Familial Cancer (2025) 24:2
https://doi.org/10.1007/s10689-024-00427-7

ORIGINAL ARTICLE

Mainstreaming cancer genetics: feasibility of an advanced nurse practitioner-led service diagnosing Lynch syndrome from colorectal cancer in Ireland

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Received: 1 August 2024 / Accepted: 26 September 2024
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Abstract

Colorectal cancer (CRC) is a common cancer in Ireland. Of all CRCs, 2–4% are attributable to Lynch Syndrome (LS), the most common CRC predisposition syndrome. LS is caused by constitutional pathogenic variants (PVs) affecting mismatch repair (MMR) genes with resultant MMR protein deficiency (dMMR). Screening of all CRCs with MMR immunohistochemistry (IHC) testing is advocated to increase the detection of LS. However, successful implementation requires appropriate downstream management. In Ireland the traditional pathway involves referral to cancer genetics services to assess eligibility for genetic testing. Cancer genetics services in Ireland face many challenges in providing uniform access to timely healthcare with current wait times for assessment in excess of 1 year. An increasingly adopted pathway is that of mainstreaming, whereby genetic testing is managed locally by a multidisciplinary team member. Our institution therefore implemented an Advanced Nurse Practitioner (ANP)-led service with responsibility for the LS Diagnostic Pathway and mainstream genetic testing. Data was extracted from a prospectively maintained database of all newly diagnosed CRC patients discussed at our institutions CRC multidisciplinary meeting (MDM) between January 1st, 2023, and May 31st, 2024. MMR IHC testing was performed in 97.9% of the 385 patients diagnosed with CRC. The median time from histological confirmation of CRC to the availability of the MMR IHC report was 6 days. All 51 patients (100%) who required sequential tumor testing underwent BRAF V600 ± MLH1 promoter methylation testing. Additionally, 100% of the 14 patients eligible for mainstream genetic testing were referred to the ANP-led genetics service. The median time from the initial MDM discussion to the initiation of genetic testing was 69 days, while the median time from testing to the availability of results was 19 days. Patients received their results within a median of 21 days. MMR IHC testing increases the detection of LS through identification of dMMR tumours. Successful downstream delivery of clinical services, however, requires appropriate subsequent management, in a resource-limited environment. Our institutional experience demonstrates the feasibility, efficiency, and effectiveness of an ANP-led mainstreaming model of care for hereditary colorectal cancer.

Keywords Lynch syndrome · Mainstreaming · Colorectal cancer · Advanced nurse practitioner · Cancer genetics

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Introduction

In Ireland colorectal cancer (CRC) represents a significant disease burden, accounting for the second and third most common cancers in males and females respectively. Approximately 2,800 new cases are diagnosed annually in a population of 5.13 million, with an increase in patients diagnosed under the age of 50 (early onset colorectal cancer, EOCRC) [1–5]. EOCRC is thought to be due in large part to environmental factors although inherited risk factors such as Lynch Syndrome (LS) also play a role in up to 30% of cases [3, 6, 7]. Screening programs result in earlier cancer diagnosis, which is associated with improved survival and reduced morbidity [8]. Ireland's Bowel Screen programme started in 2012 for those aged 60–69 yet 22% of cases from 2017 to 2019 occurred in people under the age of 60; similar outcomes are observed in other countries [1, 9]. The average age of diagnosis of CRC in a patient with LS is 44–52, which is before the age at which the Irish national screening programme commences [10]. This highlights the importance of identifying those with CRC due to an inherited predisposition so that predictive genetic testing and gene-specific surveillance can be offered to genetically related family members [11]. Up to 35% of CRCs display familial clustering, with 6% due to defined genetic tumour syndromes following Mendelian inheritance, such as LS [12, 13]. LS is the most common hereditary colorectal cancer predisposition syndrome, affecting up to 1 in 280–400 people [14]. However, most LS carriers remain unaware of their status [15, 16].

