Germline lynch syndrome testing: Are we there yet?

Shalini Agnihotri[1], Himanshi Diwan[2], Surender Dhandha[2], Anurag Mehta[2]

Departments of Research[1]& Molecular Diagnostics[2], Rajiv Gandhi Cancer Institute & Research Centre, New Delhi

INTRODUCTION

- Lynch syndrome is the most common of all hereditary cancer predisposition syndromes accounting for approximately 3-5% of all colorectal cancers (CRC) and endometrial cancers (EC).[1]
- Identifying these patients helps predict prognosis, optimize treatment, plan future surveillance, and family screening.
- Currently, the most cost-effective and best screening strategy is screening patients with Mismatch repair (MMR) deficiency/ Microsatellite instability (MSI) for further genetic testing.

OBJECTIVE

- To evaluate MMR/MSI across all tumors, along with uptake of germline testing for Lynch syndrome in India.

METHODS

- This is a single centre cross sectional study in which MMR and MSI status was evaluated across all tumours, along with uptake of germline testing for Lynch syndrome from 2021 to 2015.
- Mismatch repair status was assessed by testing the somatic tumour by either immunohistochemistry (IHC), for MLH1, PMS2, MSH2 & MSH6 (on Ventana platform), or MSI by fragment length analysis using Promega kit (SeqStudio/Applied biosystems).
- The germline testing was performed on peripheral blood using custom DNA panel for the four MMR genes (*MLH1*, *PMS2*, *MSH2*, *MSH6*), interrogating single nucleotide variants and indels by Next generation sequencing (Ion Torrent).

