**Supplementary Materials**

**Integrating Tumour Sequencing into Clinical Practice for Patients with Mismatch Repair-Deficient Lynch Syndrome Spectrum Cancers**

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**Supplementary Table 1. Demographic and clinical information by predicted cancer origin**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Lynch syndrome | MLH1 promoter hypermethylation | Double somatic variants | Unexplained |
| **Total (*n* = 84)** | 23 (27) | 22 (26) | 19 (23) | 20 (24) |
| **Age at earliest diagnosis**, median (range) | 52 (32-86) | 71.5 (33-87) | 53 (28-77) | 55.5 (24-84) |
| **PREMM5 score**, median (range) | 7.7 (0.9-50) | 2.2 (0.9-14) | 2.9 (1.7-9.0) | 2.9 (1.2-50) |
| **Clinical testing criteria** |  |  |  |  |
|  Amsterdam I/II (*n* = 7) | 5 | 1 | 0 | 1 |
|  Revised Bethesda (*n* = 59) | 16 | 15 | 13 | 15 |
|  None (*n* = 18) | 2 | 6 | 6 | 4 |
| **PREMM5 score** |  |  |  |  |
|  < 2.5% (*n* = 35) | 5 | 15 | 8 | 7 |
|  ≥ 2.5% (*n* = 49) | 18 | 7 | 11 | 13 |
| **Colorectal (*n* = 52)** | 14 (27) | 19 (37) | 10 (19) | 9 (17) |
|  *Sex* |  |  |  |  |
|  Female | 5 | 7 | 3 | 6 |
|  Male | 9 | 12 | 7 | 3 |
|  *TNM stage* |  |  |  |  |
|  I/II | 0 | 1 | 2 | 4 |
|  III/IV | 12 | 17 | 4 | 4 |
|  Unknown | 2 | 1 | 4 | 1 |
|  *Histologic grade* |  |  |  |  |
|  Well- to moderately-differentiated | 11 | 7 | 5 | 6 |
|  Poorly- to undifferentiated | 2 | 12 | 5 | 2 |
|  Unknown | 1 | 0 | 0 | 1 |
| **Endometrial (*n* = 26)** | 7 (27) | 2 (8) | 9 (35) | 8 (31) |
|  *TNM stage* |  |  |  |  |
|  I/II | 4 | 2 | 6 | 6 |
|  III/IV | 1 | 0 | 2 | 1 |
|  Unknown | 2 | 0 | 1 | 1 |
|  *FIGO grade* |  |  |  |  |
|  1 | 6 | 1 | 4 | 4 |
|  2-3 | 1 | 1 | 5 | 3 |
|  Unknown | 0 | 0 | 0 | 1 |
| **Other (*n* = 6)** | 2 (33) | 1 (17) | 0 | 3 (50) |

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**Supplementary Figure 1. Tumour characteristics and sequencing results for dMMR Lynch syndrome spectrum cancers identified by IHC-based tumour screening.** CN-LOH, copy neutral loss of heterozygosity; CRC, colorectal cancer; EC, endometrial cancer; IHC, immunohistochemistry; MPH, *MLH1* promoter hypermethylation; MSI, microsatellite instability; MSI-H, MSI high; MSI-L, MSI low.



**Supplementary Figure 2. Updated testing algorithm for dMMR colorectal cancers and distribution of cases based on data from the current study.** \*One *PMS2* carrier would not have been referred for germline genetic testing based on *MLH1* promoter methylation in their tumour and absence of a personal or family history suggestive of Lynch syndrome.



**Supplementary Figure 3. Updated testing algorithm for dMMR endometrial cancers and distribution of cases based on data from the current study.** \*Testing for constitutional methylation was indicated for one individual meeting Amsterdam I criteria.