Description of Additional Supplementary Files

File Name: Supplementary Data 1
Description: Characteristics of cell lines used in this study, as published previously (Stem Cell Reports. 2021 Dec 14;16(12):3036-3049) [16]. © 2021 The Author(s), released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license.

File Name: Supplementary Data 2
Description: Experimental metadata for **(A)** the original experiments **(B)** and the coculture experiments.

File Name: Supplementary Data 3
Description: Cardiotoxic and non-cardiotoxic small molecule tyrosine kinase inhibitors and monoclonal antibodies.

File Name: Supplementary Data 4
Description: Drug-induced DEGs in each cell line. DEGs were calculated using the negative-binomial test implemented in the 'exactTest' functionality of the edgeR package. The spreadsheet contains the top 600 most significant DEGs induced by each drug in each treated cell line. Notice that all DEGs were subjected to our SVD-based pipeline.

File Name: Supplementary Data 5
Description: Averaged drug-induced DEGs. Signed -log10(p-values) were averaged across cell lines for each drug.

File Name: Supplementary Data 6
Description: Top 600 genes of the first eigenarray.

File Name: Supplementary Data 7
Description: Enrichment analysis of the first eigenarray. The top 600 genes with the highest absolute expression values of the first eigenarray were subjected to pathway enrichment analysis using MBCO level-2 SCPs and Fisher's exact test. P-values are nominal p-values.

File Name: Supplementary Data 8
Description: Drug-induced DEGs in each cell line after removal of the first eigenarray. Significance p-values were transformed into $-\log_{10}$(p-values). We defined $-\log_{10}$(p-values) of up- and down-regulated genes as positive and negative, respectively. Signed $-\log_{10}$(p-values) were integrated into a gene expression matrix that was subjected to singular value decomposition (SVD). After removal of the first eigenarray the matrix contained decomposed $-\log_{10}$(p-values). Since our SVD pipeline acts on the $-\log_{10}$(p-values) and not on the $\log_2$(fold changes), we removed the $\log_2$(fold changes) from the gene expression profiles

after any decomposition step. Notice that all DEGs after removal of the first eigenarray were further processed by our SVD-based pipeline.

File Name: Supplementary Data 9
Description: Drug-selective gene expression profiles after projection into drug-selective subspaces. Drug-selective subspaces were identified using SVD. Projection of the complete gene expression profiles into drug-selective subspaces gave drug-selective gene expression profiles with decomposed -$\log_{10}$(p-values). As explained for Supplementary Data 8, these profiles do not contain $\log_2$(fold changes).

File Name: Supplementary Data 10
Description: Averaged drug-selective gene expression profiles. Signed -$\log_{10}$(p-values) of drug-selective gene expression profiles were averaged across cell lines for each drug.

File Name: Supplementary Data 11
Description: Enrichment analysis results of drug-selective gene expression profiles. After projection of gene expression profiles into drug-selective subspaces, we ranked the genes within each cell line/drug combination by decreasing absolute decomposed -$\log_{10}$(p-values). Up- and downregulated genes among the top 600 ranked genes were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values.

File Name: Supplementary Data 12
Description: Enrichment analysis results of the complete gene expression profiles. Up- and downregulated genes among the top 600 most significantly differentially expressed genes of the complete dataset were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values.

File Name: Supplementary Data 13
Description: Enrichment analysis results of gene expression profiles after removal of the first eigenarray. Up- and downregulated genes among the top 600 most significantly differentially expressed genes after removal of the first eigenarray were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values.

File Name: Supplementary Data 14
Description: SCPs with a potential association with cardiotoxic responses. Precision, recall, F1 scores and F1 AUCs were calculated as described in the methods section for MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs.

File Name: Supplementary Data 15
Description: Cluster marker genes identified by single cell RNAseq of hiPSC-derived cardiomyocytes. Single cell RNAseq analysis of four of our six different hiPSC-derived cardiomyocyte cell lines identified six different clusters. Cluster marker genes were calculated by comparing gene expression profiles in each cluster versus all other clusters using the Wilcoxon Rank Sum test implemented in the Seurat functionality 'FindMarkers'.

File Name: Supplementary Data 16
Description: Enrichment analysis of cluster marker genes obtained by single cell RNAseq of hiPSC-derived cardiomycytes. Marker genes of each cluster with a maximum adjusted p-value of 0.05 were ranked by significance. Top 500 ranked genes were subjected to enrichment analysis using Fisher's exact test and **(A)** cell type marker genes of the adult human heart, **(B)** the developing human heart as well as MBCO **(C)** level-1, **(D)** -2, **(E)** -3 and **(F)** -4 SCPs. P-values are nominal p-values.

