ginsburg

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Abstract Whole blood gene expression profiling has the potential to be informative about dynamic changes in disease states and to provide information on underlying disease mechanisms. Having demonstrated proof of concept in animal models, a number of studies have now tried to tackle the complexity of cardiovascular disease in human hosts to develop better diagnostic and prognostic indicators. These studies show that genomic signatures are capable of classifying patients with cardiovascular diseases into finer categories based on the molecular architecture of a patient's disease and more accurately predict the likelihood of a cardiovascular event than current techniques. To highlight the spectrum of potential applications of whole blood gene expression profiling approach in cardiovascular science, we have chosen to review the findings in a number of complex cardiovascular diseases such as atherosclerosis, hypertension and myocardial infarction as well as thromboembolism, aortic aneurysm, and heart transplant.

Keywords Cardiovascular · Genomic techniques · Microarray analysis · Whole blood gene expression profiling

H. Aziz
School of Medicine, Duke University, Durham, USA

A. Zaas · G. S. Ginsburg
Department of Medicine, Duke University Medical Center, Durham, USA

G. S. Ginsburg (✉)
Institute of Genome Science & Policy, Duke University, 101 Science Dr, Rm 2111 Ciemas Bldg Durham, Durham, NC 27708, USA
e-mail: Geoffrey.ginsburg@duke.edu

Introduction

Despite significant advances in our understanding of the molecular mechanisms of cardiovascular disease, diagnostic tests for judging its severity and response to therapeutic interventions remain invasive (angiography, intravascular ultrasound) or suffer from lack of precision. The need for improved diagnostic tools for assessment, risk stratification, therapy selection, and monitoring has become all the more urgent in the context of an aging population that is living longer and with increasing risk factors of cardiovascular disease.

In contrast to DNA based testing that generally provides information on disease predisposition and susceptibility, dynamic genomic markers from disease tissues may provide insights into mechanism based processes associated with disease states as well as biomarkers that can be used for diagnosis, prognosis, drug response, and monitoring of disease activity. Cardiovascular diseases, unlike other disease entities where the primary disease tissues can be obtained for diagnostic or prognostic analyses, do not readily lend themselves to tissue collection. With increasing feasibility and reliability in genomic technologies to probe for disease and an awareness of the practical limitations of collecting primary cardiovascular disease tissue specimens, the need for reliable blood based biomarkers that can report on disease states has grown tremendously. Not only is blood easier to obtain compared to a tissue biopsy, but it also contains a number of circulating cell types such as platelets, neutrophils, peripheral blood lymphocytes, and circulating stem cells that are mechanistically associated with both myocardial and vascular disease processes. Thus capturing the global genomic response through changes in RNA expression in blood may provide a useful tool for developing diagnostic and

prognostic indicators for complex diseases, particularly ones involving the vasculature or its circulating components.

Instead of analyzing single genes, global gene expression provides a "molecular signature" that may distinguish between one disease state and another. In addition to identifying signatures or patterns of gene expression that represent a disease state, analyses can be constructed to identify representative pathway genes that might point to novel pathophysiology relevant to the underlying disease state. Peripheral blood gene expression signatures have now been reported in a variety of conditions including rheumatoid arthritis (Lequerré et al. 2006; Shou et al. 2006), systemic lupus erythematosis (Rus et al. 2004), multiple sclerosis (Bomprezzi et al. 2003; Singh et al. 2007), asthma (Brutsche et al. 2002), solid malignancies (Alizadeh et al. 2000; Golub et al. 1999; Valk et al. 2004), solid organ transplantation (Baron et al. 2007; Horwitz et al. 2004), as well as environmental exposures (Lodovici et al. 2007; Wu et al. 2003; Dressman et al. 2007) (see Table 1). Many of these conditions have an inflammatory component and thus affect immune cells in the vascular compartment. It is hypothesized that these cellular changes are the basis for the differences in gene expression that is observed in RNA extracted from whole blood specimens or from specific circulating cell types.

