**Supplementary Figure 1. ERG represses PI3K signaling.** A) mRNA expression analysis of Pten demonstrates no significant change in expression in the setting of ERG. B) Bar graph representing mean and standard deviation for protein quantification across three independent experiments of dox-inducible ERG over-expression in normal murine prostate organoids, normalized to control. C) AR inhibition with MDV3100 and/or shERG both led to reduced levels of ERG and increased PI3K signaling in the VCaP human prostate cancer cell line which harbors the TMPRSS2-ERG genomic rearrangement. D) ChIPseq analysis of ERG and AR spanning the IRS2 gene and promoter region.

**Supplementary Figure 2. Impact of ERG on RTK component expression and phosphorylation.**

A) Bar graph representing mean and standard deviation for protein quantification across three independent experiments of dox-inducible ERG over-expression in normal murine prostate organoids, normalized to control. B) *In vivo* western blot analysis of VCaP tumors treated with AR inhibition (castration+MDV3100) showing decreasing ERG levels, increasing IRS2 levels, and enhanced PI3K signaling. C) Bar graph representing mean and standard deviation for protein quantification across three independent experiments of siRNA knock-down of IRS2 *ERG Pten-/-* CrisprERG prostate organoids, normalized to control. D) RNAseq expression analysis in our prostate organoids for select RTKs relevant to prostate cancer demonstrates no differential expression based on ERG status. Three independent lines for each genotype were analyzed with error bars reporting standard deviation from the mean.

**Supplementary Figure 3. Validation of the impact of ERG on RTK signaling and IRS2 regulation.**  A) Phospho-RTK array across Pten deficient prostate cancer organoids demonstrating decreased phosphorylation of several RTKs in the setting of ERG expression. B) Bar graph representing mean and standard deviation for protein quantification across three independent experiments of IRS2 over-expression in *ERG* prostate organoids, normalized to control. C) In silico analysis of ChIP seq data sets for the VCaP cell line demonstrating across multiple samples the pile up of read peaks at the IRS2 transcription start site. Analysis performed using ChIP-Seq Atlas.

**Supplementary Figure 4. Loss of Pten in the setting of ERG aberrant expression promotes a cell migratory phenotype.** A) Inhibition of PI3K signaling in the *ERG* organoids over-expressing IRS2 demonstrates a modest impact on cell proliferation. B) BYL719 (1uM) and AZD8186 (250nM) results in inhibition of PI3K signaling in *ERG-IRS2* organoids. C) The increase in cell migration observed with IRS2 overexpression is dependent on PI3K signaling as inhibition of PI3K (BYL719, p110a, 1uM + AZD8186, p110b, 250nM) significantly blocked cell migration. Experiment performed in triplicate with error bars reporting standard deviation from the mean. D) Loss of Pten promotes a cell migratory phenotype in the setting of ERG aberrant expression. Experiment performed in triplicate with error bars reporting standard deviation from the mean. E) The migratory phenotype observed in *ERG Pten-/-* is reduced by inhibiting PI3K. Experiment performed in triplicate with error bars reporting standard deviation from the mean.

**Supplementary Figure 5. IRS2 over-expression is not sufficient to promote tumorigenesis in the context of ERG aberrant expression.**  Prostate organoids from Rosa26-*ERG* mice with (n=10) and without (n=10) IRS2 overexpression were injected into the flanks of SCID mice and after 6 months, neither genotype developed tumors. Specimens were harvested and histology (200x) confirmed no significant microscopic disease.

**Supplementary Table 1.** Top 50 differentially regulated genes up and down in *ERG Pten-/-* organoids following Crispr ERG.