**Figure Legend**

**Figure 1**

Schematic of the EN-CODEC companion resource showing available assays (row) across cell types (column). **Pink box**: “Top-tier” cancer-associated resources in ENCODE highlighting the depth of the resource. **Yellow box**: Cell types with several assays in the main ENCODE Encyclopedia highlighting the breadth of the resource. **Green box**: Cell type-specific analyses based on deep annotations of top-tier cell lines. **Blue box**: Merged analyses based on wide-coverage of many cell types. The actual content of our resources (annotations, background mutation rate, networks) are shown in the dotted black box.

**Figure 2**

Background mutation rate (BMR) modeling and burdening analysis. (**A**) Improvement of BMR estimation by accumulation of principal components of multiple genomic features. (**B**) Regression coefficients of remaining features in breast cancer after incorporating MCF-7 replication timing. (**C**) Schematic of extended gene including regulatory elements and RNA-binding sites. (**D**) Significantly burdened genes using coding regions, noncoding elements  (TSS), and extended genes, alongside germline mutational status in liver cancer. (**E**) Expression of BCL6, which is only identified as recurrently mutated using extended genes, is correlated with patient survival.

**Figure 3**

Integration of ENCODE networks with expression profiles from cancer patients. (**A**) Heatmap of regulatory potentials of TFs/RBPs to drive tumor-to-normal expression changes; red indicates up-regulation and blue means down regulation. (**B**) Elevated MYC regulation activity is associated with reduced disease specific survival (DSS) in breast cancer (top); MYC knockdown in MCF-7 leads to significantly larger expression reduction in MYC target genes (bottom). (**C**)  (**i**) MYC expression is more positively correlated with its target genes as compared to other TFs; (**ii**) MYC frequently form FFLs with NRF1, and these are mostly coherent; (**iii**) in the MYC-NRF1 FFLs, or-gate logic predominates. (**D**) Elevated SUB1 regulation activity is associated with increased overall survival (OS) in lung cancer (top); SUB1 knockdown in HepG2 leads to reduced target gene expressions (bottom).

**Figure 4**

Regulatory network hierarchy analyses. TFs are organized into layers such that TFs that tend to regulate other TFs are placed on top, and TFs that tend to be regulated by other TFs are placed on bottom. (**A**) Generalized network: TFs in top layers are enriched with cancer associated genes and demonstrate larger regulation potentials to drive tumor-to-normal gene expression changes. (**B**) Cell type-specific network using K562 and GM12878: top layer TFs more significantly drives tumor-normal differential expression; also, bottom layer TFs are more often associated with burdened binding sites.

**Figure 5**

TF-Gene network rewiring analysis. Green and red arrows designate edge gain and loss, respectively. (**A**) Rewiring index in a model for CML by direct edge counts using both proximal and distal networks (top) and by gene community analysis (bottom). TFs that gain edges tend to rewire away from stem cell-like state while TFs the lose edges tend to rewire toward stem cell-like state. (**B**) Examples of network rewiring for specific TFs in multiple cancer types. (**C**) Conceptual schematic for rewiring towards or away from a stem cell-like state. (**D**) Genomic features associated with gained or lost edges.

**Figure 6**

(**A**) Stepwise variant prioritization scheme utilizing EN-CODEC resources; we prioritize large-scale regulators at gene-level based on network and expression; element based on mutation burden; then pinpoint single nucleotide using motif and conservation. (**B**) Small-scale validation of prioritized noncoding mutations using luciferase reporter assay. (**C**) Multiscale integrative analysis on Sample 5. The figure shows multiple scales of functional genomics data. From large-scale Hi-C linkages, further zooming into an individual element highlights regulatory histone marks and DNase hypersensitivity tracks and a variety of TF binding events. At the nucleotide level, a motif of FOSL2 is disrupted.