The course of any disease is determined by a complex interplay between innate characteristics and environmental triggers. Accordingly, evidence-based risk factor assessment in heart disease requires a detailed family history to gauge inherited features and accurate estimates of smoking, diet, exercise, and other aspects that constitute important extrinsic disease modifiers. The value of traditional risk assessments for individual prognostication is limited, however, by a lack of a precise family history to reveal specific genetic makeup on one hand and by interindividual variation in response to environmental events on the other. In diseases such as familial hypertrophic or dilated cardiomyopathies, in which the innate component is far more important than external factors in determining disease onset and progression, genetic testing is increasingly being used to assess individual risks for developing disease and to personalize therapy.1

However, although there have been some intriguing potential applications,2–3 the clinical utility of genetic profiling is less clear in nonischemic or idiopathic heart failure syndromes that are polygenic in origin or for which there is greater contribution of environmental factors. Thus, there is a need for clinical tests that not only will reveal a patient’s static genetic makeup but also will define the dynamic changes in gene transcript and protein expression that are a consequence of gene-environment interactions.

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The studies of Heidecker et al4 in this issue of Circulation help reveal the promise of transcriptional profiling to predict long-term heart failure outcome. Endomyocardial biopsies were obtained early in the course of heart failure from a well-characterized cohort of idiopathic cardiomyopathy patients6 and were the source of RNA used for microarray analysis of transcript levels. Forty-five differentially expressed genes were identified and incorporated into a panel of transcriptional biomarkers that predicted heart failure prognosis with 74% sensitivity and 90% specificity. No individual gene in the panel was upregulated >1.8-fold in good-prognosis patients compared with poor-prognosis patients, but taken together, modest individual changes in multiple transcripts predicted outcome.

These results herald exciting developments in the management of heart failure. The goal of many previous transcriptome analyses of cardiomyopathy was to identify new disease mechanisms or to provide fresh insight into complex pathways of heart failure.6–9 In contrast, the primary goal here was to develop a useful clinical tool. Clinical applicability is supported by 2 strengths in experimental design. First is a focus on early heart failure in which transcriptional changes should more accurately reflect a specific myocardial response to primary injury or disease, with fewer confounding effects of the genetic signature for end-stage heart disease. Second is the comparison between 2 extremes of disease outcome: good prognosis defined as event-free survival for 5 years after initial presentation and poor prognosis defined as death, left ventricular assist device (LVAD) implantation, or cardiac transplantation within 2 years of presentation. If these findings are confirmed in prospective studies of larger independent patient cohorts, the ability to more accurately predict the course of idiopathic cardiomyopathy and therefore to tailor therapy and early intervention to those who will derive the greatest benefit could justify routine transcriptional profiling of biopsied myocardium in new-onset heart failure.

The implication of different transcriptional signatures for rapidly progressive heart failure compared with more stable, compensated heart failure is that some hearts early in the course of idiopathic cardiomyopathy exhibit a tendency for recovery, whereas others enter a downward spiral of functional decompensation leading to early death. Because transcriptional profiling defined gene expression patterns typical of one or the other phenotype, the microarray studies could predict outcome. The idea that failing hearts have variable capacity for healing also is supported by reverse remodeling that occurs as a consequence of LVAD support.10 By acting as an auxiliary pump, LVADs were intended to improve cardiac output and to enhance systemic homeostasis until more definitive and permanent therapy could be implemented. Unexpectedly, this strategy of providing a mechanical “bridge to cardiac transplantation” also generated collateral benefits of hypertrophy regression (reverse remodeling) and improved contractile performance as a consequence of hemodynamic unloading. Accordingly, several studies have suggested that LVAD therapy can correct the characteristic transcriptional signature of end-stage heart failure.6,11,12

Taken together, these LVAD transcriptional profiling studies and the present findings of Heidecker et al suggest a molecular and functional plasticity of failing myocardium that warrants clinical evaluation and directed management. However, not all studies of LVAD-treated hearts have shown reversal of the pathological pattern of gene expression. In one of the most comprehensive surveys of heart failure transcripts to date, Margulies et al found that some abnormalities of cardiac gene transcription were reversed after LVAD treat-
ment but that many did not change and most were inconsistent. The "recovery" transcriptional signature of an LVAD-supported heart is confounded by the superimposed genetic signature of cardiac atrophy that occurs as a consequence of hemodynamic unloading. A further explanation for the relatively immutable transcriptional signature of end-stage heart failure observed by Margulies and colleagues compared with the different transcriptional profiles of stable heart failure and rapid progression seen in the present study may be genetic profiling by the Heidecker group at the very onset of heart failure. Just as heart failure is the final common pathway for severe cardiac injury of any cause, the transcriptional profile of end-stage heart failure may reflect the terminal status of the organ rather than any capacity that might previously have existed for its recovery. LVAD unloading in end-stage heart failure could therefore be "too little, too late" to cause a major change in the pathological status of the heart. This idea is supported by observations that destination LVAD therapy achieves permanent cardiac recovery after device removal in only a small minority of cases. Thus, both the capacity for recovery and its transcriptional manifestations may be greatest early in the course of heart failure. It is interesting to speculate that mechanical support earlier in the course of heart failure might have longer-lasting benefits in patients with the more favorable "recovery" molecular profile.

