Table S1. Ingenuity Pathway Analysis results for the specified classes

Category	Overrepresented pathways	-log (p-value)
Genotoxicity	p53 signaling	6.79
	Cell cycle: G2/M DNA damage checkpoint regulation	3.10
	VDR/RXR activation	2.25
	Eicosanoid Signaling	1.50
ER	Endoplasmic reticulum stress pathway	6.14
	NRF2-mediated oxidative stress response	3.10
	Glycine, Serine and Threonine metabolism	2.56
	One carbon pool by folate	2.40
	Alanine and Aspartate metabolism	1.89
	Neurotrophin/TRK Signaling	1.56
Microtubule inhibitor	Cell cycle: G2/M DNA damage checkpoint regulation	1.98
	Lysine biosynthesis	1.45
HDAC inhibitor	Death receptor signaling	2.52
	Xenobiotic metabolism signaling	2.34
	Endoplasmic reticulum stress pathway	2.25
	p38 MAPK signaling	2.10
	Huntington's disease signaling	2.06
	Synaptic long term potentiation	1.83
	Sphingolipid metabolism	1.79
	Fc epsilon RI signaling	1.69

Ingenuity Pathway Analysis is shown for subset of genes from Fig. 2, whose response was common for a particular class of stress agents. Pathways showing significant over-representation, $p \leq 0.05$, for each class are shown.

Table S2. Ingenuity Pathway Analysis for 65-gene classifier

Overrepresented pathways	-log (p-value)
p53 signaling	6.44
Cell cycle: G2/M DNA damage checkpoint regulation	3.50
ATM signaling	3.10
GADD45 signaling	2.78
Hereditary breast cancer signaling	2.28

The top five over-represented Ingenuity pathways are shown for the 65-gene genotoxicity signature taken from Fig. 4A. Our TGx-28.65 signature overlapped substantially with many of the same genes identified in genotoxic subclusters using an unsupervised method; e.g., half of the genes from Fig. 3A are in the TGx-28.65 biomarker.

Table S3. Ingenuity Pathway Analysis for alcohol treatment

Overrepresented pathways	-log (p-value)
TNFR2 signaling	5.52
Endoplasmic reticulum stress pathway	3.77
ATM signaling	3.54
Selenoamino acid metabolism	3.15
TNFR1 signaling	2.68

The top five over-represented Ingenuity pathways are shown for genes showing at least 1.7-fold response with significance of $p \leq 0.01$ after 2% ethanol exposure. Interestingly, tumor necrosis factor alpha (TNFα) is a proinflammatory cytokine that appears to play a crucial role in the pathogenesis of alcoholic liver disease (ALD). For example, a previous study using TNFR1 knockout mice showed that TNFα makes an appreciable contribution to alcohol-induced ALT elevation, necroinflammation, and apoptosis in liver tissue (Ji, C., Deng, Q., and Kaplowitz, N. (2004). Role of TNF-alpha in ethanol-induced hyperhomocysteinemia and murine alcoholic liver injury. Hepatology *40*, 442-451).