The important role of inflammation in a number of cardiovascular conditions like atherosclerosis (Libby 2002), essential hypertension (Yasunari et al. 2002), and post-myocardial infarction (MI) remodeling (Frangogiannis et al. 2002), has been well established. This relationship makes the study of peripheral blood leukocyte or whole blood gene expression particularly well suited for developing more refined diagnostic and prognostic tests in cardiovascular medicine (see Table 2) as circulating cells 'sense' the pro-inflammatory state. The greatest potential of this approach would be the enhancement in accurately classifying patients by the type and severity of their disease and to individualize the therapy based on the biology of the disease in an individual patient. This review broadly looks at studies that used peripheral blood gene expression profiling to develop a non-invasive tool for assessing vascular disease burden or to provide a patient-specific risk profile for patients with atherosclerosis risk factors, myocardial

Table 1 Peripheral blood gene expression profiling in a variety of conditions

	Target cell	Results	References
Autoimmune	Whole blood RNA	41 gene signature differentiated Infliximab responders from non-responders.	(Lequerré et al. 2006)
	Whole blood RNA	28 gene signature differentiated between blood samples from arthritic and non-arthritic rats.	(Shou et al. 2006)
	Whole blood RNA	29 gene signature best differentiated active versus inactive SLE	(Rus et al. 2004)
Inflammatory	Peripheral monocytes	A 53 gene signature distinguishes between patients with active multiple sclerosis and healthy controls.	(Bomprezzi et al. 2003)
	Peripheral monocytes	A 136 gene signature distinguishes active MS patients on TNF-alpha therapy from treatment naïve patients.	(Singh et al. 2007)
	Whole Blood RNA	10 genes based composite score for diagnosing atopy and asthma performed better than total IgE count with sensitivity and specificity of 96% and 92%, respectively.	(Brutsche et al. 2002)
Neoplasm	CD27+ and CD19+ B cells; CD4+ T cells	2,984 gene signature could distinguish subtypes of diffuse large B cell lymphoma.	(Alizadeh et al. 2000)
	Bone marrow mononuclear cell RNA	From 6817 genes tested, 50 found to be most highly correlated with AML-ALL distinction and used to develop the classification scheme.	(Golub et al. 1999)
	CD34+ blast cells RNA	A set of 2856 genes allowed classification of AML into 16 distinct groups.	(Valk et al. 2004)
Transplant	CD4+ and CD8+ T-cell RNA	17 gene signature identified donor samples likely to cause GVHD with 80% accuracy.	(Baron et al. 2007)
	Whole Blood RNA	From 22, 125 gene profiled, 91 genes were differentially expressed between rejection (grade 3A) versus controls (grade 0).	(Horwitz et al. 2004)
Environmental exposure	Whole blood RNA	216 gene profile differentiated oxidative damage from active oxidative damage in active and passive smokers	(Lodovici et al. 2007)
	Whole blood RNA	62 gene profile correlated with severity of arsenic poisoning.	(Wu et al. 2003)
	Whole blood RNA[a]	25 gene signature differentiated between irradiated and non-irradiated human blood with overall accuracy of 90%	(Dressman et al. 2007)

[a] Used gradient centrifugation to separate leukocyte fraction

Table 2 Peripheral blood gene expression profiling in cardiovascular diseases

Indication	Target cell	Results	Ref
Dyslipidemia	Whole blood RNA	895 genes correlated with LDL, 687 with HDL, and 364 with total cholesterol. 188 genes correlated both with LDL and total cholesterol.	(Ma et al. 2007)
Essential hypertension	Whole blood RNA	680 genes were found differentially expressed in untreated hypertensives compared to normotensive controls. On the other hand only 7 genes were differentially expressed in treated normotensives compared to normotensive controls.	(Chon et al. 2004)
Type 2 Diabetes	Whole blood RNA[a]	Among the various pathways analyzed, 48 genes of JNK correlated with diabetes and glycemic control while 92 genes of OXPHOS correlated only with diabetes status irrespective of glycemic control.	(Takamura et al. 2007)
Myocardial infarction	Platelet RNA	From >18,000 probe sets, 54 probe sets showed differential expression between STEMI and stable CAD. Moreover, MRP8/14 predicts risk of future cardiovascular event.	(Healy et al. 2006)
Aortic Aneurysm	Whole blood RNA	A 41 gene signature identified between patients with aortic aneurysm and controls with 78% accuracy along with a sensitivity and specificity of 72% and 90% respectively.	(Wang et al. 2007)
Venous Thromobo-embolism	Whole blood RNA	From 24, 650 genes profiled, 106 gene signature identified (1) patients with APS vs non-APS patients with VTE. (2) Predicticted likelihood of APS in patients with VTE. (3) Predicted likelihood of VTE in patients with aPLAs but not APS.	(Potti et al. 2006)
Cardiac transplant	Whole blood RNA	From 252 genes profiled, an 11 gene test discriminated between moderate/severe rejection and quiescence.	(Deng et al. 2006)
Pulmonary hypertension	Whole blood RNA[a]	A 106 gene signature identified with 95–100% accuracy patient with pulmonary hypertension versus controls.	(Bull et al. 2004)

