GeneType for Colorectal Cancer

Integrated Colorectal Cancer Risk Assessment
November 2019

Highlights
GeneType for Colorectal Cancer may help to identify people who could benefit from targeted screening or prevention, particularly in clinical genetics settings when mutations in high-risk genes cannot be identified.

GeneType for Colorectal Cancer is the only validated, genomic-based colorectal risk assessment that combines genetic risk markers, single Nucleotide Polymorphisms, with clinical risk markers to provide an integrated colorectal cancer risk score for the patient. This test minimises the uncertainty associated with self-reported risk factors and incorporates an unambiguous combination of SNPs to calculate the CRC polygenic risk score.
Introduction

Globally in 2018, an estimated 1.8 million people were diagnosed with colorectal cancer (CRC), which makes up almost 10% of all cancers. In the United States, 1 in 22 men and 1 in 24 women will receive a colorectal cancer diagnosis during their lifetime.1,2 Detection relies on screening programs that unaffected individuals typically avoid, despite how crucial early detection is to survival.

Accurate risk assessment to determine those individuals at higher risk is important for providing personalized screening and intervention plans. Questionnaire-based risk assessment models such as the NCI's Colorectal Cancer Risk Assessment Tool (https://ccrisktool.cancer.gov/) perform well on a population level, but are less able to predict “individual” risk. GeneType for Colorectal Cancer is designed to address this and enable “personalized” risk assessment. Most national screening programs only use age as a risk factor, where all patients within an age range are invited to screening. Tests that more accurately identify those patients at increased risk of colorectal cancer, such as GeneType for Colorectal Cancer, have the potential to impact healthcare from the system level down to the patient level. One reason being, patients can be flagged as “high risk” and therefore offered more intensive surveillance and/or risk reducing options.

GeneType for Colorectal Cancer is the only validated, genomic-based colorectal risk assessment that combines genetic risk markers (Single Nucleotide Polymorphisms, SNPs) with clinical risk markers to provide an integrated colorectal cancer risk score for the patient. This test minimizes the uncertainty associated with self-reported risk factors and incorporates an unambiguous combination of SNPs to calculate the CRC polygenic risk score (PRS).

The GeneType SNP analysis was validated by a large international study that modelled over a million cases and controls and was then cross-validated on >1,000 colorectal cases.3,4 These studies confirmed the application of case-control genetic stratification for discriminating between high and low risk PRS. Furthermore, PRS can be combined with clinical risk factors, such as first degree relatives with CRC, to further stratify patient risk. The impact and value that PRS incorporation has on absolute lifetime risk scores is evident in reclassification tables which highlight screening-start-age of patients based on calculated risk-level (relative to age 50 as the gold standard for average-risked individuals). Identification of adults at increased-risk through an integrated genetic-risk approach such as GeneType for Colorectal Cancer, could result in improved screening protocols for the population of individuals that often “fly under the radar.”

GeneType for Colorectal Cancer is currently available to individuals of Caucasian descent between the ages of 30-80 years old. The risk assessment is conducted in patients using a buccal swab, from which DNA is extracted for genotyping. Results combine the patient’s PRS with clinical risk factors including sex, age, first degree family history of CRC, and ethnicity to provide an absolute risk score. Patients are stratified into risk categories of either average or increased risk compared to that of the population average. Tailored prevention and surveillance options for those at increased risk include (i.) Personalized screening regimens, (ii.) Risk reducing medications and (iii.) Lifestyle changes.
Background

Colorectal cancer (CRC), the neoplastic disease of the colon or rectum, is the second most fatal cancer in the United States.1,2 In 2019, CRC in the United States will cause more than 50,000 deaths. Moreover, about 150,000 new CRC cases will be identified.2 The mean 5-year CRC survival rate is ~65%. Rates are dramatically reduced when the initial diagnosis is made at a more advanced stage. Approximately 20% of first CRC diagnoses are made at Stage IV2,5 (Figure 1).

