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Integrating personalised genomics into risk stratification models of population screening for colorectal cancer

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Colorectal cancer (CRC) accounts for about 4,000 deaths each year in Australia and is the second most common cause of cancer-related death after lung cancer.[1] The 10-year risk of developing CRC for 60-year-old males is 1.2%; for females it is 0.8%. The good news is that the median five-year survival for those diagnosed with CRC has increased from 55.0% (1981-83) to 65.3% (2005-11) due to improved early diagnosis and advances in surgical and adjuvant therapy.[2]

Based on evidence from randomised controlled trials, screening with the faecal occult blood test (FOBT), followed by diagnostic colonoscopy for those testing positive, could prevent 14% of new CRC cases and 19% of deaths at an incremental cost of $58,540 per life-year saved compared with no screening.[3,4]

In 2006, Australia began the National Bowel Cancer Screening Program (NBCSP) with the aim of reducing mortality rates associated with CRC.[5] Once fully implemented, the NBCSP will offer free screening to those aged 50 to 74 years, with biennial immunochemical faecal occult blood test (iFOBT). This is the most appropriate cohort for population screening because 93% of people diagnosed with CRC in Australia in 2011 were aged 50 years or older.[5]

While the sensitivity of the NBCSP is high – 83.4% of CRC identified within the program were first flagged by a positive iFOBT[6] – its effectiveness is limited by a low uptake potentially due to cultural and linguistic diversity and psychological factors (faecal aversion). Although screening with FOBT in the United Kingdom (UK) has uptake of around 55%,[7] just 36% of the Australian target population participated in the NBCSP in 2013-14.[5]

Colonoscopy is currently the gold standard for detection of CRC however, limited capacity (especially in the public system), high costs and test acceptability make it impractical for whole-population screening. Therefore, alternative approaches are required to improve screening participation and CRC detection, allowing more efficient and appropriate allocation of colonoscopy services. While the traditional public health CRC screening approach has stratified individuals for risk based primarily on age, other factors such as family history and lifestyle factors are known to affect individual risk. In addition, presence of adenomatous colonic polyp and adenoma characteristics (e.g. size, villosity, dysplasia grade and location in the colon) are predictive factors for future CRC.[8] The NHMRC Clinical Guidelines for Colorectal Cancer detail how to stratify the population into risk categories based on family history.[9] The guidelines recommend an increased level of surveillance via colonoscopy for those who have a strong family history of the disease or known genetic susceptibility.

Family history, lifestyle and genetic prediction

Individuals vary in their levels of CRC risk based on differences in a complex array of factors including age, gender, family history, detected adenoma, genetic makeup and lifestyle or environmental factors including obesity and physical inactivity, diet and alcohol consumption. About 10-15% of the population have a family history of CRC, which increases an individual's risk by 2–4 fold.[10] The increased risk associated with a family history of CRC in a first degree relative is equivalent to advancing the risk of developing CRC by about 10 years in both males and females.[11] It seems logical that the age of entry into CRC screening programs should be adjusted based on family history.

According to current evidence, the approximate two-fold risk associated with a family history of CRC has been attributed to genetic factors. Some of these are known mutations in specific genes that, when inherited, result in substantially increased risk of CRC.[12] However, these genetic mutations are sufficiently rare (about 1 in 300 of the population) that they cannot account for the majority of the familial risk. This suggests that other genetic factors, if identifiable, could be used to predict CRC risk.[12]

To date, the search for other genetic risk factors for CRC has primarily uncovered common, low-risk genetic variants, the majority being single-nucleotide polymorphisms (SNPs).[13,14] So far, about 45 SNPs have been identified that together contribute 23% of the heritable risk. A further 5% can be attributed to the inheritance of high-penetrance mutations (Lynch, APC and MUTYH) in known genes.[15]

It is clear that there remain as yet unidentified genetic factors contributing to a substantial proportion of the risk to developing CRC. To address this issue (and many other questions related to health and the genome), the United States (US) and the UK governments have independently announced large population-based genome sequencing projects. The US Government has announced the Precision Medicine Cohort Program proposing to sequence the genomes of one million US participants, while the UK Government has commenced the 100,000 Genomes Project to sequence the genomes of 100,000 people enrolled through the National Health Service. The investment in these two projects (US$215m and £300m respectively), is equivalent to A$935m. The expected outcomes are comprehensive knowledge of genetic risk profiles that can be used together with known lifestyle and environmental risk factors for better earlier diagnosis and personalised care for patients with cancer and other diseases.

Risk stratification

Much recent attention has focussed on strategies to improve the acceptability of iFOBT for CRC and other non-invasive screening tests, in addition to the development of risk stratification models for CRC screening. Risk stratification and personalised surveillance could substantially increase the detection rate and earlier detection for cancers in younger individuals

(especially for those under 50 years of age and therefore not eligible for the NBCSP), reduce the number of investigations for false-positive results, reduce the harm due to overuse of diagnostic or invasive treatments so that resources can be allocated to those who would benefit most from more regular surveillance.[13] Furthermore, it has been suggested that personalised risk stratification could improve compliance with population CRC screening strategies.[16]

The accumulated evidence suggests that a stratified risk screening strategy incorporating family history, age, gender, lifestyle, socio-economic status with genetic profiling of multiple novel risk variants could improve CRC risk prediction. Although it cannot be applied to the prediction of individual risk for CRC at this time, it is possible to stratify a population into risk categories, using a panel of 10 common genetic variants associated with CRC susceptibility. Such a model is demonstrably superior to using family history alone.[17] Risk stratification incorporating polygenic risk variants with family history, lifestyle and age can refine the risk prediction to identify 7% of the population at increased risk of developing CRC and for whom additional screening is warranted, through regular colonoscopic surveillance.[17] A recent simulation study incorporating all the 45 published SNPs for CRC estimated that 20% of the population could be identified that were 1.8-times the average risk[15]. A person in this category reaches the average risk of a 63 year-old by the time they are 56 years. If they also have a family history of CRC, they reach the risk of a 63 year-old at only 49 years.[15]

There is ample evidence to support genetic risk stratification for early identification of younger individuals at increased risk of CRC who are currently ineligible for population screening programs.[18] Alternatively, the knowledge of increased CRC risk for age due to genetic predisposition, could promote participation in population CRC screening programs, such as the NBCSP.[19]

Challenges

Despite the evidence and potential health gains, currently no population-level genetic risk stratification program exists anywhere in the world. We recognise that any proposal to incorporate such measures will introduce a range of new challenges for current population screening policy makers. Before implementing a risk stratification model for CRC screening, there are many fundamental economic, ethical and policy issues to be resolved, including the secure sample storage, privacy and confidentiality of identifiable personal data and linking these to other phenotypic data, and consent to access to genetic, lifestyle and medical records over a person's lifetime.[20] These may or may not support genetic risk stratification, but must be investigated thoroughly to ensure that any decisions concerning whether or not to introduce a new risk-based paradigm are based on sound evidence and community acceptability. If it were to be introduced, a communication strategy will be required to educate the public about how to use genetic information to balance the risks and benefits of risk stratification. Individual consent will be required that includes provision for re-contact to communicate new information or incidental findings, limitations on the scope of genetic testing, linkages to other databases and implications for employment and insurance. It is time that these matters are brought to the attention of the funders of research, policy makers and the general public so that they can be considered and planned to meet societal standards.

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