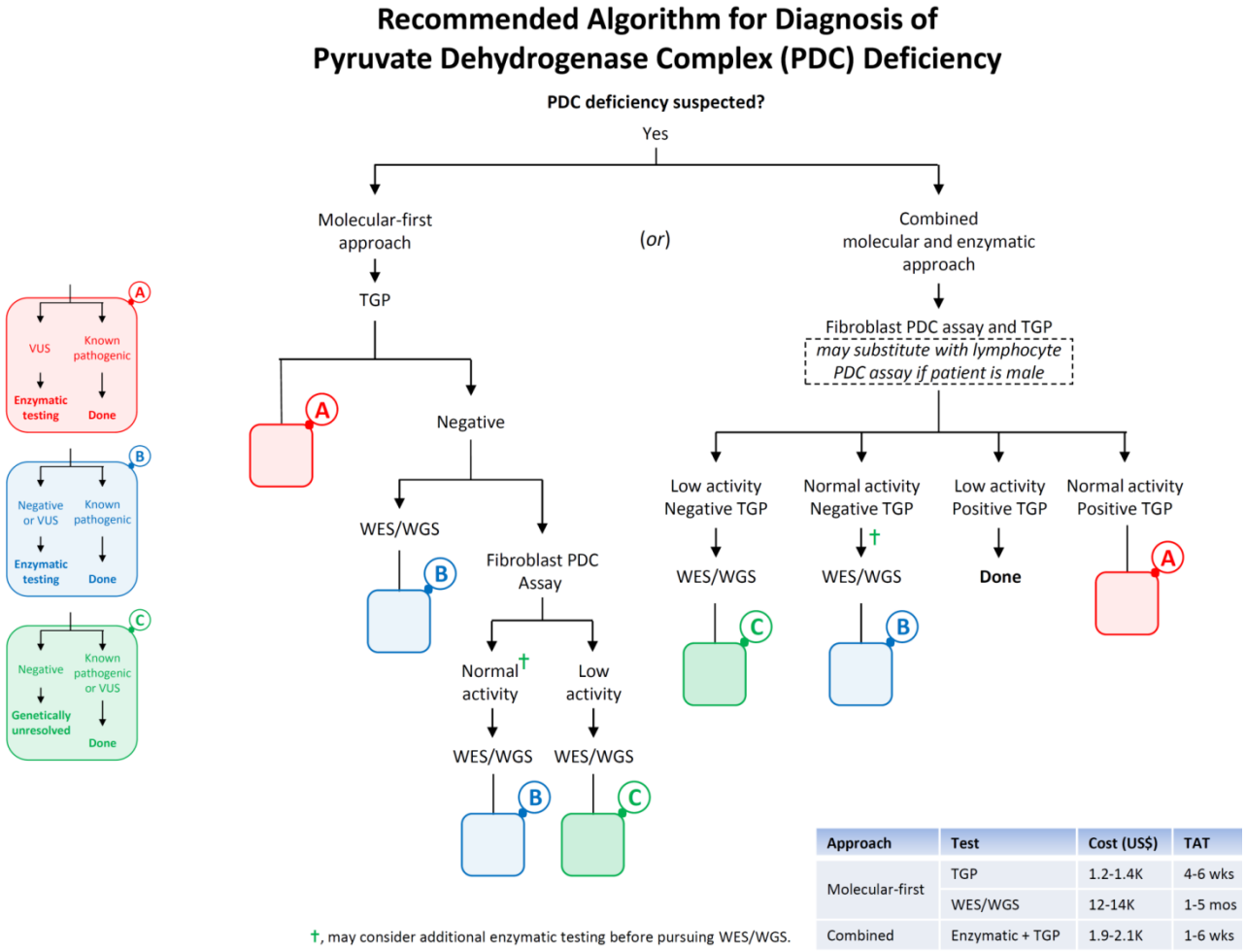

Approach	Test	Cost (US$)	TAT
Molecular-first	TGP	1.2-1.4K	4-6 wks
	WES/WGS	12-14K	1-5 mos
Combined	Enzymatic + TGP	1.9-2.1K	1-6 wks

Recommended algorithm for the diagnosis of PDC deficiency. "Enzymatic testing" is an all-inclusive descriptive term for various enzyme-based testing options noted below (after the initial pursuit of PDC testing in a specific cell/tissue). Enzymatic (functional) testing, when molecular testing is negative or a variant of uncertain significance (VUS) in a specific gene is identified, may include assaying PDC (in a different cell/tissue type than the initial testing), α-ketoglutarate dehydrogenase complex (KDC), pyruvate carboxylase (PC), phosphoenolpyruvate carboxykinase (PEPCK), propionyl-CoA carboxylase (PCC), succinyl-CoA ligase (SUCL), branched-chain α-ketoacid dehydrogenase complex (BCKDC), electron complex chain complexes (ETC), and/or oxidative phosphorylation (OxPhos) activities. Please refer to Discussion for when to suspect PDC deficiency and what tests to pursue in a patient with lactic acidosis and hyperalaninemia in order to differentiate between primary (specific and generalized) and secondary PDC deficiencies. For brevity, left side colored blocks "A" (pink), "B" (blue) and "C" (green) represent steps (algorithmic options) that are repeated (as smaller pink, blue and green blanks) within the algorithm. "Positive TGP" implies identifying a pair of known pathogenic mutations, VUSs or a combination of both in a known autosomal PDC-associated gene; for the X-linked PDHA1 gene, either a single known pathogenic mutation or VUS is expected. Abbreviations used are as follows: TAT, turn-around-time; TGP, targeted gene panel; and WES/WGS, whole exome/genome sequencing.