![Figure 1. Proportion of colorectal cancer cases by stage, at time of diagnosis, indicates nearly half of patients are diagnosed at stages III or IV. Figure adapted from Moghadamyeghaneh et al. 2016.5](image)

CRC screening campaigns have been successful in increasing public awareness and have resulted in decreased CRC incidence rates over the past 40 years. Early detection has played a role in the decreased mortality rates associated with CRC. Despite this, a third of adults between 50 - 75 years are not up to date with screening recommendations.2 Eligible adults often avoid recommended screening due to fear of receiving adverse findings and the misunderstanding that CRC screening is unnecessary due to a lack of family history.6 Family history is a significant contributor to CRC risk, but it is important to note that only 2-5% of CRC patients have a cancer syndrome (high penetrant, inherited mutation) and only another ~20% of have a family history of the disease (not associated with a cancer syndrome).7,8 Thus, it is important to dispel this misconception associated with cancer-family-history as being the sole high-risk factor; the majority (>70%) of CRC cases are in fact, sporadic.

Even more concerning is the steadily rising incidence of CRC among younger adults (aged 20-49).2,9 This rising incidence of CRC among young adults is not a result of increased screening from early detection because these individuals are below screening age. While there is no clear reason for this increase, environmental factors including Western diet and lifestyle choices are believed to play a role. The American Cancer Society has accordingly updated their recommendations; average-risk adults should begin CRC screening at the age of 45.10 Starting CRC screening at a younger age for average-risk individuals may aid in early detection for a few patients, but at the cost of “over-screening” a large majority of the population. It is therefore important to consider other risk factors that contribute to risk of CRC to better identify at-risk individuals that would benefit from early onset screening.
As the healthcare sector moves toward preventative medicine, GeneType for Colorectal Cancer is designed to deliver personalized access to screening and prevention plans that meet the individualized needs of the patient. GeneType for Colorectal Cancer follows in the footsteps of its companion breast cancer risk assessment test, which was initially released in 2011 as BREVA®. The test is now called GeneType for Breast Cancer and it stratifies women’s sporadic breast cancer risk. The GeneType product series provide validated disease risk prediction by integrating polygenic and clinical risk factors, supported by peer-reviewed evidence.

**GeneType for Colorectal Cancer utilizes a simple buccal swab to determine a patient’s polygenic risk, which is combined with clinical risk factors resulting in 5-year, 10-year, and lifetime risk scores that better stratify the patient based on their individual risk of developing CRC.**

**Routine Screening for Average Risk Adults**

CRC survival rates are primarily dependent on the tumor stage (I – IV) at the time of diagnosis, thus highlighting the importance of early detection. At a population level, screening onset at age 50 for an average risk individual makes sense in the context of the average age of CRC diagnosis: 68 for men and 72 for women. However, we have discovered through large population studies, that so-called “average-risk individuals” can be stratified into higher and lower risk populations.

While the American Cancer Society recently lowered their recommended screening age to 45 for all average-risk individuals, in an effort to increase early detection, not all medical bodies have followed suit. Broad screening guidelines have been agreed upon by the American College of Gastroenterology (ACG, gi.org), American Gastroenterological Association (AGA, gastro.org) and American Society for Gastrointestinal Endoscopy (ASGE, asge.org), known as US Multi-Society Task Force of Colorectal Cancer (MSTF). This body along with the USPSTF recommend CRC screening starting at age 50 in average risk individuals. The primary methods of CRC screening requires monitoring the gastrointestinal tract for disease, using one of a number of different screening options such as fecal occult blood testing (FOBT), or colonoscopy. In average-risk Caucasian adults (i.e. those not identified as having a hereditary cancer syndrome) a ‘colonoscopy every 10 years or annual fecal immunochemical test (FIT) are the preferred (first-tier) methods of screening.’

