Wilson et al unveil a high-quality, fast, flexible and cheap way to screen for heart disease related mutations.

The identification of mutations associated with specific cardiovascular diseases is useful for understanding disease mechanisms as well as for diagnostic and prognostic purposes. However, current options for analyzing patient DNA samples have significant limitations. Whole-genome or whole-exome sequencing provides maximal information, but the vast quantities of data generated by the analysis could be difficult to handle and interpret. On the other hand, commercially available gene panels, which detect mutations in limited sets of known disease-associated genes, may not contain the most up-to-date collection of gene probes. Wilson and colleagues therefore devised a new screen. They employed a recently developed probe technology called complementary long padlock probe (cLPP) to target, amplify and sequence 88 genes and 40 microRNAs previously implicated in cardiomyopathies. The team gathered DNA samples from families with cardiomyopathies to test the approach and found that it successfully and precisely detected 15 known mutations in 24 positive control individuals. The cLPP assay costs just $100 per sample—a small fraction of the cost of whole-genome or -exome sequencing, and a third of the cost of commercial panels. Furthermore, it can be readily expanded to include additional probes as new disease genes are discovered, say the authors.

The potassium channel Kv1.5 connects heart cell metabolism with coronary blood flow, say Ohanyan et al.

As the workload of the heart increases, so too does its oxygen demand. To meet the increased need, coronary vessels dilate maximizing blood flow to the cardiac muscle. This dilation is induced by, among other things, the release of metabolites (such as redox factor H2O2) from heart cells, and is mediated by the opening of potassium channels. But it is unclear which of the many types of cardiac potassium channel are responsible. Ohanyan and colleagues have focused on one called Kv1.5 because it is known to be redox sensitive and is expressed in vascular smooth muscle cells (VSMCs). They showed that mice with a genetic knock-out of this potassium channel did not exhibit a normal increase in coronary blood flow or vasodilation in response to cardiac stress (norepinephrine infusion). This lack of dilation was associated with tissue ischemia and reduced heart function. Importantly, the deficiency was reversed by expressing Kv1.5 specifically in the VSMCs of knock-out mice. These results suggest that Kv1.5 plays a crucial role in metabolic dilation—a finding that could be relevant for patients with non-obstructive coronary disease (microvascular disease) in which coronary vasodilation is compromised.

Granton et al report on the first in-human trial of gene-enhanced cell therapy for pulmonary arterial hypertension.

Pulmonary arterial hypertension (PAH) is a life-threatening condition in which an increase in blood pressure in the lungs puts severe strain on the heart. The disease is thought to be triggered by vascular endothelial cell injury that leads to remodeling and loss of lung microvasculature. Researchers have investigated the potential of endothelial progenitor cells (EPCs) for PAH therapy because the cells home to vascular injury sites where they are believed to aid regeneration. In animal models of PAH, doses of unmodified EPCs improved symptoms only modestly. But if the EPCs were first transfected with the gene encoding nitrogen-oxide synthase, more significant improvements were observed. Seven patients with severe PAH have now been given this gene-enhanced EPC therapy. The cells were delivered by catheter into the patients’ pulmonary arteries for three consecutive days. Although the patients showed a reduction in blood pressure over these three days, this improvement was no longer apparent by three-months. There was, however, a general long-term improvement in the patients’ exercise capacity. One patient died shortly after release from hospital, which was deemed “possibly related” to the treatment. The authors suggest future clinical trials are needed to build upon these preliminary results.