The cheques and balances of national universal screening of patients with new colorectal cancer for Lynch syndrome

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Tiered universal screening systems that save lives are cost-effective

About 15–20% of colorectal cancers exhibit microsatellite instability (MSI) caused by deficient DNA mismatch repair (MMR).[1] Most of these cancers (80%) are sporadic, associated with hypermethylation of the *MLH1* gene promoter. Lynch syndrome is caused by germline mutations affecting one of the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*), and accounts for 15–20% of MMR-deficient (dMMR) colorectal cancers, or 2–5% of all colorectal cancers, making it the most common hereditary colorectal cancer predisposition syndrome.[2] People with Lynch syndrome are at increased risk of several cancer types, especially colorectal cancer: the risk by age 70 years is 10–82%, depending on the mutant gene, considerably higher than that of the general population (4.5%).[3]

Genetic diagnosis and regular colonoscopy surveillance are highly effective for reducing the incidence, stage, and mortality of colorectal cancer in people with Lynch syndrome,[3] so there is a strong clinical incentive to systematically implement standardised diagnostic strategies. Historically, clinical and pathology-based guidelines advised identifying patients who warrant genetic testing for Lynch syndrome according to their family history, young age of onset, and tumour MSI status.[2] Universal testing of people with newly diagnosed (incident) colorectal and endometrial cancers — the two major Lynch syndrome cancers — offers a more generalised approach. Universal testing strategies differ in detail, but essentially apply a tiered approach, first identifying tumours that exhibit MSI or are dMMR (MMR protein expression loss identified by immunohistochemistry) and then applying a second test (either for *MLH1* methylation or the coincidental *BRAF* V600E mutation) to exclude Lynch syndrome in the many patients with sporadic MSI/dMMR. Finally, patients with MSI/dMMR tumours without *MLH1* methylation or *BRAF* mutation are referred for testing for a Lynch syndrome-causing germline MMR mutation.

Since 2005, when the feasibility of universal testing of patients with incident colorectal[4] or endometrial[5] cancers for Lynch syndrome was confirmed on a population basis, many professional organisations in the United States and Europe have recommended it as the standard of care.[6–8] As multiple genes can now be screened simultaneously using next-generation sequencing cancer gene panels, it has been suggested that the tiered universal testing scheme for Lynch syndrome could be bypassed by offering universal cancer gene panel testing, which would identify other hereditary colorectal cancer conditions as well.[9]

Universal testing of people with incident colorectal cancer for Lynch syndrome is now being considered in Australia. National implementation of a systematic testing scheme to identify the 2–5% of colorectal cancers caused by Lynch syndrome would come at considerable cost to the national health care service provider (Medicare), and would therefore need to be cost-effective. The key question asked by health care policy makers is: "Would the clinical benefits come at an acceptable price?" The usual parameter used for decision-making is the "price per life-year saved (LYS)", which compares the cumulative costs of all diagnostic tests undertaken to identify the few patients with the disorder with the downstream costs of treatment and life-years lost should no testing be conducted. In Australia, the willingness-to-pay threshold is broadly considered to be under $30 000–$50 000 per LYS.

A study reported in this issue of *MJA* investigated this question and explored which universal testing strategy would be the most cost-effective.[10] Kang and her colleagues modelled the costs of each of the available tiered universal testing strategies for Lynch syndrome, and also for universal cancer gene panel testing, and compared them with the price of not testing patients. They found that the tiered universal testing schemes would indeed be cost-effective, costs ranging between $28 926 and $31 910 per LYS, depending on the molecular pathology tests employed. The authors calculated that this approach would reduce colorectal cancer-related mortality by 184–189 deaths per 1000 patients with new colorectal cancer with Lynch syndrome and their mutation-carrying relatives if an average of just four relatives at (50%) risk of Lynch syndrome also underwent cascade genetic testing. The most cost-effective scheme involved immunohistochemistry followed by *BRAF* mutation testing, the most common approach in the US and Europe. In contrast, universal cancer gene panel testing was not cost-effective for diagnosing Lynch syndrome; however, the modelling did not take into consideration other hereditary cancer syndromes that would also be diagnosed by this approach.

The findings of Kang and colleagues are consistent with an earlier US study, although the cost benefits in the latter were

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realised with cascade genetic testing and cancer prevention in relatives.[11] Also worth considering, although difficult to quantify, would be the cost savings for future generations should descendants at risk opt to undergo pre-emptive genetic testing and preventive health care. Another factor not examined in the study by Kang and her co-authors is that patients with colorectal cancer are now routinely tested for MSI/dMMR for treatment stratification, as response to systemic therapies differs according to tumour MMR status.[12,13] One might therefore argue that the cost of specifically testing for Lynch syndrome only includes tests conducted following the identification of MSI/dMMR tumours; from this perspective, the cost-effectiveness of testing would be even greater.

Given the intrinsic limitations of cost-effectiveness modelling, it will be interesting to evaluate the real world impact of national systematic universal testing for Lynch syndrome on cancer prevention and costs. This would provide the reality check on the balance of cheques paid for preventive colorectal cancer health care for those at greater risk.

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