| ID     | Name       | Age at Presentation, Years | Sex | Race         | eDNA Variant | POT1 Variant | Protein Variant | Domain | VAF Rump | Serial NGs, n | Homologic Malignancy | Somatic/Germline Classification | Molecular Studies | Disease-Associated Co-Variants (VAF) |
|--------|------------|---------------------------|-----|--------------|--------------|--------------|-----------------|--------|----------|----------------|-----------------------|----------------------------------|-----------------|-----------------------------------|
| PENN02 |            |                           | 59  | F            | c.1107delT   | p.K369fs17   | TPP1            | 0.51-0.53 | 1        |               | MDS                   | Presumed Germline               | A, D               | JAK2 (0.04), TET2 (0.42)          |
| PENN03 |            |                           | 73  | F            | c.1107delT   | p.K369fs17   | TPP1            | 0.49        | 1        |               | MDS                   | Presumed Germline               | A, D               | JAK2 (0.04), TET2 (0.42)          |
| PENN04 |            |                           | 45  | F            | c.197C       | p.V326A      | TPP1            | 0.25-0.46 | 7        |               | MDS to AML             | Presumed Somatic               | B, G              | -                                |
| PENN06 |            |                           | 60  | F            | c.1234A      | p.G2781      | OBI             | 0.52        | 1        |               | CML                   | Presumed Germline               | A, D, E             | Germline*                         |
| PENN07 |            |                           | 60  | F            | c.1434G      | p.S472G      | TPP1            | 0.39        | 1        |               | MDS                   | Presumed Somatic               | B, G              | -                                |
| PENN08 |            |                           | 54  | F            | c.10-2A-C    | p.7          | OBI             | 0.51        | 1        |               | MDS                   | Presumed Germline               | A, E               | Germline*                         |
| PENN09 |            |                           | 70  | M            | c.699T       | p.R231S      | OBI             | 0.00-0.47 | 6        |               | AML                   | Confirmed Somatic              | F, G               | Somatic                          |
| PENN10 |            |                           | 68  | M            | c.762A       | p.T977C      | TPP1            | 0.49        | 1        |               | AML                   | Presumed Germline               | E, B               | Germline*                         |
| PENN11 |            |                           | 51  | M            | c.1033A      | p.G351S      | TPP1            | 0.46        | 1        |               | AML                   | Presumed Somatic               | E, I               | Presumed Germline               |
| PENN12 |            |                           | 81  | M            | c.1328G      | p.K442V      | TPP1            | 0.5        | 1        |               | MDS/AML                | Presumed Germline               | A, L               | Germline*                         |
| PENN13 |            |                           | 68  | M            | c.1832G      | p.N611S      | TPP1            | 0.52        | 1        |               | CML                   | Presumed Somatic               | E, I               | Somatic*                         |
| PENN14 |            |                           | 52  | M            | c.1617T      | p.Q274R      | OBI             | 0.00-0.46 | 6        |               | AML                   | Confirmed Somatic              | F, G               | Somatic                          |
| PENN15 |            |                           | 72  | M            | c.1733A      | p.A511S      | OBI             | 0.5        | 1        |               | MDS                   | Presumed Germline               | E               | -                                |
| PENN16 |            |                           | 87  | M            | c.1870G      | p.R241V      | TPP1            | 0.51        | 1        |               | MPN (PV)               | Presumed Germline               | E                 | -                                |
| PENN17 |            |                           | 60  | M            | c.1229G      | p.Q406R      | TPP1            | 0.5         | 1        |               | AML                   | Presumed Somatic               | D                 | -                                |
| PENN18 |            |                           | 80  | F            | c.117A       | p.A36E       | OBI             | 0.49-0.50 | 2        |               | AML                   | Presumed Somatic               | A                 | -                                |
| PENN19 |            |                           | 46  | F            | c.1851_1852del| p.D617Efs9   | TPP1            | 0.48-0.52 | 8        |               | CML to AML             | Presumed Somatic               | D, E               | Somatic                          |
| PENN20 |            |                           | 64  | M            | c.1194C      | p.L398P      | TPP1            | 0.53        | 1        |               | MDS/AML                | Presumed Germline               | E                 | -                                |
| PENN21 |            |                           | 82  | F            | c.874G       | p.S291F      | OBI             | 0.00-0.01 | 7        |               | AML                   | Presumed Somatic               | C                 | Somatic                          |
| PENN22 |            |                           | 12  | M            | c.932C       | p.Q311H      | OBI             | 0.01        | 0.5      |               | AML                   | Presumed Somatic               | C                 | -                                |
| PENN23 |            |                           | 62  | M            | c.229C       | p.Q76P       | OBI             | 0.01-0.04 | 2        |               | AML                   | Confirmed Somatic              | C, G               | Somatic                          |
| PENN24 |            |                           | 57  | M            | c.3590A      | p.H119Q      | OBI             | 0.32        | 1        |               | AML                   | Presumed Somatic               | C                 | Normal                           |
| PENN25 |            |                           | 59  | F            | c.542G       | p.L181S      | OBI             | 0.53        | 1        |               | CLL                   | Presumed Germline               | E                 | -                                |
| PENN26 |            |                           | 56  | F            | c.1513_1515del| p.S505del6   | TPP1            | 0.49        | 1        |               | CLL                   | Presumed Germline               | E                 | -                                |
| PENN27 |            |                           | 67  | M            | c.1664_1666del| p.7          | TPP1            | 0.55        | 1        |               | CLL                   | Presumed Somatic               | A, B               | Germline*                         |
| PENN28 |            |                           | 61  | M            | c.1029C      | p.S343P      | OBI             | 0.49        | 1        |               | CLL                   | Presumed Germline               | E                 | -                                |
| PENN29 |            |                           | 59  | F            | c.5326A      | p.G176B      | OBI             | 0.48        | 2        |               | CLL                   | Presumed Germline               | E                 | -                                |
| PENN30 |            |                           | 66  | M            | c.11036C     | p.R369G      | TPP1            | 0.56        | 1        |               | BCR-ABL                | Presumed Germline               | E                 | -                                |
| PENN31 |            |                           | 54  | M            | c.5820A      | p.G724R      | OBI             | 0.48        | 1        |               | CLL                   | Presumed Somatic               | E                 | -                                |
| PENN32 |            |                           | 56  | M            | c.4670A      | p.G1554S     | OBI             | 0.48        | 1        |               | CLL                   | Presumed Germline               | E, H               | Germline*                         |
| PENN33 |            |                           | 63  | F            | c.3086G      | p.H1026D     | OBI             | 0.35        | 1        |               | CLL                   | Presumed Somatic               | B                 | Somatic*                         |
| PENN34 |            |                           | 61  | M            | c.1174C      | p.M391I      | OBI             | 0.36        | 1        |               | CLL                   | Presumed Somatic               | B                 | Somatic*                         |
| PENN35 |            |                           | 70  | M            | c.1007T      | p.S336L      | OBI             | 0.49        | 1        |               | CLL                   | Presumed Germline               | E                 | -                                |
| PENN36 |            |                           | 71  | M            | c.5326A      | p.G176B      | OBI             | 0.50-0.51 | 2        |               | NPMI                  | Presumed Germline               | E                 | -                                |
| PENN37 |            |                           | 78  | M            | c.223C       | p.P79L       | OBI             | 0.00-0.05 | 2        |               | NPMI                  | Presumed Germline               | G                 | Somatic                          |