[a] Used gradient centrifugation to separate leukocyte fraction

infarction, structural heart disease, transplantation, and pulmonary hypertension. This field is in its infancy, but it will contribute a series of novel tools for the practice of genomic cardiovascular medicine.

Hyperlipidemia

Hyperlipidemia is a known risk factor for atherosclerosis and developing a genomic signature of hyperlipidemia is an important step in improving the assessment of disease burden from atherosclerosis. Given the important role of inflammatory cells (i.e. PBMCs) in atherosclerosis, Ma et al. investigated the effect of lipids on the gene expression profile of PBMCs. The researchers found that PBMC gene expression profile varied with serum lipid levels (Ma et al. 2007). Analyzing mRNA from 32 healthy subjects, researchers found that 895 genes correlated with LDL levels (480 negatively; 415 positively) and 687 genes showed correlation with HDL (434 negatively; 253 positively). Many of the identified genes mapped to a previously known QTL that is associated with regulating plasma lipid levels. Functional categorization of these genes revealed that inflammatory genes were positively correlated with LDL, triglyceride, and total cholesterol levels, but negatively correlated with HDL. Moreover, genes involved with fatty acid metabolism and electron transport chain showed positive correlation with low-density lipoprotein (LDL) levels and negative correlation with high-density lipoprotein (HDL) levels. Finally, platelet activation genes (PF4 and PPBP), which the team had earlier shown up regulated with CAD (Ma and Liew 2003), demonstrated inverse correlation with HDL levels. Although the diagnostic or predictive accuracy of this approach was not determined in this investigation, this work does provide a framework for doing so in future investigations. Other work in this area has shown that blood genomic profile can also serve to distinguish between familial and non-familial hyperlipidemia. Working with immortalized monocyte cell lines from individuals with familial combined hyperlipidemia (FCHL), Morello et al. showed that 166 genes were differentially expressed between FCHL derived cells and normal control cells. The 166 gene profile was tested in an independent cohort of control subjects that were not matched for age, BMI, or FCHL status, but had similar lipid levels (Morello et al. 2004). The transcriptional analysis not only separated groups of FCHL and control cells, but also showed further sub-categorization of FCHL cell lines. That peripheral gene expression signatures can be defined for hyperlipidemia suggests that it should be possible to develop similar profiles for more complex vascular disease phenotypes such as atherosclerosis or plaque vulnerability.

Hypertension

Evidence accumulated over the past five decades has established indisputable relationship between hypertension and risk of cardiovascular disease, which includes many sequelae of atherosclerosis like ischemic heart disease and stroke (Chobanian et al. 2003). Results from the Framingham study have shown that risk of cardiovascular disease (CVD) doubles in even pre-hypertensives (130–39/85–89) compared to normotensives (<120/80) (Chobanian et al. 2003). Antihypertensive therapy can reduce but not completely normalize the risk of developing atherosclerosis. Current modalities, however, do not allow identification of such individuals who are at risk despite normalization of blood pressure. To begin tackling this problem, Chon et al looked at the responsiveness of gene expression profiling of PBMCs to antihypertensive medications (ACE inhibitor and beta blocker). Not surprisingly, untreated hypertensives showed upregulation of oxidative stress and inflammatory genes while suppression of antioxidant genes. However, the expression of such genes returned to baseline once the patients were controlled to <140/85 with pharmacotherapy (Chon et al. 2004). Using six uncontrolled hypertensives (>140/85) and six pharmacologically managed hypertensives (<140/85), gene expression patterns of hypertensives revealed 680 genes that were upregulated as compared to patients who were normotensive on medication. The overall pattern of gene expression in untreated hypertensives showed upregulation of proinflammatory interleukins and cytokines and down regulation of anti-inflammatory interleukin receptors. Moreover, upregulation of the serotonin 2b receptor was observed in the untreated hypertensive patients. This receptor is involved in the activation of T cells and B cells and raises the possibility of this receptor being a possible contributor to blood pressure regulation and inflammation. While small in scope, this hypothesis-generating study is a basis for further evaluation of the gene expression profile in both untreated and treated hypertension. Larger studies of hypertensive individuals may provide insight into varying pathophysiologic entities that lead to the final common pathway of elevated blood pressure. Moreover, these studies suggest the possibility that gene expression may be developed further as a useful tool to assess average blood pressure over time. Ultimately, clinicians may be able to utilize gene expression patterns in hypertensive patients to guide optimal drug selection, to assess blood pressure control over time, or to predict end-organ outcome.

