Albeit not a new concept, the current millennia ushered in the practical proposition of precision medicine at a whole genome level and with it raised expectations of "individualized therapy". Realizing this compelling concept continues to be an endeavour fraught with significant obstacles a number of which will be rehearsed. In particular, molecularly matched clinical study designs are more efficient over unselected designs when the sensitivity/specificity of the proposed molecular diagnostic is high and the benefit in the diagnostic negative population is low. Key goals of the pre-registrational clinical study programme have now become to characterise these two criteria through parallel development of a companion diagnostic and intentional enrollment of a diagnostic negative population in the initial clinical studies of investigational agents. Furthermore, we have learned that the molecular phenotype of the tumour evolves both with time and following exposure to treatments. A contemporaneous tumour sample to the care-giving episode is now demanded but obtaining further tumour biopsies is invasive to the patient, burdensome on the health care system and for inaccessible tumours significantly challenging. This has opened up the field of "virtual"/"liquid" biopsies accessing circulating tumour-presumed material in blood. Sensitivity remains a residual challenge in this rapidly evolving field; although specificity is high. Finally, enrolling for a single molecular aberrations studies can be logistically challenging particularly when the prevalence is low. Patients who meet all other of the stringent protocol eligibility criteria find they are unable to take part in the clinical study being diagnostic negative. This can impact motivation in patient and clinical trial team both at sponsor and investigator site, and can result in the costs of screening exceeding the costs of conducting the clinical study. The frustrations of single molecular aberration clinical studies has led to the emergence of "multi-arm", "basket", "molecularly matched" studies in which putative actionable molecular aberrations are identified from whole genome sequencing and the patient assigned to the drug treatment thought most likely to impact the driving molecular phenotype.