Mismatch repair (MMR) immunohistochemistry (IHC) can identify CRC patients whose tumour may be due to underlying LS [17, 18]. However, evidence indicates that the identification and surveillance of individuals who may be predisposed to LS varies considerably in Ireland [10, 18]. Those with or suspected of having a CRC predisposition syndrome are typically referred to cancer genetic services for evaluation [19]. However, Ireland's current clinical genetics services are inadequate to meet the increasing demand driven by advances in cancer genetics [20, 21]. Long waiting lists result in delays for genetic assessment and testing, with negative psychological consequences for patients as well as knowledge deficits for their treating team in determining the optimal treatment and surveillance pathway for the patient [20]. Delays in referral also risk missed opportunities to diagnose cancers with subsequent health economic impacts [22, 23].

In recent years cancer genetic testing has grown from niche to normality [24]. Cancer genetic testing has become mainstream, prompting Ireland's National Cancer Strategy (2017–2026) to prioritize improved hereditary cancer services [24, 25]. The Health Service Executive (HSE) established a National Genetics and Genomics Strategy, involving experts, patient advocates and stakeholders. In 2022, the HSE unveiled the National Strategy for Accelerating Genetic and Genomic Medicine, emphasizing patient involvement [26]. Subsequently, the Hereditary Cancer Model of Care, published in June 2023, outlines priorities for cancer control and surveillance in individuals with inherited risk of breast, ovarian, and colorectal cancer, providing a framework for developing Ireland's hereditary cancer services [27].

An Advanced Nurse Practitioner (ANP) -led Familial Colorectal Clinic was established in our institution, embedded in the colorectal surgical service with the goal of enhancing care for individuals with or suspected of having a heritable predisposition to CRC. The ANP participates in the weekly CRC multidisciplinary meeting (MDM), oversees the Lynch Syndrome Diagnostic Pathway (Fig. 1) and facilitates mainstream genetic testing.

The aim of this study is to evaluate the effectiveness and feasibility of an ANP-led service in managing the Lynch syndrome diagnostic pathway for CRC patients. The study assesses the downstream management of genetic testing within an ANP-led model of care, aiming to improve timely access to genetic testing and service delivery in a resource-limited environment.

Methods

A retrospective review of the activity of the ANP-led Familial Colorectal Clinic was conducted over the period January 1st, 2023, and May 31st, 2024. All newly diagnosed cases of CRC at our institution are discussed at the CRC MDM. The incidence of dMMR CRCs detected by IHC, and downstream management of those with dMMR were evaluated. Data were collected from electronic patient records, histopathology reports, and from a prospectively maintained electronic database of all newly diagnosed CRC's, using a standardised template. The collected data included demographic details, clinicopathological features, tumor MMR status, IHC results, and the outcomes of genetic testing, including the identification of any Pathogenic Variants (PV) or Variants of Uncertain Significance (VUS). Additionally, the timeframes for each step in the process were recorded.

All patients with a histologically confirmed diagnosis of CRC between January 1st 2023 and May 31st, 2024, were included. Cases where diagnosis was not confirmed histologically were excluded e.g. radiological suspicion. The number of specimens tested by reflex IHC and the percentage of tumours exhibiting MMR protein loss were recorded. In cases where IHC identified MLH1/PMS2 MMR protein loss and additional *BRAF* testing was positive for a

