Genetics inMedicine | CORRESPONDENCE

Response to Benusiglio et al.

We read with interest the correspondence by Dr. Benusiglio and colleagues, wherein they describe some of the real world challenges they face in implementing universal Lynch syndrome testing for individuals with colorectal and endometrial cancer.[1] These include the time and resource-consuming series of tests required that ultimately yield negative or inconclusive results for 71–72.5% of cases. They describe an integrative Mendelian model under development that they hope will not only guide tumor testing and germline sequencing decisions, but also patient management strategies. We look forward to publication of their risk prediction model in due course.

The optimal strategy for Lynch syndrome testing unselected colorectal cancers is well established.[2] A growing consensus supports testing all endometrial cancers too, since an equivalent 3% of individuals are expected to test positive.[3] Selective testing based on clinical features like age, family history or tumor phenotype, misses many cases of Lynch syndrome. [Ryan NAJ, Evans DG, Crosbie EJ. The Proportion of Endometrial Tumours Associated with Lynch Syndrome (PETALS) study. Personal Communication]. This is important not just for the proband, but also for her at risk family members, who may choose to undergo Lynch syndrome testing themselves.

Often the first indication of an underlying Lynch syndrome diagnosis, endometrial cancer provides a unique diagnostic opportunity. It enables enrollment in colonoscopic surveillance and aspirin chemoprevention to reduce the risk of death from subsequent cancers.[4] Further, it facilitates targeted immunotherapy in advanced or recurrent endometrial cancer, since Lynch syndrome–associated tumors, characterized by heavy immune cell infiltrates, are particularly sensitive to immune checkpoint inhibition.[5]

Rather than referring all patients with non–methylated mismatch repair (MMR) deficient tumors to the genetics service, we in Manchester have developed a new evidence-based pipeline for the unselected screening of endometrial cancer for Lynch syndrome that avoids many of the problems that Dr. Benusiglio and his colleagues describe. While it is true that only a tiny proportion of women test positive for Lynch syndrome, our comprehensive, streamlined, sequential testing strategy allows most women to be reassured without any additional burden to themselves or their families in terms of anxiety, unnecessary clinic appointments or surveillance.

Lynch syndrome testing is led by gynecologists, who consent women and store blood for germline testing during routine outpatient review following primary treatment for endometrial cancer. [Ryan NAJ, Evans DG, Crosbie EJ. Feasibility of gynaecologist led Lynch syndrome testing in women with endometrial cancer. Personal Communication]. Tumors are then subjected to a series of tests that triage women for definitive germline Lynch syndrome testing, reducing costs and improving cost-effectiveness.[6–8] Immunohistochemistry (IHC) for MMR deficiency followed by reflex targeted *MLH1* methylation testing reduces the proportion of women for whom germline Lynch syndrome testing is required. Somatic sequencing of tumors from germline-negative women explains the vast majority of MMR deficient tumors not caused by Lynch syndrome, with very few residual "Lynch-like" cases remaining. This may be below 1% of all cases in endometrial cancer (2/500; 0.4%), [Ryan NAJ, Evans DG, Crosbie EJ. The Proportion of Endometrial Tumours Associated with Lynch Syndrome (PETALS) study. Personal Communication] and is very similar in colorectal cancer (19/4653; 0.4%).[9] Retesting tumors that do not have explicable germline or somatic changes may reveal overcall of IHC in 4–14% of samples[8] and this should be performed prior to referral for genetic counseling. All testing is performed by specialist regional laboratories that participate successfully in external quality assurance and interpretation of MMR variants is by international multidisciplinary expert teams according to a single set of defined criteria (https://www.insight-group.org/criteria/).

The Manchester approach has several advantages. Gynecologist-led Lynch syndrome testing reduces pressures on the clinical genetics department since only women who test positive for a germline MMR pathogenic variant are referred for professional genetic counseling. The burden for women and their families is also reduced, since no additional clinic appointments are required for the vast majority of women who test Lynch syndrome negative. This is also likely to alleviate the negative psychological sequelae of Lynch syndrome testing. Upfront identification of suitable tumor blocks for genetic analysis and storage of blood for future germline testing facilitates a tightly organized multidisciplinary workflow to proceed in a timely fashion, reducing inefficiency and minimizing delays. Classification of MMR variants by an expert international panel supports clinical decision-making and minimizes the difficulty of managing variants of unknown significance (VUS). Tight regulation of test quality and the expert interpretation of results according to strict guidance ensures indeterminate test results are kept to a minimum. Finally, a dedicated project manager who oversees testing, the transfer of samples between laboratories, and uploads results to a bespoke database allows workflow procedures to be audited and data analyzed and outcomes published for international scrutiny. A similar approach could be used for colorectal cancer with surgeons taking the lead for patient consent and results ratified through the multidisciplinary team meeting.

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DISCLOSURE

The authors declare no conflicts of interest.

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