The exciting results of Heidecker et al derive entirely from 43 experimental subjects, 25 with good prognosis and 18 with poor prognosis. Statistical validation was performed using random partitioning of the original data set, which is sufficient to confirm the findings in this cohort but require independent replication. It also is necessary to determine whether the present findings can be extrapolated to forms of heart failure that are defined more clearly than idiopathic cardiomyopathy. Although the investigators were rigorous in excluding specific causes of heart failure, idiopathic cardiomyopathy remains a diagnosis of exclusion, and origin is a powerful predictor of outcome in heart failure. Thus, it is possible that partitioning the study sample into good and poor prognoses also stratified the group by origin in a manner that was not detected and that the transcriptomic signatures reflect these differences. Elucidation of a transcriptomics profile associated with prognosis in heart failure of unambiguous origin such as ischemic heart disease could help resolve these uncertainties.

It is of interest that these studies did not identify just 1 or a small number of highly regulated genes that distinguish between idiopathic cardiomyopathy patients who will have more favorable or less favorable outcomes; rather, they discovered a larger number of modestly but coherently regulated transcripts. Thus, these findings do not identify specific genetic factors or functional pathways/gene clusters that determine a myocardial recovery phenotype. We do not view this as a weakness of the study or even as an especially surprising result. Instead, we think it suggests that the ability to compensate for myocardial injury is determined by a combination of many factors and that the genetic program associated with long-term compensation reflects a general and multifactorial capacity for healing/recovery.

Increasing the Power of Prediction: Beyond the Single Chip

The standard metrics used to evaluate heart failure prognosis have evolved little in 20 years. These measures rely almost entirely on categorization of clinical phenotype through assessments of ventricular function (presence of a third heart sound or depressed left ventricular ejection fraction), decreased exercise tolerance (VO₂max), and cause (ischemic versus nonischemic). To date, the most informative prognostic biomarker in clinical heart failure has been plasma norepinephrine level, which increases in proportion to sympathetic activity and portends a poor prognosis. Although useful for well-developed disease, these factors are limited in the prognostic information they provide at the time of initial presentation and within a given etiologic phenotype. There is a need for objective biomarkers that take advantage of emerging technologies allowing analyses of unamplified RNA derived from endomyocardial biopsies. To date, unbiased chip-based surveys have identified transcriptional profiles that distinguish between the underlying cause (ischemic or nonischemic cardiomyopathy) of failing hearts and can help predict outcome. In the future, they may help individualize disease management.

Although delineation of different diagnostic and prognostic transcriptional signatures has shown the promise of molecular biomarker profiling in heart failure, the most important determinants of cardiac response to injury are likely to be the constituent myocardial contractile proteins, metabolic enzymes, and signaling factors encoded by the regulated genes. Transcriptional regulation is 1 mechanism for modifying protein content, but in many instances, mRNA levels correlate poorly with immunoreactive protein assays and even less well with protein activity. Additional information might be derived from a comprehensive proteomics approach in heart failure, but this is not practical at the present time and is likely to be limited by availability of tissue even with future technological advances. It may be possible, however, to use recently developed analytical platforms to estimate protein makeup more accurately by measuring each of the 3 major determinants, mRNA level, mRNA splicing, and microRNA level.

Although there are only ~20 000 human genes, there may be 5 times that many distinct protein isoforms generated through alternate splicing of mRNA transcripts. Differential splicing is known to contribute to human heart disease, and it is possible to measure splicing events with comprehensive microarrays containing markers for all exons in all genes. Differential expression of single exons within the same gene indicates alternate mRNA splicing and therefore expression of different protein isoforms, even if the total amount of identifier mRNA for that gene does not vary. mRNA levels themselves are a function both of transcriptional regulation in the nucleus and of altered mRNA stability controlled by microRNAs that are regulated in heart disease. MicroRNAs also regulate the efficiency of translation of protein from mRNA and therefore have dual consequences on myocardial protein content. Because it is now possible to measure total mRNA levels, the proportions of differentially spliced mRNAs, and microRNA levels from the same RNA sample,
combining conventional mRNA chips with the newer generation of RNA-based tools has the potential to further improve both the diagnostic and prognostic power of microarrays.

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**References**


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