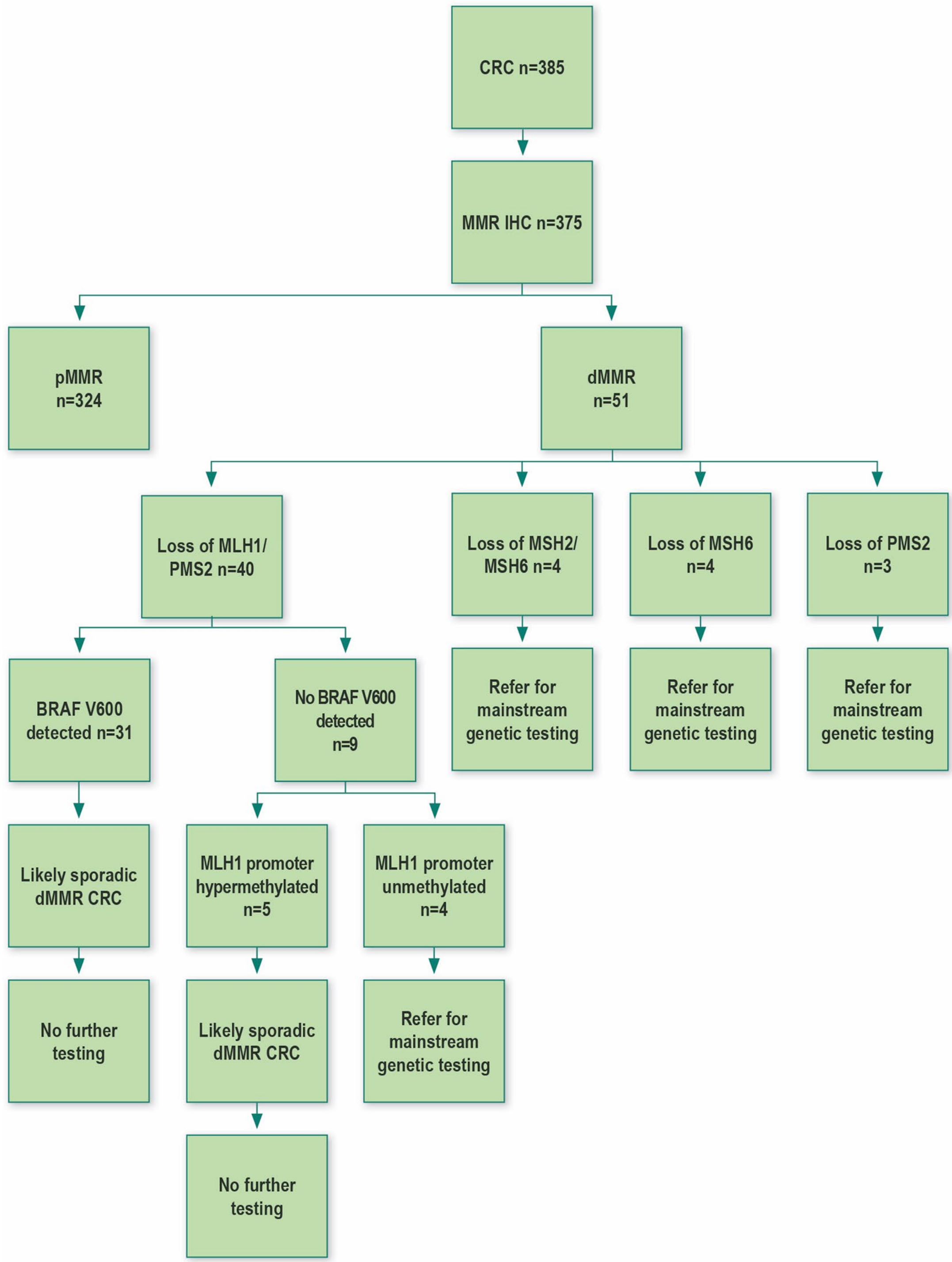

Fig. 1 Lynch syndrome diagnostic pathway

V600E mutation, tumours were considered likely sporadic, and onward referral to the Familial Colorectal Clinic was not required. Similarly, in cases where *BRAF* testing was negative for V600E mutation tumour samples were sent for *MLH1* promoter analysis. If the *MLH1* promoter was hypermethylated, tumours were considered probably sporadic, and onward referral to the Familial Colorectal Clinic was not required. The number of patients who were referred to the Familial Colorectal Clinic, and those who subsequently were offered and consented to constitutional (germline) testing were recorded. Identified constitutional PVs and VUS were recorded. In cases where dMMR remained unexplained after the above steps, the patient's tumour sample was referred for somatic genomic analysis to an external accredited clinical laboratory to assess for a second somatic event to explain dMMR, i.e. somatic MMR gene analysis (Fig. 2). Constitutional testing was conducted with a 5-gene panel evaluating known pathogenic variants causative of LS; *MSH1*, *MSH2*, *PMS2*, *MSH6*, *EPCAM*.

