Hereditary & familial colorectal cancer
Kallenberg, F.G.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 10

THESES SUMMARY
AND FUTURE PERSPECTIVES
THESIS SUMMARY

Recognition of persons with familial colorectal cancer (FCC) and hereditary colorectal cancer (CRC) syndromes could result in prevention or early detection of CRC as well as other cancer types, by performing adequate screening and surveillance and timely removal of cancer or precursor lesions. However, only a minority of persons at risk is appropriately recognized, potentially leading to unnecessary morbidity and mortality. Once recognized, each syndrome has its own specific surveillance strategies. In adenomatous polyposis syndromes, not all extra-colonic manifestations are well reported, and for some that are well described and warrant surveillance, strategies for surveillance can be improved. Therefore, depending on the syndrome, more knowledge is needed to determine if, how and when screening and surveillance of extra-colonic manifestations need to take place.

The research reported in this thesis covers several topics that are related to increasing the identification of persons with a hereditary CRC syndrome or FCC, and detection and prevalence of extra-colonic manifestations in adenomatous polyposis syndromes.

In Chapter 2, we described the development and validation of a questionnaire to document familial cancer history, to facilitate the detection of persons with a familial or hereditary CRC risk. This self-administered questionnaire was based on nationwide criteria for referral to genetic specialists due to a Lynch syndrome suspicion, as well as existing criteria for surveillance colonoscopies because of an increased risk of FCC. In a two-phase validation process in patients scheduled for colonoscopy, we observed that this questionnaire has a high sensitivity of 90% (95% CI 55%-98%) at a specificity of 98% (95% CI 87%-100%) for detecting an indication for referral to a clinical geneticist or gastroenterologist, compared to referral decisions based on pedigree data collected by a genetic counselor. In the second validation phase data were verified in a telephone interview, with similarly high sensitivity (100%; 95%CI 63%-100%) and specificity (97%; 95%CI 91%-99%). Risk assessment based on the given answers in the questionnaire showed a very good inter-observer agreement. We concluded that this online questionnaire seems to be an accurate tool that can be easily implemented in several health care situations to increase the detection of patients with FCC and Lynch syndrome.

After it was combined with an automated risk assessment, the questionnaire was implemented in the multidisciplinary outpatient clinics for CRC patients of five hospitals, as described in Chapter 3. Unexpectedly, in this comparative trial with a stepped-wedge design, implementation of the questionnaire did not increase the proportion of patients receiving a screening or surveillance recommendation for familial or hereditary CRC, when compared to hospital-based standard practice. In the control strategy 12.0% of patients received a screening and/or surveillance recommendation versus 9.4% in the intervention strategy. In
the model-based intention-to-treat analysis, in which we accounted for possible time trends and hospital effects, the difference was found not to be significant (p=0.58). We concluded that the questionnaire does not necessarily assist in increasing the number of patients and relatives enrolled in surveillance recommendations for familial or hereditary CRC.

Data on the familial occurrence of CRC may also be used to improve fecal immunochemical test (FIT) based population screening for CRC. In Chapter 4, we reported an analysis to evaluate the performance of a hypothetical, combined CRC screening strategy, by offering colonoscopy to those with a positive FIT as well as to those with one or more first-degree relatives with CRC. We evaluated the incremental yield of this combined strategy relative to FIT-only screening in a post-hoc analysis of data collected previously in a colonoscopy screening trial. At a cut-off of 10 µg Hb/g faeces FIT-positivity, the combined strategy would increase the yield from 3.2% (95% CI 2.4%-4.5%) to 4.8% (95% CI 3.7%-6.2%) cases of advanced neoplasia, at the expense of 148 additional negative colonoscopies per 1112 participants. Sensitivity in detecting advanced neoplasia would increase from 36% (95% CI 26%-46%) to 52% (95% CI 42%-63%), whereas specificity would decrease from 93% (95% CI 92%-95%) to 79% (95% CI 76%-81%). Our analyses show the potential of combining FIT with family history in CRC screening programs. Depending on the number of negative colonoscopies one accepts, this combined approach can be considered for improving CRC screening.