Diabetes Mellitus

Type 2 diabetes is a well established risk factor for cardiovascular complications owing to oxidative stress, high levels of glucose, insulin, and free fatty acids. Given the significant morbidity and mortality associated with the cardiovascular complications of type 2 diabetes, developing biomarkers reflective of underlying pathology and predictive of disease progression remain an important objective. PBMCs are exposed to the systemic effects of type 2 diabetes and were therefore postulated by Takamura et al. to change their genomic expression in response to the disease state and reflect the oxidative stress associated with vascular damage. Takamura et al. (2007) compared samples from 18 patients with type 2 diabetes and 16 non-diabetics and found that 48 genes in the c-Jun N-terminal kinase (JNK)[1] pathway were the only ones with consistently elevated gene expression among poorly controlled diabetics and down-regulated with glycemic control. The JNK pathway has been implicated in pancreatic β cell dysfunction as well as in promoting insulin resistance through its action in the hepatocytes (Kaneto et al. 2004). This differential expression of the JNK pathway could provide a better marker of evaluating glucose induced stress in diabetes as opposed to inflammatory markers like C-reactive protein (CRP) and tumor necrosis factor (TNF) α which are not affected by glycemic control. Moreover, genes associated with mitochondrial oxidative phosphorylation (OXPHOS)[1] were down-regulated with diabetes and remained unchanged with glycemic control. Down regulation of genes involved with oxidative phosphorylation has also been demonstrated in diabetics and pre-diabetics from gene expression profiling of skeletal muscles (Patti et al. 2003). These results not only provide additional validation to past research, but also show that peripheral blood mononuclear cell gene expression may potentially serve as an effective, non-invasive marker of diabetes or pre-diabetes. Additionally, such studies may provide starting points for researchers to identify novel genes involved in key glucose regulatory pathways.

Myocardial Infarction (MI)

There are approximately 1.3 million cases of MI each year with an annual age adjusted rate of 241 cases per 100,000 people (CDC 2005). Although, very sensitive biomarkers to detect and diagnose MI are used clinically, there is great need to develop better markers that can *predict* the risk of MI. In this direction, Healy et al. used platelet RNA expression to predict the likelihood of an acute coronary event (Healy et al. 2006). They profiled mRNA from platelets of 16 subjects who presented for catheterization for ST-elevation myocardial infarction (STEMI) and 44 subjects with stable CAD. Their analysis showed that

[1] KEGG Pathway

mRNA found in platelets of individuals having a STEMI had the strongest upregulation of CD 69 and myeloid related protein-14 (MRP-14), which are involved in platelet aggregation and calcium dependent signal transduction respectively as well as cytoskeletal reorganization and leukocyte trafficking (Donato 2003). CD69 showed a 2.7-fold higher median expression in patients with STEMI than with stable CAD. MRP-14 had a 2.2-fold higher median expression in STEMI as compared to persons with stable CAD. To correlate MRP-8 and 14 expression with occurrence of cardiovascular events, Healy et al. then evaluated MRP-8 and 14 levels in a well-characterized cohort of postmenopausal women. Using a healthy cohort of postmenopausal women from the Women's Health Study, the researchers looked at the relative risk of a first cardiovascular event according to increasing quartiles of baseline MRP-8 and 14 protein levels in serum measured with ELISA. There was an increase in relative risk of first cardiovascular event in these apparently healthy women with increasing quartile of MRP-8 and 14 levels, such that the women in the highest quartile of MRP-8 and 14 protein levels had a 4-fold elevation in risk compared to those in the lowest quartile of MRP-8 and 14 levels. Thus, platelet expression of MRP-8 and 14 are upregulated prior to acute MI and chronic elevation of these proteins can predict vascular events. Secretion of MRP 8 and 14 induces a thrombogenic, inflammatory response by upregulating proinflammatory chemokines and ICAMs in endothelial cells while decreasing the expression of cell junction proteins (Viemann et al. 2007). Therefore, dissecting the temporal relationship between vascular endothelial injury and platelet MRP-8 and 14 expressions will identify if modulation of MRP-8 or 14 levels can impact outcome in patients at risk for vascular events. This study suggests that temporal evaluation of blood RNA profiles from platelets or other circulating cells may provide predictive and prognostic information for future cardiovascular events such as ACS.