Colonoscopy, the gold-standard of CRC screening, is a critical tool in early detection despite being taxing to patients and specialists, resource-heavy, operator dependent, expensive, and occasionally associated with severe procedure-related complications. By improving risk stratification, we can prioritize CRC screening methods based on predicted risk of disease, thus ideally enhancing the benefits and minimizing the risks of screening tools such as colonoscopy. Assessment of patients’ risk of developing CRC, with a tool such as GeneType for Colorectal Cancer, can help personalize the recommended of screening methods. Patient-Clinician decision-making processes regarding screening preferences may change because of identified risk level. This may impact the method of choice, recommended onset, and/or frequency of the screening method(s) (Table 1).
### Table 1.

Risk assessment can enable more efficient population-based colorectal cancer screening by ensuring that the at-risk population is identified and given the option of modified screening onset, frequency, and method based on the identified risk.

#### The Importance of Accurate Risk Stratification in Patients Who Do Not Meet Criteria for Hereditary Colorectal Cancer Syndromes and/or Germline Mutation Testing

The U.S. Multi-Society Task Force on Colorectal Cancer, the National Comprehensive Cancer Network and the United States Preventive Services Task Force (USPSTF) recommend screening for colorectal cancer begins at age 50 for average risk Caucasian adults.\(^1\) However, combining all patients without diagnoses of Lynch, FAP, or pathogenic carrier status of a hereditary cancer variant into a single broad ‘average’ risk category is an over-simplification of risk classification. Improving classification in this population will support early detection efforts in more relevant (at-risk) populations. Although guidance exists for “average-risk” individuals with first-degree family history of CRC (to start screening at 40 years of age, or 10 years earlier than the age of relative’s diagnosis and to continue screening by colonoscopy every 5 years),\(^1\) it tries to expose at-risk individuals who may benefit from early detection based on first-degree family history alone. However, identification of at-risk individuals based on a personalized risk assessment would enable superior stratification for a more personalized approach to screening.
At this time there is no CRC risk assessment method that is clinically recommended to help stratify at-risk individuals. A comprehensive meta-analysis of the performance factors included in available CRC risk-prediction models has indicated limited predictive potential of models that were solely reliant on general clinical risk factors, i.e. family-history of CRC or patient age. Comparing case-controlled CRC risk-assessment studies that used clinical and demographic information alone to those that combined genetic biomarkers, studies that integrated genetic biomarkers showed the best discrimination. Integration of polygenic risk score (PRS) based on our panel of genetic markers improves risk discrimination over family history alone. Frampton et al. suggest the effect of adjusting CRC screening based on PRS stratification will make CRC screening more efficient by personalizing screening regimens based on risk level. Their data suggest the same number of cases could be identified through screening fewer individuals that are pre-identified as at-risk.

The Era of Genomic Medicine and a New Risk Factor: Polygenic Risk Score and Precision Health Care

With the advent of new technologies that can screen entire genomes and research consortia that enable global collaboration, over 80 million Single Nucleotide Polymorphisms (SNPs) have been identified in humans. SNPs are variants whereby individuals may have a different base pair at a particular site among the 3 billion base pairs that constitute the human genome. Until now, SNP technology has primarily been exploited for pharmacogenetics, identity testing such as ancestry, forensic and relationship testing, and of course, consumer genetics, or “hobby” science where insights to one’s distaste for cilantro can be linked to a SNP, for example. However, research has revealed SNPs are also associated with disease, including various malignancies such as colorectal cancer. The mechanisms of action for most of these disease-associated SNPs are yet unknown. Assessed individually, each of these SNPs may only augment disease risk by a small degree but, in combination, they confer clinically significant risk. This combination of disease-associated SNPs is called polygenic risk. Most importantly, polygenic risk appears to be independent of other risk factors and therefore can be integrated with other known risk factors to enhance the predictive capabilities of clinical risk assessment tools.