Fig 1: Distribution of dMMR/MSI cases according to cancer type

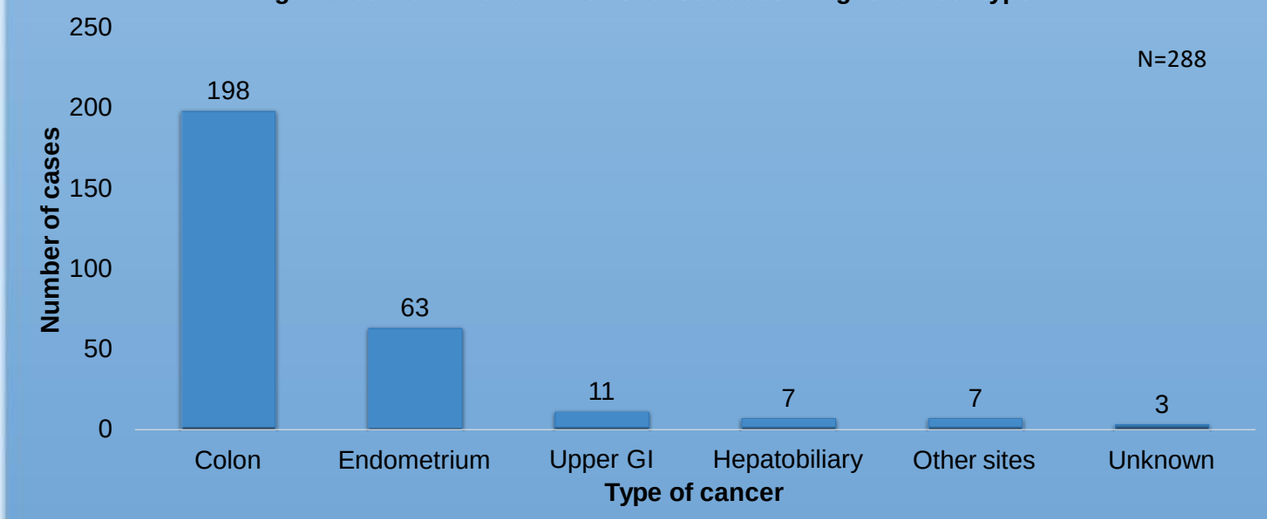


Fig 2: Extent of germline testing

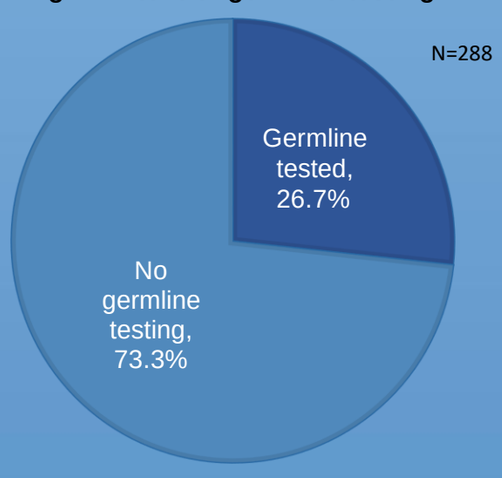


Fig 3: Extent of germline mutation

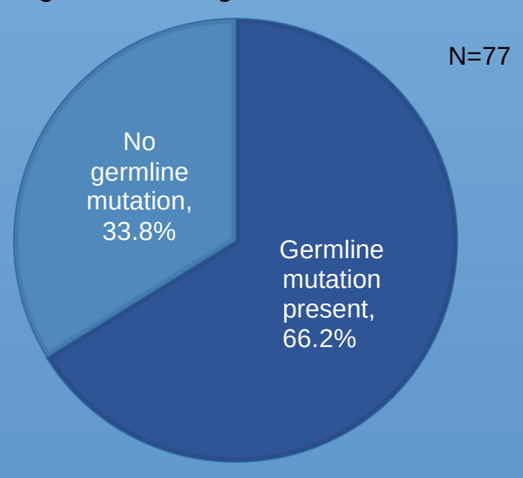


Fig 4: Distribution of genetic mutations

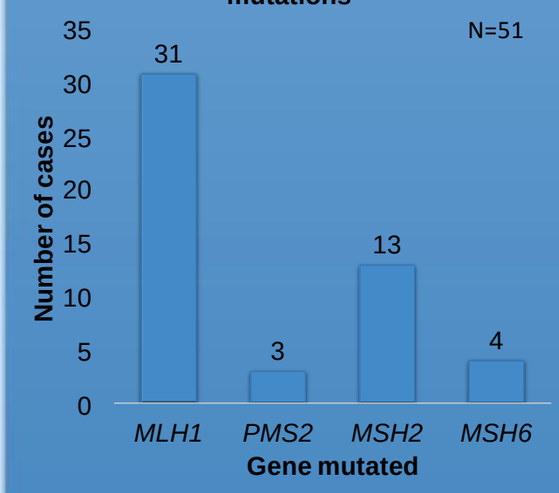


Fig 5: Nodal status in dMMR/MSI cancers

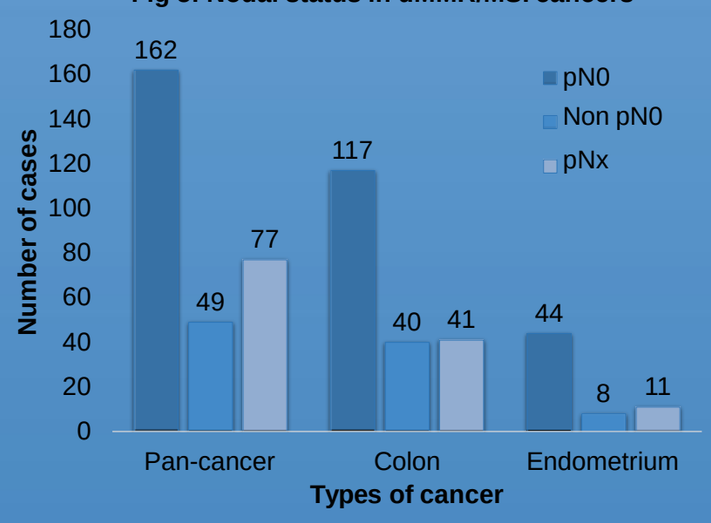


Fig 6: Nodal status in germline cancers

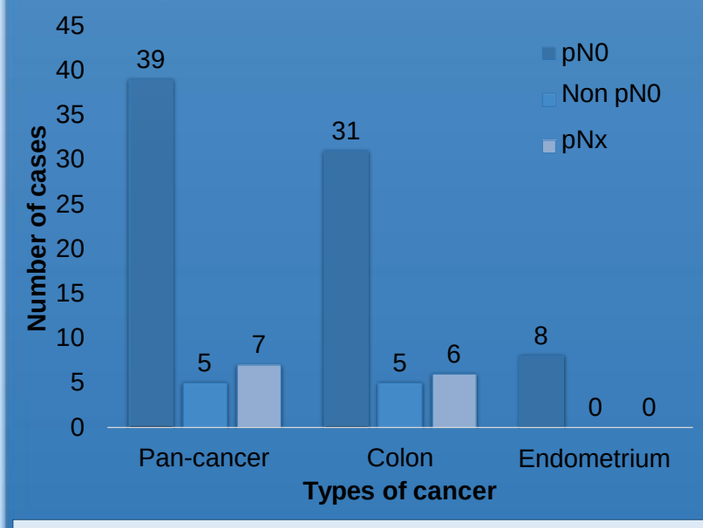
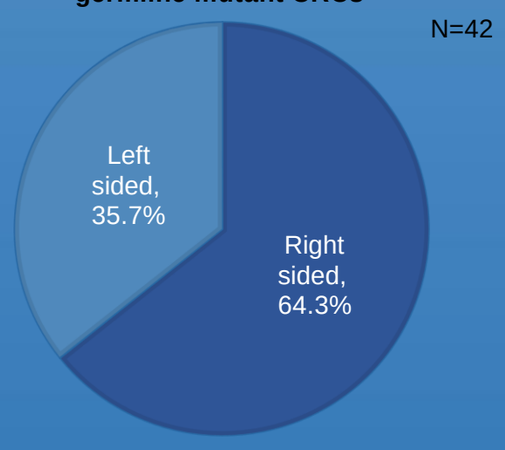


Fig 7: Anatomical distribution of germline mutant CRCs



RESULTS

- 288 (19.9%) of 1447 cases tested for MMR/MSI, revealed MMR deficiency (dMMR)/MSI.
- 198 of the 288 dMMR/MSI cases were CRCs (68.8%), followed by Endometrial cancers (21.9%).
- Germline lynch testing was done in 77 of 288 cases (26.7%).
- 51 of 77 (66.2%) cases tested, revealed a germline mutation, with the highest frequency in *MLH1* gene (60.8%).
- 60 of 288 cases (20.8%), did not undergo germline testing, had insurance coverage (p=0.0005).
- 131 of the 198 (66.1%) dMMR/MSI CRCs were right sided.
- 42/61 CRCs tested (68.9%), revealed a germline mutation, most commonly implicating *MLH1* gene (66.7%), (p<0.0001).
- Most germline CRCs were right sided (64.3%), (p=0.2561).
- Germline CRCs showed a higher frequency of node negative stage (86.1%), (p=0.0195).
- 25 of 26 germline CRCs with *MLH1/PMS2* mutation, also revealed MLH1/PMS2 loss on IHC testing (p<0.0001).
- 45 of 63 (71.4%) dMMR/MSI ECs, were low grade, while 44 (69.8%) had a node negative disease.
- 8 of 14 (57.1%) dMMR/MSI ECs tested, were germline mutant.

DISCUSSION