In the second part of this thesis we zoomed in on the subgroup of patients with an adenomatous polyposis syndrome. Some of these cases may be explained by non-genetic causes, of which one new potential cause is described in Chapter 5. This case series reports on three patients with adenomatous polyposis without a germline APC or MUTYH mutation, who had received abdominal radiotherapy, and of which two later developed gastrointestinal cancer. This case series demonstrated the potential causal role of radiotherapy in the development of intestinal adenomatous polyposis and the subsequent development of cancer. A delay in the diagnosis of gastrointestinal cancer may be prevented in cancer survivors treated with abdominal radiotherapy, if clinicians are aware of this increased risk. Further research on the etiology of adenomatous polyposis and gastrointestinal cancer in these cancer survivors and on optimal surveillance and prevention methods is needed.

A wide range of manifestations outside the colon can be identified in adenomatous polyposis syndromes, including duodenal adenomas. As only limited data on duodenal adenomas in patients with multiple colorectal adenomas without a germline APC or MUTYH mutation (MCRA) are available, evidence-based upper gastrointestinal screening and surveillance recommendations cannot be given. In Chapter 6, we reported on the frequency, extent and progression of duodenal adenomas in patients with MCRA, who had been identified from two polyposis registries. Our findings show that duodenal adenomas are detected in nearly 10% of
patients with MCRA, and these are most commonly diagnosed in their late fifties. At the time of
detection, duodenal disease was relatively mild, with all patients having Spigelman stage I or II
disease, and a maximum number of three adenomas. None of the patients developed duodenal
cancer or high-grade dysplastic lesions and no differences in demographic and endoscopic
data were found between MCRA patients with and without duodenal adenomas.

In a similar way, we reported on duodenal adenomas in patients with \textit{MUTYH}-associated
polyposis (MAP) in \textbf{Chapter 7}. Little is known about the prevalence of duodenal adenomas
and cancer in patients with MAP, but current surveillance recommendations are the same
for patients with familial adenomatous polyposis (FAP). In a historical cohort study, from
prospectively collected data held at two large polyposis registries, we found that duodenal
polyposis seems to develop less frequently (34\%) than in patients with FAP, and develops at
a later age (median of 50 years). Increasing lesion size and villous change appeared to promote
adenoma progression, rather than polyp number or dysplasia. Findings from both chapters can
impact current screening and surveillance recommendations.

Most guidelines for duodenal surveillance in patients with adenomatous polyposis recommend
to perform a forward-viewing endoscopy as well as an additional side-viewing endoscopy to
visualize the ampulla of Vater. To avoid the need for this additional procedure, we prospectively
evaluated the efficacy of a cap-assisted forward-viewing endoscopy to visualize the duodenum
and the ampulla of Vater in patients with FAP. This proof-of-concept study, reported in
\textbf{Chapter 8}, demonstrated that this technique can be used effectively and safely to visualize both
the duodenum and the ampulla of Vater in patients with FAP, thus challenging the concept that
side-viewing endoscopy is mandatory for surveillance in these patients. This practice might
reduce burden, time, risks and costs of an additional side-viewing endoscopy.

Adrenal lesions are another extra-colonic manifestation that needs to be further explored in
adenomatous polyposis. In \textbf{Chapter 9} we reported on a historical cohort study in patients with
FAP, attenuated FAP (AFAP) and MAP, and describe the frequency, characteristics and clinical
progression of adrenal lesions in those who underwent abdominal imaging. We found that up
to a quarter of patients with FAP, AFAP or MAP had at least one adrenal lesion, compared to one
in 20 in a reference group. In polyposis patients, lesions were most likely to be detected around
the age of 50 and most remained stable or exhibited slow growth after follow-up of more than
3 years. Only 2 of 30 patients with an adrenal lesion had a known hyperfunctioning lesion. Four
lesions were resected, of which three appeared benign upon resection and one was oncocytic
with uncertain malignant potential. We concluded that adrenal lesions are frequent in polyposis
patients who undergo abdominal imaging. They seem to follow a benign and slowly progressive
course and are mostly non-hyperfunctioning. These results can help to determine if, how, and
when screening and surveillance for adrenal lesions should be performed in polyposis patients.
FUTURE PERSPECTIVES

Identification of familial colorectal cancer and hereditary colorectal cancer syndromes

Over the past decades, several methods have been developed to screen patients for hereditary CRC syndromes and FCC, including germline and molecular tumor testing, the use of family history based clinical criteria and prediction models. Most of these strategies focus on Lynch syndrome, one of the most commonly missed CRC syndromes, since it has no specific endoscopic characteristics.

