Appendix Figure S4. Calling Genetic Interactions **A** A collection of 59 donor strains (containing 34 unique knockouts) and 56 recipient strains (containing 38 unique gene knockouts) were crossed in an all-by-all pooled format. Each strain contains a knockout at either a DNA repair or neutral gene. Double knockout strains were divided into four spaces based on the types of genes knocked out. Numbers in parentheses represent the number of strains and unique gene knockouts, respectively.

**B** Distribution of GIS in strain pairs containing the same gene, split by those which are well-measured (Cxy ≥ 30) and not well-measured (Cxy < 30). Non-well-measured strains were excluded from any analysis, and all scores were then re-calculated. Non-well-measured strains included 27 same-gene and 155 different-gene pairs. Most excluded same-gene pairs involved the following genes: MMS1, MMS4, MPH1, MUS81 , RAD54 , RAD55 , RTT101, RTT107, SGS1, SRS2, and CSM3.

**C** Distribution of ZGIS calculated for DNA-repair pairs (space 1 in panel A - red) and pairs involving neutral genes (spaces 2, 3, 4 in panel A - black). ZGIS for pairs involving neutral genes were used to calculate FDRneutral. Camptothecin (CMPT) was flagged for exclusion due to a marked bias towards positive GIs.

**D** Benchmarks of BFG-GI with St. Onge et al. data for strains containing a significant genetic interaction (FDRneutral < 0.01). Each graph shows precision and recall compared to St. Onge as the function of an additional GIS cutoff (left = negative interaction performance, right = positive interaction performance). Overlay text indicates performance at|GIS| = 0.075 (dashed lines), which was chosen as the effect size threshold.