**Supplemental Table 5S:** POT1 variant somatic/germline classification and co-occurring cytogenetic and molecular variants.
| Patient ID | Sex | Age | Ethnicity | Mutation Site | VAF | Diagnosis | Grade | Presumed Somatic | Normal | Abnormal Cytogenetics | Disease-Associated Somatic Variants | Flow Cytometry | Constitutional DNA | Final Classification |
|------------|-----|-----|-----------|---------------|-----|-----------|-------|----------------|--------|-------------------|---------------------------------|--------------|------------------|-------------------|
| PENN38     | F   | 65  | Caucasian | c.1641G>A   | p.?  | CLL       | Normal | Presumed Somatic | E      | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN39     | F   | 66  | Caucasian | c.G871A     | p.D291N | OB2      | 0.00-0.45 | CLL | Somatic* | F, G | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN40     | M   | 82  | Caucasian | c.T900G     | p.L300F | OB1      | 0.3    | CLL | Somatic* | F, G | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN41     | M   | 54  | Caucasian | c.A664G     | p.R222H | OB2      | 0.05   | CLL | Presumed Somatic | E      | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN42     | F   | 59  | Caucasian | c.G803A     | p.G268D | OB2      | 0.05   | CLL | Presumed Somatic | E      | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN43     | M   | 54  | Caucasian | c.A671G     | p.D224G | OB2      | 0.00-0.21 | Tonsillar Plasmacytoma | Somatic | C    | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN44     | M   | 68  | Hispanic | c.G188T     | p.R63I   | OB2      | 0.07   | Multiple Myeloma | C      | -    | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN45     | F   | 66  | Caucasian | c.C820A     | p.G274R | OB2      | 0.07   | CLL | Presumed Somatic | E      | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN46     | M   | 67  | Caucasian | c.T1144C    | p.C382R | OB2      | 0.25   | Mantle Cell Lymphoma | Presumed Somatic | B    | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |
| PENN47     | F   | 73  | Caucasian | c.A1482G    | p.I494M  | OB2      | 0.33   | Multiple Myeloma | Presumed Somatic | B    | 46,XY:del(17p11.2),del(17q) |                     |              |                  |                   |

Abbreviations: variant allele frequency (VAF), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), myeloproliferative neoplasm (MPN), myelofibrosis (MF), acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), essential thrombocythemia (ET), polycythemia vera (PV), natural killer (NK), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL).

Codes for germline/somatic determination:
- POT1 VAF: (A) Near heterozygous POT1 VAF (0.50+/- 0.03), (B) POT1 VAF <40%, (C) low POT1 VAF <10%; Validation tissue: (D) hematopoietic specimen not involved by tumor, (E) hematopoietic specimen with limited tumor involvement documented by bone marrow morphology, somatic tumor markers (abnormal cytogenetics, disease-associated somatic variants, flow cytometry), (F) non-hematopoietic constitutional DNA.

Final classifications denoted with a * indicate sample included in internal validation subset.