Results

A total of 385 patients' records and histopathology reports were reviewed over a 17-month period by the Familial Colorectal Clinic. Ten patients (2.3%) were excluded due to no histological diagnosis of CRC, or the absence of an available tumour sample. 375 (97.7%) of patients had reflex tumour IHC MMR testing of which 51 were dMMR, accounting for 13.6% of the CRC cohort. The median age at CRC diagnosis was 71 years (range 30–92 years). 31 (8%) were aged 50 or younger at the time of diagnosis. The median age of the dMMR cohort was 76 years (range 38–92 years), of these 7 (13.7%) were aged 50 or younger at the time of diagnosis. 288 of 385 (76.8%) had MMR IHC testing performed on their initial endoscopic biopsies and 87 of 385 (23.2%) on their surgical specimens. The median time from histological confirmation of CRC diagnosis to the availability of the MMR IHC report was 6 days (range 1–54). The most common pattern of MMR protein loss was combined loss of MLH1/PMS2, accounting for 40 patients of the 51 with dMMR tumours. 4 had loss of MSH2/MSH6, 3 had isolated loss of PMS2 and 4 had isolated loss of MSH6.

All patients (40 of 40) that required additional tumour sequencing with either *BRAF* V600 or *MLH1* methylation testing had appropriate tumour testing. Of those with loss of MLH1/PMS2, 31 of 40 had a *BRAF* V600 mutation detected, indicating a sporadic CRC. The median time for

