HNF4 is a highly conserved nuclear receptor critical to early development and the proper functioning of several adult organs heavily involved in metabolism, including the liver, kidney, pancreas and intestine/colon. HNF4 is also directly linked to several metabolic diseases including diabetes, atherosclerosis and the metabolic syndrome. This talk will cover the most recent advances in the identification of the HNF4 transcriptome and the significance of those findings for liver development and disease. The role of the newly identified ligand for HNF4alpha (linoleic acid) as well as HNF4 splice variants will be discussed in terms of implications for drug discovery and the evolution of nuclear receptors and their ligands. Finally, our latest work on protein binding microarrays (PBMs) to fully characterize nuclear receptor DNA binding and identify SNPs in binding sites associated with disease will be presented.