**Supplemental Data**

**Supplement 1:** InVitae Multi-Cancer Panel

The following 80 transcripts were used in analysis for Patient 1:

ALK (NM\_004304.4), APC (NM\_000038.5), ATM (NM\_000051.3), AXIN2 (NM\_004655.3), BAP1 (NM\_004656.3), BARD1 (NM\_000465.3), BLM (NM\_000057.3), BMPR1A (NM\_004329.2), BRCA1 (NM\_007294.3), BRCA2 (NM\_000059.3), BRIP1 (NM\_032043.2), CASR (NM\_000388.3), CDC73 (NM\_024529.4), CDH1 (NM\_004360.3), CDK4 (NM\_000075.3), CDKN1B (NM\_004064.4), CDKN1C (NM\_000076.2), CDKN2A (NM\_000077.4), CEBPA (NM\_004364.4), CHEK2 (NM\_007194.3), DICER1 (NM\_177438.2), DIS3L2 (NM\_152383.4), EGFR (NM\_005228.3: c.2369C>T p.Thr790Met variant only), EPCAM (NM\_002354.2: Deletion/duplication testing only), FH (NM\_000143.3), FLCN (NM\_144997.5), GATA2 (NM\_032638.4), GPC3 (NM\_004484.3), GREM1 (NM\_013372.6: Promoter region deletion/duplication testing only), HOXB13 (NM\_006361.5: c.251G>A p.Gly84Glu variant only), HRAS (NM\_005343.2), KIT (NM\_000222.2), MAX (NM\_002382.4), MEN1 (NM\_130799.2), MET (NM\_001127500.1), MITF (NM\_000248.3: c.952G>A p.Glu318Lys variant only), MLH1 (NM\_000249.3), MSH2 (NM\_000251.2), MSH6 (NM\_000179.2), MUTYH (NM\_001128425.1), NBN (NM\_002485.4), NF1 (NM\_000267.3), NF2 (NM\_000268.3), PALB2 (NM\_024675.3), PDGFRA (NM\_006206.4), PHOX2B (NM\_003924.3), PMS2 (NM\_000535.5), POLD1 (NM\_002691.3), POLE (NM\_006231.3), POT1 (NM\_015450.2), PRKAR1A (NM\_002734.4), PTCH1 (NM\_000264.3), PTEN (NM\_000314.4), RAD50 (NM\_005732.3), RAD51C (NM\_058216.2), RAD51D (NM\_002878.3), RB1 (NM\_000321.2), RECQL4 (NM\_004260.3), RET (NM\_020975.4), RUNX1 (NM\_001754.4), SDHA (NM\_004168.3), SDHAF2 (NM\_017841.2), SDHB (NM\_003000.2), SDHC (NM\_003001.3), SDHD (NM\_003002.3), SMAD4 (NM\_005359.5), SMARCA4 (NM\_001128849.1), SMARCB1 (NM\_003073.3), SMARCE1 (NM\_003079.4), STK11 (NM\_000455.4), SUFU (NM\_016169.3), TERC (NR\_001566.1), TERT (NM\_198253.2), TMEM127 (NM\_017849.3), TP53 (NM\_000546.5), TSC1 (NM\_000368.4), TSC2 (NM\_000548.3), VHL (NM\_000551.3), WRN (NM\_000553.4), WT1 (NM\_024426.4)

**Supplement 2:** Broad Profile Testing for Patient 2’s youngest sister (IV-6)

The following 67 transcripts were used in analysis:

*AIP, ALK, APC, ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, BMPR1A, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, DICER1, EPCAM, FANCC, FH, FLCN, GALNT12, GREM1, HOXB13, MAX, MEN1, MET, MITF, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PHOX2B, PMS2, POLD1, POLE, POT1, PRKAR1A, PTCH1, PTEN, RAD50, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL, XRCC2*