**"High-throughput cancer gene mutation profiling by single-molecule sequencing"**

*Principal Investigator:*
- Levi A. Garraway, MD, PhD, Broad Institute of MIT and Harvard

*Co-Principal Investigators:*
- Marc Ladanyi, MD, Memorial Sloan-Kettering Cancer Center
- Matthew Meyerson, MD, PhD, Broad Institute of MIT and Harvard
- Chad Nusbaum, PhD, Broad Institute of MIT and Harvard

Funding Category: B

**Abstract**: Large-scale cancer gene discovery efforts have empowered the identification of hundreds of tumor genomic alterations in recent years. To be truly transforming, however, knowledge of key cancer-associated mutations must be applied systematically in the clinical and translational arena to guide rational cancer therapeutics. This over-arching goal has yet to be achieved or even attempted on a large scale. Although many methodologies for comprehensive cancer genome characterization have become available, most cannot be applied reliably and efficiently in the clinic to direct patient stratification and clinical trial design. The objective of this proposal is to develop a robust and efficient method by which tumor DNA from every cancer patient might be characterized for critical genomic alterations (e.g., base mutations, gene amplifications, and deletions) in every known cancer gene. To accomplish this, we will apply a novel, solution-phase hybrid capture protocol to enrich for exonic tumor DNA, followed by single-molecule sequencing of all known cancer-associated genes. As a proof-of-principle, this method will be used to profile 200 tumors. Toward this end, we propose the following Specific Aims:

(1) Solution-phase hybrid capture and single molecule sequencing of all exons corresponding to 500 known, cancer-associated genes

(2) Cancer gene mutation profiling of DNA from 200 solid tumors using single-molecule sequencing technology

(3) Computational analyses and validation of cancer gene mutation profiles (base mutations and chromosomal copy number alterations)

This project should bring forth a transforming innovation that can be implemented by basic and translational investigators across the Starr Cancer Consortium and beyond.