Preface

What might be taken for a precocious genius is the genius of childhood. When the child grows up, it disappears without a trace. It may happen that this boy will become a real painter someday, or even a great painter. But then he will have to begin everything again, from zero.

—Pablo Picasso

AT 22, PTEN IS ACHIEVING ADULTHOOD. This volume charts its remarkable journey from discovery and early years to universal fame and appreciation of its endless bag of biological tricks. At a time when dysregulated protein phosphorylation was recognized as the main driver of cancer and protein kinases reigned supreme in the oncogene world, PTEN emerged as the first phosphatase tumor suppressor gene that, when mutated in the germline, predisposes to cancer. Among other firsts for this precocious child, PTEN was the first dual-specificity phosphatase identified in two respects: It is a lipid and protein phosphatase, as well as a tyrosine and serine/threonine phosphatase. It was initially thought to be localized in the cytoplasm, much like most other protein phosphatases. Never short of a surprise, this enfant terrible was found to traffic into and out of the nucleus, as well as out of the cell itself, and has attendant compartment-specific functions, which are yet to be completely elucidated.

Around the time of its discovery in 1997, *PTEN* was also identified as the susceptibility gene affected by germline mutations in Cowden syndrome, a rare autosomal-dominant disorder predisposing to hamartomas and breast and thyroid cancers. We now know that Cowden syndrome is largely underdiagnosed and that *PTEN* is one of the most commonly somatically altered genes in various sporadic malignancies, rivaling only p53 in prevalence. Somewhere around its late childhood, *PTEN* was found to be altered in individuals with autism spectrum disorder (ASD) and extreme macrocephaly and, after the work of the past 14 years, *PTEN* has taken its place among the most common ASD-predisposition genes. Most recent data reveal that PTEN loss also drives an unstable genome, further adding to the remarkable complexity of PTEN biology, thus raising further questions about how alterations of a single gene can predispose to seemingly disparate conditions and lead to distinct pathologies. PTEN thus remains rich fodder for multidisciplinary research for years to come.

As our knowledge about PTEN continues to expand, so do our opportunities to mitigate the pathological consequences of PTEN loss through gene-enabled risk assessment and genetic counseling, management, and predictive testing. Moreover, deep mechanistic insights into PTEN action, both canonical and noncanonical, present an opportunity to deliver the promise of precision healthcare in its breath and depth.

We dedicate this volume to our families and our patients and their families.

Veritas filia temporis.

—Anonymous

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