

## Genome Sequencing of Outlier Responders to Systemic Cancer Therapies

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Funding Category: A

**Abstract:** Profound and durable responses are often observed in early stage clinical trials of novel cancer agents in only a small minority of patients. It has long been postulated that these responses have a definable genetic basis but until now, it was not feasible to perform a comprehensive genomic analysis of such patients. Rather, at best, a few candidate genes were examined. Technical feasibility thus ensured that oncology trials were designed to identify agents that have a statistically significant benefit in a genetically unselected population, a paradigm that has led to the development of many agents that have modest or no benefit in the vast majority of patients. Agents with profound activity in only a small number of patients were on the other had deemed inactive and abandoned. In this application, we will perform integrated next generation sequencing analyses of responding patients enrolled on Phase I/II clinical trials at MSKCC and Weill Cornell Medical Center. The primary goal of this effort will be to ensure that the development of agents with profound, life alternating activity in only a minority of patients is not prematurely halted but rather redirected to the subset of patients most likely to benefit. As solid tumors, as defined by site of origin, in fact represent genetically heterogeneous collections of distinct diseases, such efforts will accelerate the shift towards individually tailored, genetically based treatment approaches.