We study an evolutionary Prisoner’s Dilemma on complex random networks. Using generating functions, we introduce a natural measure of network heterogeneity that can accurately predict, quantitatively, the equilibrium success of cooperators in the game. Moreover, the generating functional approach suggests an intrinsic interpretation for the heterogeneity of the network that helps explain local mechanisms through which cooperators thrive in heterogeneous populations. Finally, we give a simple relationship between heterogeneity, the cooperation level, and the epidemic threshold of a random network that reveals an appealing connection between epidemic disease models and the evolutionary Prisoner’s Dilemma. (Received September 17, 2008)