**Figure 1: Factors contributing to incidence of resistance mutations**

**(A)** Factors affecting drug resistance evolutionary dynamics. Without transmission, factors involved in cancer are limited to the host level. **(B)** ABL1 crystal structure. Loss of E225-K247 salt bridge is associated with imatinib resistance. **(C)** Prevalence of E255K/V mutations in imatinib clinical trials with well-characterized resistance mutation analysis. **(D)** Imatinib IC50 curves for BCR-ABL infected BaF3 cells. **(E)** Relative growth rates of BCR-ABL BaF3 variants. **(F)** Substitution-specific frequency of synonymous mutations in ABL1 and codon structure of E255.

**Figure 2: Analytic solution of probability model for two resistance allele system**

**(A)** Schematic of theoretical drug target gene with two potential resistance alleles. Allele A is assigned a high fitness and low probability; Allele B is assigned a low fitness and high probability. **(B)** Expected general timeline for mutation and outgrowth for either allele given their assigned evolutionary profiles. In cases where both mutations occur, the first resistant clone to reach detection drives relapse. **(C)** Phase plane of mutation rate and effective population size. Color indicates whether Allele A (**dark blue**) or Allele B (**red**) is more likely to drive relapse. In regions where Allele B is more dominant, we expect mutation bias to be a primary evolutionary force. **(D)** Schematic of general leukemic cell population hierarchy. Only mutations in leukemic stem cells can form stable resistance clones, effectively limiting the population size to 105-106.

**Figure 3: Analysis of epidemiologic incidences of BCR-ABL mutations**

**(A)** Crystal structure of ABL1 kinase domain and distribution of 19 most prevalent BCR-ABL resistance mutants. These 19 variants account for approximately 95% of resistance mutations observed clinically. **(B)** Drug-dose response assays underscore the range of drug resistance conferred by these mutations. Each BCR-ABL BaF3 line was dosed with 11 serial dilutions of imatinib in triplicate. **(C)** Statistical model of clinical mutation prevalence regressed on growth rates in the presence and absence of imatinib. **(D)** Evolutionary profiles of each resistance variant. **(E/F)** Statistical model of clinical mutation prevalence regressed on growth rate in the presence of drug and mutational probability.

**Figure 4: Stochastic model of CML evolutionary dynamics**

**(A)** Schematic of stochastic CML evolutionary dynamic model. Leukemic stem cells alternate between proliferating (P-LSC) and quiescent state (Q-LSC). P-LSC give rise to differentiated leukemic cells (DLC). P-LSCs may also spawn a resistant subclone P-LSCi when dividing. The allele-specific mutational probability is given by ρi. **(B)** Example stochastic simulation of model described in **3A**. **(C)** Simulation results. In the model without mutation bias (uniform ρi), the Pearson correlation between observed and predicted prevalences is 0.14. In the model with mutation bias (allele-specific ρi), the Pearson correlation is 0.78.

**Figure 5: Drug-specific mutational liability and resistance mutation incidence**

**(A)** Power curves for nilotinib and dasatinib frontline clinical trials. Labeled points indicate the power of the ENESTnd (frontline nilotinib; N=282 and 1-β=0.43) and DASISION (frontline dasatinib; N=259 and 1-β=0.54) phase 3 clinical trials. Effect size was estimated from simulation results. **(B)** Resistance profiles for imatinib, nilotinib, and dasatinib. **(C)** Mutational liabilities (defined as the sum of conditional probabilities of resistance-conferring mutations) and predicted resistance frequencies for imatinib, nilotinib, and dasatinib. **(D)** Resistance profiles for hypothetical drug, maxitinib. Maxitinib K1 targets the first through fifth most likely mutants; K2 targets the second through sixth most likely; and so on. **(E)** Maxitinib simulation results. Orange bars represent the resistance incidence of each maxitinib chemotype relative to imatinib. Green points indicate mutational liability.

**Figure 6: Cases of restricted heterogeneity**

**(A)** A spatially heterogeneous tumor with mitotically active cells in the periphery and a quiescent/necrotic core. The effective is a reduction in the number of cells able to spawn a resistant subclone. **(B)** Adjuvant therapy involves surgically debulking the tumor, restricting the effective population size. **(C)** In infectious disease, transmission bottlenecks constrain the number (and thus heterogeneity) of pathogens passed from one host to another.