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AQ: A Reply to J. Moline et al

Moline and Eng¹ have raised important points regarding universal versus age-restricted screening of endometrial cancer for features of mismatch repair (MMR) deficiency, and the debate ever what should happen ideally versus what can happen in the ablic health arena. The scheme we propose for identification of germline MMR mutation carriers in our article² suggests that all women younger than age 60 years at diagnosis should undergo tumor MMR immunohistochemistry (IHC) testing as primary triage for MMR mutation testing. Although we and others have shown that universal screening is more sensitive for the identification of MMR gene mutation carriers, implementation of universal MMR screening is largely dependent on testing facilities and financial resources. This is likely why universal screening is still not widely adopted internationally, or even in the United States.³

Previous publications in the endometrial cancer arena have suggested an age cutoff of 50 years, 4,5 and this is the age cutoff that is currently suggested for patients with endometrial cancer by the Namal Comprehensive Cancer Network^{6,7} and Comprehensive Can-Centre of the Netherlands⁸ guidelines for hereditary cancer. The gnostic yield of MMR gene mutation carriers among patients with endometrial cancer (and also colorectal cancer) decreases with increasing age. In our study, approximately 60% of the MMR IHC tests (n = 408) were performed in patients 60 years of age or older for the identification of three carriers. The age-limited scheme we propose as ptimal was selected, from the public health perspective, to substantrally reduce burden on the health care system while detecting the vast majority of mutation carriers. We note also that the recently published article by Moline states that "screening in patients diagnosed ≤ 60...[years] would have idented all patients with Lynch syndrome in their cohort." 9(pXXXX)

Compared with other guidelines (such as the National Comprehensive Cancer Network and Comprehensive Cancer Centre of the Netherlands guidelines) that suggest screening/clinical action for only patients with endometrial cancer diagnosed at or before age 50 years, our proposed scheme will greatly improve carrier detection while nevertheless considering resource limitations that are frequently encountered in the international clinical setting. We acknowledge openly that some mutation carriers will be missed by an age-restricted scheme. However, universal screening with MMR IHC is itself not without limitations because of suboptimal MMR IHC testing 10,11 or an IHC-normal profile of protein-stable mutations (mutations that will remain undetected by universal screening)—both of which would lead to so-called missing of MMR gene mutation carriers. We recommended additional IHC and/or microsatellite instability testing AQ: H as a secondary screen or direct MMR gene testing when there is a high clinical suggestion of Lynch syndrome, irrespective of age, that can assist in detecting so-called missed MMR gene mutation carriers. It is worthwhile to note that a parallel colorectal cancer screening program would identify some families missed by implementing age-limited endometrial cancer screening programs. In our study, all three mutation carriers older than age 60 years reported colorectal cancer in at least one first-degree relative (age 38 to 63 years).

Moline and Eng¹ have noted the following specific issues regarding the use of age at diagnosis of endometrial cancer as a screening criterion in the clinical setting. First, they pointed out that the frequency of MMR gene mutation carriers older than a years at diagnosis is lower in our study² than in two other reports, 12-14 highlight in Table 1 that such estimates T1, from any unselected cohort will be based on relatively small numbers. The frequency of MMR gene mutation carriers in women age 60 years or older at diagnosis did not differ significantly between all studies of unselected endometrial cancer cohorts identified from the literature^{2,12-16} (Table 1). Furthermore, the range in point estimates across studies does not seem to be explained by differences in the upper age limits between studies, which ranged from age 70 years¹⁴ to 94 years.¹²

Moline and Eng¹ next assert that placing any age cutoff on tumor screening allows an opportunity for pathologist errors. It is inevitable

Table 1. Comparison of MMR IHC Results and MMR Gene Mutation Frequency in Studies of Unselected Endometrial Cancer*						
Characteristic	Australia ² (N = 702)	$US^{12,13}$ (N = 543)	The Netherlands ¹⁴ (N = 179)	Korea ¹⁵ (N = 113)	Spain ¹⁶ (N = 173)	
Cohort age range, years	18-79	17-94	≤ 70	NA	29-90	
IHC loss, %	24.2	23.3	23.5	23.0	33.5	
MMR mutation carriers, %†	3.1	2.3	3.9	4.4	4.6	
MLH1	0.4	0.2	0	0.9	0.6	
MSH2	1.1	0.6	0	1.8	1.7	
MSH6	1.4	1.5	3.4	1.8	1.7	
PMS2	0.1	0	0.6	0	0.6	
Mutation carriers, total	22	13	7	5	8	
No. of carriers age ≥ 60 years	3	5	3	1	2	
% of carriers age ≥ 60 years	14	38	43	20	25	
95% CI, %	4 to 36	15 to 68	12 to 80	1 to 70	5 to 64	

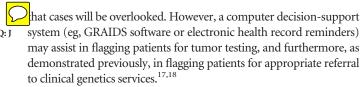
Abbreviations: IHC, immunohistochemistry; MMR, mismatch repair; NA, not available; US, United States.

*Study design was as follows: Australia was an Australian population–based case-control study; US was an Ohio population–based study, Netherlands was a Dutch multicenter study, and Korea and Spain were both single-center studies.

†Total may not add up to 100% because of rounding.

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Moline and Eng¹ also state that having an age cutoff for endometrial and not colorectal cancer constitutes unequal treatment of endometrial versus colorectal cancer for Lynch syndrome screening. From a public health perspective, decisions about screening will be implemented in the context of available resources, and it is in the best interests of the research and clinical community internationally that all relevant information be provided to develop tailored local/national guidelines that can be feasibly implemented.

Further research will almost certainly refine recommendations for the testing of patients with endometrial cancer for suspected Lynch syndrome, but the immediate need is to encourage systematic MMR IHC testing over other family history—based criteria.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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