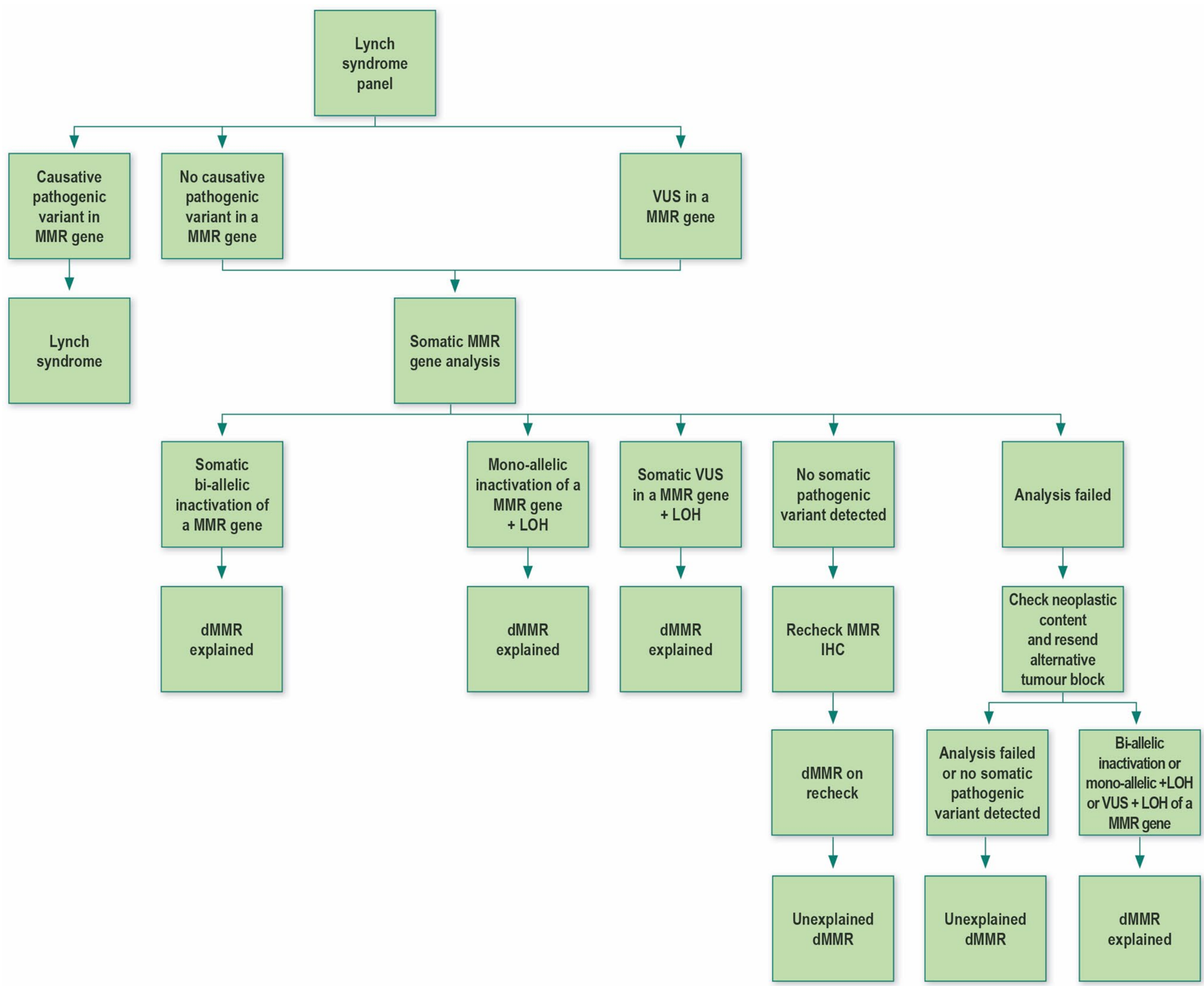

Fig. 2 Unexplained dMMR Investigative Pathway

the availability of *BRAF* V600 reports was 5 days (range 4–21). The remaining 9 had wild-type *BRAF* and were referred to an external clinically accredited lab for *MLH1* promoter methylation testing. The median turnaround time for the MLH1 methylation report was 35 days (range 32–41). Of these, 5 had epigenetic hypermethylation of the *MLH1* promoter indicating a likely sporadic CRC with no need for further testing and 4 had an unmethylated *MLH1* promoter and thus were referred to the Familial Colorectal Clinic for consideration of genetic testing. The median time from first MDM discussion to genetic testing was 69 days (range 8-232).

A total of 14 patients were eligible for mainstream genetic testing and referred to the ANP-led Familial Colorectal Clinic. After pre-test genetic counselling, 85.7% ($n=12$) consented to a LS panel with associated MLPA set (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). The median time from genetic testing to the availability of genetic test results was 19 days (range 11–28) with results returned to patients within a median time of 21 days (range 7–62). 6 of 12 patients were diagnosed with LS following identification of a causative constitutional PV. 2 had a variant of uncertain significance (VUS) found in a MMR gene and 4 had no PV detected. All patients with a PV ($n=6$) were referred to an external cancer genetics center for post-test genetic counselling in accordance with national guidelines [27].

Results of all patients with a VUS or unexplained dMMR ($n=6$) were reviewed by a genetic pathologist and discussed at the colorectal cancer genetics MDM at our institution. All (6 of 6) had a tumour sample sent for somatic MMR gene analysis in line with our institution's unexplained dMMR investigative pathway (Fig. 2).

Discussion

Historically, referral to a cancer genetics service for genetic testing was guided by the use of clinical guidelines based on age and family history, such as the Amsterdam criteria and Bethesda guidelines [28–31]. The Evaluation of Genomic Applications in Practice and Prevention group (EGAPP) initially recommended MMR IHC followed by selective screening with a 70-year age cutoff. (Jerusalem criteria) [32, 33]. Since 2017, the National Institute of Health and Care Excellence (NICE) recommends testing for dMMR by either MMR IHC or DNA microsatellite instability (MSI) analysis for all new CRC diagnoses [34].

Previous studies confirm MMR IHC feasibility and effectiveness [35–38]. Challenges in implementation and cost-effectiveness, as well as operator-dependent variability in IHC, have been noted [22, 39–41] Testing should be conducted in expert settings, with robust quality control measures [41, 42]. Although pathologists are considered the drivers of universal screening, uncertainty remains as to who is responsible for the downstream management of results [8, 18, 43]. It has been previously demonstrated in Ireland that a lack of available genetics workforce has led to delays in accessing genetic testing and loss to follow-up of patients who met criteria for referral to cancer genetics services [8, 18, 20, 21].