Thoracic Aortic Aneurysm (TAA)

Long term hypertension or cystic medial degeneration due to aging or an underlying genetic defect can lead to the development of thoracic aortic aneurysm. This poses a diagnostic challenge because thoracic aortic aneurysm remains sub-clinical until very late in the progression of disease. Therefore, early detection of aortic aneurysm is often critical to a successful treatment outcome. Given the important role of peripheral blood mononuclear cells in inflammation and interaction with diseased aortic tissue, Wang et al. (2007) demonstrated that the gene expression of PBMCs could identify patients at risk for aortic aneurysm. Comparing 56 TAA patients and 36 spousal controls, researchers developed a genomic signature that they found was specific to aortic aneurysm. Testing the model on a test set showed an overall accuracy of 78% with sensitivity and specificity of 81% and 75%, respectively. Preliminary data also suggested that such a genomic signature could also distinguish location of aneurysm such as ascending versus descending aortic aneurysm as well as familial from sporadic form. These results need further verification but highlight that genomic signatures are robust markers of disease and not simply a broad marker of inflammation and that structural heart disease may also perturb RNA profiles in blood to yield a non-invasive means for early detection and or screening of these types of disorders and the identification of patients who might benefit from imaging.

Thromboembolic disease

Venous thromboembolism (VTE) is another leading cause of morbidity and mortality from cardiovascular disease. There are approximately 250,000 cases of VTE a year and 60% of them are recurrent episodes (Cushman 2007). The risk of venous thromboembolism is especially pertinent to patients post surgery or trauma, as well as pregnant women, or patients with cancer or a hypercoagulable disorders such as antiphospholipid syndrome (APS). Current diagnostic modalities do not provide a reliable method for selecting patients with antiphospholipid antibodies (aPLAs) who are at particularly high risk for adverse outcomes. Potti et al. showed that PBMC gene expression profile could both identify a patient with APS as well as identify patients with APS who were at risk for thrombosis. The researchers compared two sets of patients: one set consisted of APS patients with VTE and the other had patients with VTE without APS. The validation group consisted of APS patients with VTE versus patients with asymptomatic aPLAs (Potti et al. 2006). Using a statistical approach similar to earlier work in breast cancer, (West et al. 2001; Huang et al. 2003) the researchers found that their genomic signature was able to pick out patients with APS among a cohort of VTE patients with 85% accuracy. Secondly, they could also predict with 100% accuracy APS patients who would develop thrombosis. This study not only showed the versatility of PBMC gene expression profiling but also the robustness of their genomic prediction model. This is a proof of concept that peripheral blood gene expression may predict recurrent thrombosis; however, the clinical significance will be a lot more if it can be extended to arterial thrombosis, such as MI. Even if it cannot, knowing which patients are at high risk for VTE will be of clear importance in the anticoagulated

populations with presumptively "idiopathic" VTE/pulmonary embolism.