Genetic disease can be categorized by varying degrees of inheritance. This variability changes depending on whether the inheritance can be linked to a monogenic versus polygenic disease (Figure 2), but also on the degree of penetrance. Penetrence levels can be modified internally (by other genes, variants, cellular pathways, epigenetics, etc.), or externally (by environmental exposures like diet, alcohol, drugs, geolocation, etc.).

GeneType for Colorectal Cancer uses several common genetic variations, or SNPs, to determine polygenic risk. As a technique, polygenic risk is described in the lead academic journal Nature as “The approach to predictive medicine that is taking genomics research by storm.”
The Science Behind GeneType for Colorectal Cancer

GeneType for Colorectal Cancer is a tool designed to provide a risk assessment for colorectal cancer in adults without suspected syndromic CRC (e.g. Lynch syndrome or FAP) by combining a personalized polygenic risk score (PRS) with general clinical risk factors. The panel of 45 SNPs were identified and prioritized for predictive accuracy using variants exhibited over multiple large-scale genome-wide association studies (GWAS).\textsuperscript{18,19} The panel of 45 SNPs has been modelled, tested, and validated for those with and without family history of CRC.\textsuperscript{3,4} The 45 SNPs are from 39 regions of the human genome that have repeatedly exhibited a significant contribution to CRC risk. These regions, or susceptibility loci, were discovered using genome-wide association studies (GWAS) from thousands of CRC cases. These data were summarized, prioritized, and collated by Jenkins et al.\textsuperscript{3} The leading SNP associations, which are the most significant, reproducible, and relevant to CRC risk are included in GeneType for Colorectal Cancer. To determine the SNP risk, GeneType for Colorectal Cancer applies the method of selecting and combining genetic variants to calculate what is known as the Polygenic Risk Score (PRS).\textsuperscript{3,4,17} Combining independent clinical risk factors and assigning appropriate emphasis on each SNP generates a PRS, which has the highest degree of risk discrimination available. The patient-specific PRS is integrated with the patient’s clinical information, followed by age stratification with population data, for disease-risk prediction. Resulting five-year-, ten-year- and lifetime-risk scores have superior discrimination to all currently available clinical models and thus enable clinicians to better advise patients on CRC prevention and screening programs. Those individuals at average risk will still receive the standard screening regimen as suggested by medical bodies. However, those individuals at increased risk of CRC may be eligible for modified screening intervals in addition to risk reducing medications.
**GeneType for Colorectal Cancer Rationale**

It is important to preface that case-control genetic data for risk prediction should be as objective as possible - while SNPs are an objective measure, patients do still self-report clinical risk factors including first-degree CRC family history.

A combined meta-analysis applied to the 45 SNPs in a modelled population size of over a million cases and controls, assessed the performance of the 45 SNP alleles, with individual Odds Ratios calculated for in the highest and lowest quintiles. Compared to the lowest quintile, individuals in the highest quintile were at 3.55-fold risk of a CRC diagnosis (Figure 3). If the average population were further stratified into deciles, there was a 5.04-fold risk of CRC between individuals in the top and bottom risk deciles (Figure 3). These data underscore the value of SNP-based polygenic risk in risk assessment in an “average-risk” population. Stratification based on PRS could effectively identify the proportion of individuals that would benefit from modified screening protocols.

**Figure 3.** Differences in population risk stratified by risk alleles show (A) a 3.55-fold in CRC risk between the top 20% versus the bottom 20% of individuals and (B) 5.04-fold in CRC risk between the top 10% versus the bottom 10% of individuals. Data adapted from Jenkins et al. 3

Cross-validation of the aforementioned results was performed on >1,000 clinical cases of CRC from the Colon Cancer Family Registry, consisting of individuals of European ethnicity from Canada, Australia and USA. The results showed that the GeneType for Colorectal Cancer SNPs used in a PRS improved CRC risk scoring and was independent of family history (Figure 4).

