The ability to predict how different individuals will respond to vaccination and to understand what best protects individuals from infection greatly facilitates developing next-generation vaccines. It facilitates the rapid design and evaluation of new and emerging vaccines and identifies individuals unlikely to be protected by vaccine. We describe a general-purpose machine-learning framework, DAMIP, for discovering gene signatures that can predict vaccine immunity and efficacy. Using DAMIP, implemented results for yellow fever demonstrated that a vaccine’s ability to immunize a patient could be successfully predicted (with accuracy 90 percent) within one week after vaccination. A gene identified by DAMIP, EIF2AK4, decrypted a seven-decade-old mystery of vaccination. Results for flu vaccine demonstrated DAMIP’s applicability to both live-attenuated and inactivated vaccines. Results in a malaria study enabled targeted delivery to individual patients. Our project leads to better vaccines to fight emerging infections, and improve monitoring for poor responses in the elderly, infants, or others with weakened immune systems. In addition, the project’s work should help with universal flu-vaccine design. (Received September 20, 2016)