Cardiac transplant

Use of PBMC gene expression profiling has made tremendous progress in the area of solid organ transplantation, with much of the effort focused on developing better tests for predicting graft rejection (Driscoll et al. 2006; Martínez-Llordella et al. 2007; Starling et al. 2006). Research in cardiac transplantation, perhaps more than any other organ, led the way in developing novel blood based test for distinguishing between quiescence and acute rejection. CARGO, a landmark three-phase, multicenter study in the area of cardiac transplantation, showed that PBMC gene expression profiling could be used to accurately distinguish between post transplant patients in quiescence versus acute rejection (Deng et al. 2006). This was achieved by first identifying a set of 11 genes that best distinguished between acute rejection and quiescence and then using an independent cohort to validate the classifying scheme in a prospective and blinded manner. Using a scoring system from 0 to 40, with low scores representing low-risk for graft rejection, researchers set 20 as a threshold for rejection and found that this criterion gave an 84% concordance with a pathologists' reading of Grade 3A/2R and a 38% concordance with quiescence or Grade 0 biopsy. However, using a threshold of 30 on patients more than one year post transplant, validation of the test yielded a 99.6% NPV and 6.8% PPV for acute rejection. This test is commercially available as Allomap™ (XDx; Brisbane, CA) and costs roughly $3000 per test. Although it is expensive, cost analysis based on data from CARGO cohort has shown that this blood based gene expression profiling test is cheaper than biopsy and is likely to save as much as $12 million in healthcare costs annually (Evans et al. 2005). In order for this to be true, however, the need for biopsy would have to be obviated and gene expression profiling would have to suffice in patients considered "low risk" for rejection. Toward that end, a prospective, multi-center, randomized but non-blinded trial called The Invasive Monitoring Attenuation Through Gene Expression (IMAGE) has been initiated. The main hypothesis of the study is that a primarily non-invasive rejection surveillance strategy utilizing GEP testing is not inferior to endomyocardial biopsy in diagnosing cardiac allograft dysfunction in rejection and hemodynamic compromise (HDC) along with all-cause mortality. Should this study show favorable results, this will represent a key example where PBMC gene expression profiling can be used practically to guide therapeutic decision making in real-time.

Pulmonary hypertension

Inflammation is purported to play a significant role in the development of pulmonary hypertension (Dorfmuller et al. 2003). Bull et al. looked at the gene expression profiling of PBMCs to look for genetic signatures of pulmonary arterial hypertension (PAH). The gene expression profile of 16 patients with PAH showed 106 differentially expressed genes that distinguished between controls and PAH patients with 95–100% accuracy ($P < 0.002$) (Bull et al. 2004, 2007). However, within the PAH patients, unsupervised cluster analysis failed to show a genetic signature that reliably distinguished between secondary pulmonary arterial hypertension and idiopathic pulmonary arterial hypertension. The small sample size, however, may have decreased the power to ask this question. Nonetheless, PBMC gene expression profiling provided a method of approaching a very difficult problem in a disease where invasive procedures are both dangerous and costly. Moreover, PBMC gene expression profiling highlighted some novel genes like herpesvirus entry mediator (HVEM) that raise hope of continued work in this direction. HVEM is associated with Human Herpesvirus-8 (HHV-8) infection. Earlier work by Bull et al. has shown that HHV-8 infection has been associated with idiopathic PAH (IPAH) and upregulation of a gene associated with that viral infection gives more validity to the claim and highlights the versatility of this approach. Given the broad-based nature of therapies currently available for PAH, identification of novel genes involved in the pathophysiology of this disease may enable targeted therapeutic development. Additionally, gene expression determination over time in a given patient may inform the treating clinician of therapeutic efficacy or failure.

Summary and conclusions

Studies of gene expression profiling of PMBCs, platelets or whole blood mRNA highlight the versatility of using gene expression profiling and the strength of this technique in identifying genetic signatures associated with a disease, identification of candidate genes involved in a pathological process, and in assessing the response to pharmacotherapy. Beyond its scientific merit, this approach could provide a more cost effective and less invasive alternative to biopsy or invasive physiologic measurements. Given this success, the question remains, how far is this technology from changing the standard of practice in cardiology clinics? The answer to that question will depend not only on the nature of scientific questions one can answer with this approach, but also on the feasibility of this test in the

clinical setting and the impact the test will have on clinical decision making and outcomes. Although the success of a test like Allomap™ would suggest that genomic technology is ready for clinic, but the reality is that the diagnostic power of the current genomic tools is limited. In order for gene expression studies to have widespread impact on daily practice, gene expression tests are going to have to be able to be specific enough to distinguish between complex diseases that may have common underlying inflammatory mechanisms or where multiple diseases may be present such as in patients with atherosclerosis, diabetes, and rheumatoid arthritis. The use of whole genome expression as a technology for detection and prognosis is its infancy. But the results to date are quite promising in that signatures can be developed and in some cases reproduced in replication cohorts. This latter hurdle is an important one that can be overcome if investigators are motivated and careful to collect the relevant biological samples associated with clinical data. The disease tissues for many aspects of cardiovascular disease are largely inaccessible for study. The complexity of genomic information in blood based 'sensors' of these remote disease processes may be just what the cardiovascular medicine field needs to propel it in to the era of genomic and personalized medicine.

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