Similarly, reclassifying the age at which an individual should begin screening (based on polygenic risk) showed a significant difference in age at which the 0.3% 5-year risk threshold was reached (Table 2). A 5-year risk threshold of 0.3% was chosen because it represents the risk score of an average 50-year-old Caucasian adult.
Figure 4: Distribution of lifetime CRC risk stratified by polygenic risk and family history. Figure adapted from Jenkins et al.4

We highlight two scenarios described in this manuscript where polygenic risk can aid in modified screening regimens in accordance with current medical body recommendations. First, based on this 0.3% threshold, the highest quintile of (in conjunction with a family history of CRC), conveyed an at-risk age of 34 years old and by extension, suggests initiating screening programs 15 years earlier based on commensurate risk (Table 2). Importantly, this is consistent with the magnitude of risk conveyed by individuals with pathogenic variations related to Lynch syndrome or FAP. In the second scenario, the highest quintile of polygenic risk, in patients with no first-degree family history, is suggested to reach the 0.3% threshold at the age of 45 in men (46 in women; Table 2). This supports, in part, the American Cancer Society’s (ACS) change in screening recommendations for average risk adults from 50 to 45 years of age 10. However, the benefit of GeneType is the stratification of the at-risk population to highlight the top 20% of these “average” adults that would benefit from screening starting at 45 in accordance with ACS; the remainder (80%) of adults can adhere to USPSTF/MSTF recommendations11,12 of screening onset at age 50.

At this stage, until understanding of CRC aetiology is improved we do not advocate for less screening in a “low risk” population. This reverse scenario was hypothetically modelled; the lowest risk group of low SNP risk (without first-degree relatives having had CRC) could have screening relatively delayed up to 60 and 65 years of age for men and women respectively. This would result in a significant reduction in the number of tests and procedures. This data provides a compelling argument to begin looking at prospective trials in which CRC screening protocols are modified based on either high or low risk of disease.
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<td></td>
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<td>44</td>
<td>43</td>
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**Table 2.** Age (years) at which a person’s 5-year risk of colorectal cancer (CRC) reaches or exceeds the threshold of 0.3%, by quintile status of the 45 SNP-based risk and categories of family history of CRC, separately for women and men. Figure adapted from Jenkins *et al.*

It should be emphasized that the recalculation of risk described above is relative to what is interpreted as ‘average risk’ based on screening initiation at 50 years old. The recommended onset of clinical screening is based on age, as no established absolute risk threshold exists to identify high-risk over average-risk individuals. This ‘higher level of screening’, described in these studies only acknowledges screening onset at earlier age, but similar justification can be made for more frequent screening in individuals at increased risk based on PRS.

**GeneType for Colorectal Cancer Validation**

This test is only applicable to men and women of Caucasian descent. Efforts to validate genetic epidemiological data in other ethnicities are on-going. Analytical validation of the 45 SNP panel was performed using a panel of internal control samples to assess the sensitivity (>95%) and specificity (100%) of our custom-designed Taqman probes on the ThermoFisher OpenArray platform. The risk associated with a patient’s age is based on ethnic-specific incidence and mortality data from the Surveillance, Epidemiology, and End Results Program database. The risk (odds ratio) associated with a family history, age, ethnicity and each individual SNP are based on a large-scale epidemiological study.

The performance of the 45 SNP panel and its correlation with CRC risk predicted from detailed family history was estimated in 1,181 cases and 999 controls. The important conclusion being that this 45 SNP panel in conjunction with family history, can identify people who could benefit from earlier screening. Risk reclassification by the 45 SNP test could inform targeted screening for CRC prevention, particularly in clinical genetics settings when mutations in high-risk genes cannot be identified.
**Summary**

GeneType for Colorectal Cancer:

- Incorporates a “personalized risk score” based upon the patient’s genotype for 45 known colorectal cancer susceptibility variants (polygenic risk). Importantly, the validation studies were performed in the general population highlighting the applicability in risk assessment within this population. The SNPs in GeneType for Colorectal Cancer have been tested, validated and optimized for predictive accuracy utilizing the general clinical risk factors to provide patients and their clinicians with the most accurate and complete CRC risk assessment.

