Among the most intensively studied tumor-derived biomarkers is circulating tumor DNA in the blood plasma, as a subset of cfDNA. cfDNA in the blood was first described in 1948 by Mandel and Metais, but it was not for another four decades that tumor-derived DNA was first observed in the plasma of cancer patients. Interestingly, cfDNA is naturally fragmented with lengths that correlate with DNA wrapped around individual nucleosomes. Since both healthy cells and cancer cells release their DNA into the circulation, a major challenge is attaining enough sensitivity to identify and quantify tumor-derived circulating DNA (circulating tumor DNA [ctDNA]) against a potentially large background of normal constitutional or germline DNA, the majority of which derives from hematopoietic sources. Methods based on next-generation sequencing offer a way to achieve this. Over the past two decades, ctDNA has been established as an important biomarker for studying tumor biology and for detection of cancers. Here, we summarize key applications of ctDNA in the context of early cancer detection, noninvasive tumor genotyping and classification, molecular response during therapy, and MRD after definitive therapy **(Fig. 490-3)**.