- Guidelines recommend that all CRCs, and lately all ECs, be assessed for dMMR/MSI, followed by germline testing, in order to increase identification of patients with Lynch syndrome.
- In the present study, the referral rate of genetic testing for Lynch syndrome was 26.7%, compared to an Australian study that revealed a referral rate of 11% in dMMR CRCs.[2]
- Meanwhile, Muller et al, reported that the highest referral rate was seen in Non-Hispanic whites (21.2%), while it was as low as 10.9% in Hispanic patients, in the United states.[3]
- In contrast, a study from Iceland revealed that, genetic testing was done in almost 80% cases.[4]

CONCLUSION

- Germline testing helps in early identification of recurrence & in screening of kindred. In our experience, the uptake of germline testing is low in India, owing to socioeconomic restraints.
- This unmet need can be met by clinicians and molecular pathologists with adequate counselling, helping eradicate the associated social stigmata.

REFERENCES

1. Mehta A, Gupta G. Lynch syndrome—It's time we start detecting it. J Curr Oncol 2018;1:55-60
2. Steinberg J, Chan P, Hogden E, et al. Lynch syndrome testing of colorectal cancer patients in a high-income country with universal healthcare: a retrospective study of current practice and gaps in seven australian hospitals. Hered Cancer Clin Pract. 2022 May 4;20(1):18.
3. Muller C, Lee SM, Barge W, et al. Low Referral Rate for Genetic Testing in Racially and Ethnically Diverse Patients Despite Universal Colorectal Cancer Screening. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1911-1918.
4. Haraldsdottir S, Rafnar T, Frankel WL, et al. Comprehensive population-wide analysis of Lynch syndrome in Iceland reveals founder mutations in MSH6 and PMS2. Nat Commun. 2017 May 3;8:14755.