Identification based on family history

The use of clinical criteria is the easiest of all screening strategies, as it can be performed by any health care professional, both in patients with and without CRC. These criteria include family history-based referral criteria for suspicion of Lynch syndrome, such as the Amsterdam II criteria. Alternatively, clinical prediction algorithms like the PREM and MMRpro model can be used. These models provide a family history based risk estimation for Lynch syndrome. If one fulfills any of these criteria, genetic counseling can subsequently be performed by molecular tumor testing (microsatellite instability (MSI) and/or immunohistochemistry (IHC) testing for protein expression of the mismatch repair genes) in the proband. If indicated, this tumor test is followed by germline testing to further evaluate the presence of Lynch syndrome.

To detect families with Lynch and FCC, clinicians should routinely collect an adequate family history in all patients and have knowledge of the referral criteria for genetic testing and for surveillance colonoscopies, as described in the introduction of this thesis. Unfortunately, in daily practice both conditions are often not fulfilled. We hypothesized that the family history questionnaire that we used in Chapter 2 could make up for not collecting a systematic family history. We provided an online questionnaire for a thorough family cancer history and facilitated easy application of clinical referral criteria for Lynch syndrome and FCC. We demonstrated that a Western population, increasingly familiar with computers and internet, can use such an online application, relying on complex conditional questions and an automated risk assessment. Nevertheless, further validation in non-Dutch speakers and in persons with limited health literacy is needed before implementing this questionnaire more widely.

A next step in the identification process is to decide how and where to implement the family history questionnaire. As reported in Chapter 3, implementation of our questionnaire in CRC outpatient clinics did not increase the number of CRC patients and their relatives diagnosed with FCC or hereditary CRC syndromes. Based on our results, we have suggestions for adjustments in the implementation of the questionnaire in daily practice. Before considering the implementation of a tool, one could first assess the proportion of detected familial and
hereditary CRC in daily practice in each hospital. If this proportion is less than the generally expected 15-20% of CRC patients with familial or hereditary CRC, it could be worthwhile to implement the questionnaire. Besides, in our study not all patients had been invited to complete the questionnaire, possibly caused by the extra time and workload needed for introducing patients to the online tool. A pre-existing electronic patient record might overcome this issue, i.e. by showing pop-ups to invite new patients, inviting them by clicking on a link in the pop-up screen, and automatically inserting questionnaire data and referral advice in the record, visible to all involved health care providers. To enhance continuity, one or two trained persons could be assigned to use the family history tool and make sure all patients have been evaluated and refer patients when indicated.6, 7 As we felt that patients as well as health care providers do not prioritize genetic referrals in the early stages of the CRC work-up, these trained persons could implement it after surgery instead, including a clear information leaflet for invitees to further increase participation rates.

Next to focusing on patients presenting with CRC, family history based identification of those at increased risk could also take place in other health care situations, such as in CRC population screening or in primary care settings. In these situations the tool might be more effective, as these persons have not yet been seen by a CRC specialist and therefore the likelihood that a familial or hereditary CRC risk is missed is much larger.8 However, the actual yield will be lower, as the prevalence of FCC and hereditary CRC syndromes is not as high in healthy individuals compared to CRC patients.

As a first step in evaluating the added value of implementing family history data in a FIT-based screening program, we performed the study reported in Chapter 4. We concluded that, depending on the number of extra negative colonoscopies one would be willing to accept, this combined approach could be considered for improving FIT-based CRC screening. This strategy could also potentially identify persons with a familial or hereditary CRC risk. For a prospective evaluation of the yield of such an approach, we currently perform a study named Family Matters, evaluating the participation rate and yield when adding our family history tool to a FIT-based screening program. This study also aims to identify participants with a hereditary CRC syndrome or FCC. If successful, one could consider updating family history biannually, in parallel with FIT testing, or less frequently so, since family history is not very likely to change rapidly.

Invitees for such a population-based screening strategy for a hereditary and familial risk of CRC should be well informed about the potential consequences of such an assessment, before they can decide whether they wish to participate or not. Generally, healthy individuals with questions on potential hereditary risks/diseases contact their general practitioner, or may be advised to do so by family members diagnosed with an increased risk for CRC. If indicated, a referral to a clinical geneticist will then be made. However, in the Family Matters study, all
screening participants are invited to complete the online questionnaire, which could result in a referral to a clinical geneticist and therefore requires a different information strategy.

