

# Challenges to the adoption of risk algorithms for colorectal cancer screening programmes: perspectives for future research

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Colorectal cancer (CRC) is the third most common cancer worldwide and accounts for 10% of all cancer new cases.<sup>1</sup> There is concrete evidence for the effectiveness of screening in reducing CRC-related mortality.<sup>2</sup> In some developed nations such as the US, colonoscopy has been used as a primary screening tool.<sup>3</sup> Because not all countries are equipped with adequate colonoscopy resources for population-based screening, it is recommended for individuals with increased risk for CRC only.<sup>4</sup> Hence in many countries, the concept of risk-based screening is gaining appeal, particularly the use of scores to risk-stratify subjects and classify screening participants as average-risk or high-risk. A prominent example is the risk score devised and validated by the Asia-Pacific CRC working group, named the Asia-Pacific Colorectal Screening (APCS) score.<sup>5</sup> It uses age, gender, smoking habit, and presence of a history of CRC in a first-degree relative to identify high-risk individuals (score 4-7 out of 7) who are more likely to benefit from colonoscopy screening due to the higher yield of advanced colorectal neoplasia. Subjects who score 0-3 are advised to undertake faecal occult blood tests. The APCS score has a high level of validity and was developed following rigorous statistical analysis.<sup>6</sup> Other validated risk scores have been constructed using similar methods and have potential for use in clinical practice.<sup>7,8</sup>

Yeoh et al<sup>5</sup> also identified some issues related to the application of the APCS score. The objective of this commentary is to discuss the potential challenges and perspectives for future research into risk-based CRC screening.

First, not all known risk factors for CRC can be incorporated into the model due to practical difficulties. Some information is difficult or too time-consuming to be accurately collected in a clinic scenario, such as dietary habits and level of physical activity. Second, increasing the number of variables will inevitably reduce the practical utility of the scoring systems, and not all risk factors possess good predictive value. This might explain why some scoring systems suggest a need for further work,<sup>9,10</sup> as several

algorithms have relatively modest concordance statistics, barely exceeding the acceptable level of “satisfactory” (0.6-0.7). Furthermore, the derivation process of these scoring systems usually employs a split-cohort strategy without external validation. Subsequent validation in other populations might not result in similar discriminatory capabilities.<sup>11</sup> Third, there are concerns about the generalisability of these scores in people residing in different regions around the world. It is well recognised that the prevalence and distribution of advanced colorectal neoplasia differ for different ethnicities. Fourth, in order for a local government to use these risk scoring tools, their efficiency and cost-effectiveness must be evaluated in the local context. Formal cost-effectiveness analysis based on various risk factors should be performed for each population to be served.<sup>12-14</sup> There are also concerns about the acceptability and distributive justice of such an approach. Whilst some unhealthy lifestyle habits such as smoking, drinking alcohol, and consuming red meat are risk factors for CRC, it is hard to justify why people ‘choosing these lifestyle habits’ deserve to be screened by a more expensive screening option such as colonoscopy.

These risk scores are scientifically robust and nicely constructed. Nonetheless, at the health care system level, their generalisability remains uncertain. The different opinions of various stakeholders also complicate matters—the perception of risk is subjective and it is likely that screening participants will be destined to undergo colonoscopy despite having an average risk as assessed by the risk scores, not because they wish to.

Prior to 2016, there was no population-based CRC screening programme in Hong Kong. In response to the increasing health burden posed by CRC, the government has since launched a 3-year subsidised, CRC screening pilot programme in the population for asymptomatic individuals aged 61 to 70 years. The screening modality uses a 2-yearly, two-specimen faecal immunochemical test, followed by colonoscopy if any one sample is positive. This pilot programme collects data on its feasibility and

cost-effectiveness. It is yet to be discussed whether a risk-based approach can be incorporated into future programmes.

We believe each country will need a screening programme tailored to the characteristics of its own population. Nonetheless, collaboration among specialist personnel may be helpful to establish several initiatives. First, we need to enhance the discriminatory capability of screening tests. Currently the predictive variables are presented as categorical variables in most scoring systems that are more user-friendly and more convenient. Appropriate statistical adjustments could be made to obtain more precise weightings for each risk factor, and this might increase the concordance statistics of the algorithm.

Second, development of non-invasive biomarkers affordable to the general public should be an important focus. There is increasing evidence to support the use of newer modalities, such as computed tomographic colonography and faecal DNA testing. These may serve as useful tools in the screening of CRC.<sup>15</sup> Despite the potential risk of radiation exposure, the benefits outweigh potential harm when computed tomographic colonography is used in CRC screening.<sup>16</sup> A multi-target faecal DNA test that detects circulating methylated septin 9 gene DNA has also been approved for CRC screening.<sup>17</sup> Magnetic resonance colonography and capsule endoscopy are mainly used for diagnosis rather than screening.<sup>18,19</sup> Although magnetic resonance colonography does not expose the individual to radiation and requires no sedation, use of intravenous contrast agent is required.<sup>20</sup> Capsule endoscopy is non-invasive and also requires no sedation but the bowel preparation is more complicated than that required for colonoscopy.<sup>21</sup> A recent report showed that faecal quantification of *Fusobacterium nucleatum* could be a useful supplement to faecal immunochemical test in the diagnosis of CRC and advanced adenoma. This non-invasive approach may improve the screening accuracy of current faecal immunochemical test.<sup>22</sup>

Third, effective education programmes for the general public about the risk of CRC should be formulated. In order for risk-based screening to be efficient, the effectiveness and sustainability of health education about the various risk factors for CRC should be enhanced in order to heighten community awareness.<sup>23</sup> Acceptability, perception, attitude, and satisfaction of risk-based screening should also be evaluated. Previous studies have identified various barriers to CRC screening, including economic concerns, limited access to screening services, screening-induced discomfort, perceived bodily harm, embarrassment, and anxiety induced by screening.<sup>24</sup> Individuals at high risk of CRC who are targeted for screening should have their attitude and perception identified in a systematic manner under

a theoretical framework, such as the health belief model.<sup>25</sup>

Lastly, cost-effectiveness analysis of competing screening strategies in different patient groups should be performed in different settings. This warrants further research funding, particularly in population groups at high risk of CRC, including patients with medical conditions such as non-alcoholic fatty liver disease, diabetes, and metabolic syndrome.

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