

## **SIGNIFICANCE STATEMENT**

Kidney transplantation is the treatment of choice for patients with end stage renal failure. Despite improved outcome early after transplantation, annually 3%–5% of grafts show late graft failure. Chronic allograft injury represents a leading cause for this late graft loss, and it has been linked to ischemia-reperfusion injury occurring during transplantation. How ischemia-reperfusion induces late allograft survival failure and how this adverse outcome can be predicted remain largely unknown. Here, we describe how DNA hypermethylation of renal transplants after ischemia is directly proportional to the duration of cold ischemia. We identify a validated methylation biomarker that—measured at implantation—predicts chronic allograft injury 1 year later. Our study, for the first time, highlights an epigenetic basis for ischemia-induced chronic allograft injury.