At our institution, implementation of a mainstreamed model with ANP-led delivery of the Lynch syndrome diagnostic pathway and co-ordination of further management has resulted in significantly enhanced outcomes. Reflex MMR IHC is routine, with 97.7% of newly diagnosed CRCs undergoing MMR testing. This compares favorably to previously published data, where the rates of CRC assessment for dMMR have been reported between 17 and 71%, despite international guidelines recommending universal tumor screening (UTS) [16]. The median time from histological confirmation of CRC diagnosis to the availability of the MMR IHC report is 6 days, compared to a median of 24 days from initial diagnosis to MMR IHC testing reported elsewhere [16]. The early identification of dMMR carriers as potential candidates for immunotherapy justifies a push for faster turnaround times, regardless of the patient's LS status [44]. The median time from first MDM discussion to genetic testing is 69 days, showing a notable improvement compared to the median of 315 days observed in other settings [16]. All patients deemed eligible for germline testing were referred to the ANP-led service for pretest counselling, with no loss to follow-up. Results were provided in a timely manner, with a median turnaround of 19 days from testing to result availability and 21 days for the return of results to patients. This shows a positive contrast to previously published data, where referral rates for genetic testing in eligible patients have been reported as low as 33%, with delays observed in the return of MMR IHC, somatic (BRAF V600 ± MLH1 promoter methylation), and constitutional genetic test results [8, 16, 34, 42, 45]. Specifically in an Irish context, an unmet need for downstream referral pathways post-identification of suspected constitutional MMR deficiency has been identified, with previously described referral rates to cancer genetics services in Ireland as low as 30% for eligible patients and a wait time from referral to testing of up to 4 years [8, 18]. Our data suggests that the mainstreamed ANP-led model is both feasible and highly effective in addressing this unmet need.

In this model, the role of the ANP is crucial for successfully implementing a mainstream CRC genetics service [16, 46]. ANPs are acknowledged as clinical leaders, driving change and healthcare transformation [47–50]. Their clinical leadership role involves utilizing evidence-based practice to enhance patient care and optimize treatment for specific patient groups [48, 49]. Leadership as a key component of the ANP role is acknowledged internationally, including in research from Canada, Ireland, and Australia [48, 50]. In a mainstreamed model of hereditary colorectal cancer care the ANP acts as the clinical champion in overseeing the LS diagnostic pathway, guiding patients through genetic testing, coordinating care, and improving adherence to surveillance pathways [51]. Collaborating with the multidisciplinary team, including clinical geneticists, genetic pathologists, histopathologists, medical scientists, surgeons and genetic counselors, the ANP ensures timely and appropriate management [52]. At our institution the ANP-led service includes coordinating endoscopic surveillance, referral to relevant specialties and ensuring patients are on pharmacologic prophylaxis where appropriate [53–56]. To fully realize their potential in such roles, nurses must be resourced and supported with adequate training in genetics, ensuring they are equipped to navigate the complexities of genetic-based patient care [57, 58].

Conclusion

In the Republic of Ireland, access to and timely delivery of specialist cancer genetics services represents a substantial unmet need, the requirement for which is projected to increase significantly over the coming years. Our institutional experience confirms the feasibility, efficiency and efficacy of an ANP-led mainstreamed model of care for hereditary colorectal cancer. The development of this service aligns with national healthcare priorities to deliver timely and appropriate cancer genetics services in a coordinated way integrated with the patient's cancer care pathway. Development and expansion of similar services would facilitate enhanced delivery of cancer genetics services into routine clinical practice, ensuring uniformity, safety, high quality, and cost-effective care. However, this will necessarily require appropriate resourcing and investment.

Author contributions M.L. led the conception of the study, data collection, analysis, and manuscript writing. L.V.O'C. contributed to the drafting of each version of the manuscript and oversaw referencing. I.M.F., L.Mc.S., K.S., and R.K. reviewed the manuscript, provided constructive feedback, and assisted with editing. All authors reviewed and approved the final version of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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