- Has been validated in peer-reviewed studies.

- Restricts non-SNP risk factors to age, sex, family history, and ethnicity. This provides the ability to screen most individuals who will not fall into a high-risk category with a test that is simple and efficient to administer.

- Has clinical utility for risk reduction medications offered by the USPSTF for patients at increased risk of CRC (contingent on various contraindications).²¹

- Is designed to report the 5-year, 10-year, and lifetime risk scores for CRC.

**GeneType for Colorectal Cancer: Product Design Features**

The test is designed to facilitate better informed decisions about screening and preventative treatment plans. It is applicable to individuals aged 30 years or above who have not been diagnosed with colorectal cancer.

The test takes into account the following:

**Clinical Risk Factors**

- Age
- Sex
- 1st Degree family members having had CRC
- Ethnicity

**Genomic Risk Factors**

- 45 SNP Polygenic Risk Score*

*test includes a painless quick cheek swab collection.

**Genomic Markers**

There are no existing single mutations that can (with precision) predict for non-syndromic colorectal cancer, nor a repository of information about compounding SNP contributions to complex disease such as colorectal cancer. At present, the measurable genetic markers associated with complex disease are identified using genome wide association studies (GWAS). 45 SNPs were identified from over 500,000 SNPs in multiple GWAS involving thousands of CRC cases.³⁴,⁴,¹⁴,¹⁸ GeneType for Colorectal Cancer generates objective actionable results that can be used in medical consultation, genetic counselling, and ultimately in the development of a patient’s personalized Colorectal Health Care Plan for screening and risk reduction.
Proactive Health Solutions: Colorectal Health Care Plan for Screening and Risk Reduction

Maintaining a healthy lifestyle is a simple way to reduce one’s risk of colorectal cancer. However, despite acknowledging the benefits of a healthy lifestyle, many adults are reluctant to modify behavior. A risk assessment may provide incentive for adults to make lifestyle changes\textsuperscript{22-25} although a paucity of data exists to support this assumption in CRC risk assessment. Major risk factors that can be modified as a consequence of elevated risk results are generally lifestyle risk factors (predominantly diet), prophylactic (risk-reducing) medication, and modifying screening onset, frequency, and method.

For individuals identified as having an increased risk of CRC, personalized screening regimens can be generated. Modifications to individual regimens may include early-onset screening (beginning screening at an earlier age), a change in screening frequency (every few years), and the addition or subtraction of a screening modality.

There is substantial evidence in support of risk reducing medication in the reduction of CRC incidence. Although not yet a stand-alone guide, the USPSTF released a recommendation in 2016 for low-dose aspirin-use in individuals at increased risk of CRC.\textsuperscript{21} Contraindications aside, long term aspirin-use reduced CRC incidence rates by 20-40\%, percentages vary by the study, as outlined by the USPSTF final recommendation. These data reinforce the need to better identify individuals at increased risk of CRC, particularly in the context of the new cardiovascular disease guidelines that recommend against low-dose aspirin use in the general population.\textsuperscript{26}

Conclusion

The future of preventative medicine will rely on the capacity to stratify patients into risk categories to enable more efficient screening practices and more efficacious risk reduction strategies. GeneType for Colorectal Cancer improves upon current CRC clinical risk assessment by integrating a polygenic risk score generated from 45 validated SNPs with relevant clinical information to provide a calculated risk score. By identifying individuals at increased risk, GeneType for Colorectal Cancer enables personalized screening and risk reduction approaches to be tailored to each patient.
References

13. NCCN Guidelines: NCCN clinical practice guidelines in oncology (NCCN guidelines®) colorectal cancer screening
17. Warren M: The approach to predictive medicine that is taking genomics research by storm. Nature 562:181-183, 2018