The promise of genomic medicine includes personalizing diagnoses and therapies, if not to the level of the individual, then to a small population of individuals with shared pathophysiology. The availability of commodity-priced genome-scale assays has led to increased popular demand and expectation for the application of these assays to clinical care. Yet there are several structural impediments to the safe practice of genomic medicine, all of which fall within the domain of biomedical informatics. These include A) the growth of the Incidentalome, the tsunami of false positives that inevitably result from application of massively parallel tests, B) the lack of systematic interpretations of genomic tests and evaluation of their performance. C) The absence of a mechanism to transfer the growing knowledge of genomics to the physician at the point of care. D) The increasingly blurry line between clinical research and clinical care. Fortunately there are several developments in biomedical informatics that address these impediments. Foremost among these is the movement to treat subjects as full and autonomous partners in research collaborations even as they continue to be treated as patients and secondarily the industrialization of phenotyping and sample acquisition methodologies to match the efficiencies of genome-scale measurements. I will review both the challenges and leading exemplars of the solutions brought to bear.