The 2011 National Human Genome Research Institute (NHGRI) Strategic Plan recognized the potential benefits to patients of comprehensive genomic data that soon will be available to clinicians with the rapid deployment of new DNA sequencing instruments and methods. NHGRI subsequently crafted the Clinical Sequencing Exploratory Research (CSER) initiative to: 1) leverage NHGRI's long-standing experience in genomic sequencing and analysis to ease the adoption of these methods into clinical care; 2) guide the development and dissemination of best practices for the integration of clinical sequencing into clinical care; and 3) research the ethical, legal, and psychosocial implications of bringing broad genomic data into clinical decision-making. The CSER Consortium is currently composed of nine multi-disciplinary projects (six awarded in 2011 and three added in 2013; three are co-funded by NCI), nine Ethical, Legal, and Social Implications (ELSI)-specific projects which formerly comprised the Return of Results Consortium (one is NCI-co-funded), and a Coordinating Center. Members of NHGRI's Intramural ClinSeq program also participate. Aims of the research include: generating and interpreting genomic sequence data on patients in a variety of clinical contexts; outlining the principles and processes guiding the definition and reporting of an "actionable" variant across the Consortium; and exploring standardized approaches to addressing the unique ELSI challenges related to generating sequence information in clinical settings. The Consortium of grantees will cooperate to generate a knowledge base to advance best practices and communicate lessons learned to the community. The organization of the Consortium across study sites and Working Groups, Consortium progress to date, anticipated products and results, and the Consortium's role in broader efforts at NHGRI relating to genomic medicine will be described.