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A robust gene signature predicting deficient homologous recombination DNA repair

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Abstract

Homologous recombination-mediated DNA repair deficiency (HRD) predisposes to cancer development, but also provides therapeutic opportunities with poly(ADP ribose) polymerase (PARP) inhibitors being synthetically lethal with HRD. Here, we identified an HRD gene signature that robustly predicted HRD and sensitivity to PARP inhibitors. Unexpectedly, concurrent loss of *PTEN* in *BRCA1*-deficient cells may extensively rewire the HR repair network and confer resistance to PARP inhibitor, partially through over-expression of TTK. We used the HRD gene signature as a drug discovery tool and found several PARP-inhibitor-synergizing agents through the connectivity map. Thus gene expression profiling can be used to define the functional status of the HR repair network providing prognostic and therapeutic information.