File Name: Supplementary Data 17
Description: Cell type marker genes of the adult human heart. Cell type marker genes were calculated for each cell type in the adult human heart, using the Wilcoxon Rank Sum test implemented in the Seurat functionality 'FindMarkers'.

File Name: Supplementary Data 18
Description: Enrichment analysis of cell type marker genes of the adult human heart. The top 500 marker genes of each cell type in the adult human heart with a maximum adjusted p-value of 0.05 were subjected to enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-vales are nominal p-values.

File Name: Supplementary Data 19
Description: MBCO enrichment results of DEGs in iPSC-derived cardiomyocytes obtained from a juvenile patient with DCM. Up- and downregulated genes among the top 600 most significant DEGs with a maximum adjusted p-value of 0.05 in hiPSC-derived cardiomyocytes of an infant DCM patient, were subjected to enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-vales are nominal p-values.

File Name: Supplementary Data 20
Description: MBCO enrichment results of DEGs in cell types of the adult heart of DCM patients. Up- and downregulated genes among the top 600 most significant DEGs with a maximum adjusted p-value of 0.05 in adult heart cells of DCM patients generated by single cell RNAseq were subjected to enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-vales are nominal p-values.

File Name: Supplementary Data 21
Description: MBCO enrichment results of DEGs in cell types of the adult heart of DCM and HCM patients. Up- and downregulated genes among the top 600 most significant DEGs with a maximum adjusted p-value of 0.05 in adult heart cells of DCM or HCM patients generated by single nucleus RNAseq were subjected to enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-vales are nominal p-values.

File Name: Supplementary Data 22
Description: Pazopanib- and dabrafenib-induced DEGs in each cardiomyocyte cell line in presence or absence of endothelial cocultures. (A) Cardiomyocyte cell lines MSN08 and MSN09 that were either cocultured with human coronary arterial endothelial cells (HCAECs) or kept in single cell culture were treated with pazopanib or dabrafenib. DEGs were calculated using the negative-binomial test implemented in the 'exactTest' functionality of the edgeR package. The new and original lists of DEGs for both treatments were merged and filtered for the top 600 most significant DEGs. Original lists of DEGs contain cell line labels without any additions and are also part of Supplementary Data 4. Additional lists of DEGs contain cell lines labeled with 'Alone' or 'WithHCAEC', if they were stimulated in absence or presence of HCAECs, respectively. **(B)** Top 600 DEGs for the same treatments after subtraction of the first eigenarray that was identified by subjecting the original 266 lists of DEGs to SVD. Original datasets are also part of Supplementary Data 8. **(C)** Top 600 DEGs for the same treatments after projection into drug-selective subspaces that were identified by analysis of the original 266 lists of DEGs. The original datasets are also part of Supplementary Data 9. Notice that our SVD pipeline processes all DEGs at each step, not only the ones within this spreadsheet.

File Name: Supplementary Data 23
Description: MBCO enrichment results of pazopanib and dabrafenib-induced drug-selective DEGs in presence or absence of endothelial cocultures. Up- and downregulated genes among the top 600 most significant DEGs after projection of the DEGs into drug-selective subspaces were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values. Original results are also part of Supplementary Data 11A-D.

File Name: Supplementary Data 24
Description: MBCO enrichment results of pazopanib and dabrafenib-induced complete DEGs in presence or absence of endothelial cocultures. Up- and downregulated genes among the top 600 most significant DEGs of the complete DEGs were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values. Original results are also part of Supplementary Data 13A-D.

File Name: Supplementary Data 25
Description: MBCO enrichment results of pazopanib and dabrafenib-induced DEGs in presence or absence of endothelial cocultures after removal of the first eigenarray. Up- and downregulated genes among the top 600 most significant DEGs after removal of the first eigenarray were subjected to pathway enrichment analysis using Fisher's exact test and MBCO **(A)** level-1, **(B)** -2, **(C)** -3 and **(D)** -4 SCPs. P-values are nominal p-values. Original results are also part of Supplementary Data 14A-D.

File Name: Supplementary Data 26
Description: Genomic variants with potential influence on pharmacodynamics or pharmacokinetics. Genomic variants with alleles that are underrepresented in the general population, overrepresented in a cell line that showed an outlier response to a drug of interest, if compared to all other cell lines and that map to genes involved in the PK or PD of the same drug were curated. See methods for details.

File Name: Supplementary Data 27
Description: Genomic variants with potential influence on SCPs up- or downregulated at higher ranks by cardiotoxic or non-cardiotoxic TKIs. Genomic variants with alleles that are underrepresented in the general population and that map to genes involved in SCPs associated with cardiotoxicity were curated. See methods for details.