**Supplemental Figure 1.** Dendrogram and heatmap of WGCNA results for WT V vs. *Ezh2*cKO V comparison. As detailed in (31), the heatmap represents the Topological Overlap Matrix (TOM) for all analyzed genes. Lighter colors in the heatmap depict low overlap and darker red colors indicate greater overlap. Along the diagonal, blocks of darker colors represent the different color modules. The gene dendrogram and module assignment are shown at the left and top of the image.

**Supplemental Figure 2.** Protein-protein interactions for proteins encoded by genes within the Green module in the WT V vs. *Ezh2*cKO V comparison, as determined by STRING (<https://string-db.org/>). As shown, several interactions exist for proteins encoded by genes within this module. The main cluster of genes is present within the center and notably, includes ESR1 (higher magnification of this region included as an inset).

**Supplemental Figure 3.** Protein-protein interactions for proteins encoded by genes within the Sky Blue3 module in the WT V vs. *Ezh2*cKO V comparison, as determined by STRING (https://string-db.org/). As shown, several interactions exist for proteins encoded by genes within this module. with one large cluster composed of several proteins in the center that is connected to the top cluster that includes SREBF2 and the bottom cluster with DAG1.

**Supplemental Figure 4.** Hub gene analysis of Green module for WT V vs. *Ezh2*cKO V comparison with Cytohubba app (11) in Cytoscap.. *Esr1* is one of the top hub genes in this module (51).

**Supplemental Figure 5.** Dendrogram and heatmap of WGCNA results for WT E2 vs. *Ezh2*cKO E2 comparison. As detailed in (31), the heatmap represents the TOM for all analyzed genes. Lighter colors in the heatmap depict low overlap and darker red colors indicate greater overlap. Along the diagonal, blocks of darker colors represent the different color modules. The gene dendrogram and module assignment are shown at the left and top of the image.

**Supplemental Figure 6.** Protein-protein interactions for proteins encoded by genes within the Plum1 module for WT E2 vs. *Ezh2*cKO E2 comparison. Five clusters are evident. The one main cluster in the center includes BCL6, CREBBP, MYB, PLRG1, HNRNPF, BCAS2, and RBM22.

**Supplemental Figure 7.** Protein-protein interactions for proteins encoded by genes within the Dark Green module for WT E2 vs. *Ezh2*cKO E2 comparison. Five clusters were present but of these, four of the clusters only included two genes. The one main cluster in the center contains several genes encoding ribosomal proteins and associated genes, including RPS6, RPS3A1, RPS24, RPS19, RPS25, RPS24, RPL10A, RPP38, RPL8, RPL23, RPS11, RPS15A,and RPS13.

**Supplemental Figure 8.** Positive and negative control for MKI67 IHC.Thenegative control panel shows uterine sections from WT mice stained in the absence of the primary antibody. The positive control shows uteri from WT mice stimulated with a maximal E2 dose. All images are the same magnification. Magnification bar = 0.05 mm.