Discussions about population screening for hereditary CRC syndromes and FCC have focused on the emotional burden for participants.\(^9\), \(^10\) The identification of a hereditary syndrome or an increased cancer risk can have a significant impact on quality of life.\(^11\) The genetic test result could also affect family members, who can be at increased risk as well.\(^12\) Other reasons for declining an invitation to genetic screening are concerns about insurance, costs, and unclear benefits of genetic testing.\(^13\) Despite these consequences, most persons seem to be interested in genetic screening.\(^14\), \(^15\) As this issue has mostly been studied in family members of persons with a known hereditary syndrome, it should be further explored in a CRC screening setting. In the Family Matters study, we also evaluate considerations in decision-making to participate.

**Identification based on germline testing and universal tumor testing**

Although relatively easy and inexpensive to apply, family history based clinical criteria and prediction models have limited sensitivity and specificity in detecting persons at risk.\(^1\) As a first step in the identification of Lynch patients, other strategies could also be used. The ultimate procedure for making a definite diagnosis, i.e. germline testing for mutations in the mismatch repair genes, is not likely to be cost-effective when routinely performed in all patients with CRC or at a population-level.\(^17\) Universal tumor-testing in those diagnosed with CRC might be a more efficient alternative strategy. This would imply systematic tumor testing: MSI and IHC testing for protein expression of the mismatch repair genes. This strategy is increasingly implemented for patients diagnosed with CRC, and can be performed in all patients with CRC or those of a certain age.\(^1\), \(^18\), \(^19\) The recently introduced Dutch guideline on hereditary CRC now recommends that IHC testing should be performed in all CRC patients diagnosed under the age of 70 years.\(^3\) The yield of this recommendation should be evaluated and if successful, one could consider to test the tumors of all patients regardless of their age, and assess cost-effectiveness.

The downside of routine molecular tumor testing as primary screening strategy for Lynch syndrome is that patients with non-genetic FCC will be missed as they can only be identified through their family history. Tumor testing can also be false-negative (sensitivity for IHC and MSI is up to 83%) and data on cost-effectiveness of this approach are conflicting, as it will result in many negative tests.\(^1\), \(^17\), \(^20\), \(^21\) The approach also has to be feasible, to ensure that all CRC tumors are tested, results are interpreted adequately by clinicians taking care of the patients and their consequences are taken well care of.\(^1\), \(^22\)

In conclusion, we suggest the following identification strategy. To increase the yield of Lynch syndrome and FCC identification, we propose a combined strategy for all patients with CRC,
including a thorough family history and universal tumor testing, with or without an age restriction. This will also compensate for the downsides of universal tumor testing as a single strategy. For patients without CRC, a family history based identification will be the first screening strategy, until other strategies are developed. This could be implemented in population screening or in primary care.

**Etiology, characteristics and surveillance in adenomatous polyposis syndromes**

**Etiology**

For patients with adenomatous polyposis, an evaluation of etiology allows for appropriate screening and surveillance recommendations for each specific syndrome. If possible and relevant, relatives can also be tested for their risk. When trying to determine the etiology, one important question comes first: when is a diagnosis of adenomatous polyposis syndrome made? A syndrome is undeniably present if someone with multiple adenomas has a germline mutation in one of the polyposis genes. The higher the number of adenomas, the likelier that a germline mutation in one of the most common polyposis-associated genes, *APC* and *MUTYH*, is detected. However, in only 5-10% of patients with 10-100 adenomas a germline mutation is identified. The lack of a genetic diagnosis does not imply that this attenuated phenotype is sporadic, as the genetic cause might still be unknown. This seems most likely when several relatives are affected. Such unknown genetic causes include unclassified or unrecognized mutations in polyposis-associated genes, mutations in unidentified polyposis-associated genes or mosaicism. Recently, mutations in several genes have been identified and could explain some of these cases, such as mutations in *POLE*, *POLD1* and *NTHL1*. Performing next generation sequencing panel testing in polyposis patients, assessing mutations in multiple polyposis related genes at the same time, could identify these mutations. If systematically implemented, as is currently being done in many centers, the number of unexplained polyposis cases might gradually decrease. International databases for DNA variants, such as the InSiGHT database, can further help to identify pathogenic mutations in new polyposis associated genes and the pathogenicity of unclassified variants.

But how to define the remaining patients with multiple adenomas who do not have an identified germline mutation? Patients presenting with hundreds of adenomatous polyps early in life clearly have a clinical diagnosis of FAP. However, when a patient has only ten metachronous adenomas, especially when diagnosed above the age of 60 and without a family history of CRC or polyposis, the diagnosis is debatable. This situation is more frequent nowadays and might reflect improvements in endoscopic imaging techniques, which lead to an increased number of detected adenomas and to more patients with multiple adenomas. To account for these issues and in absence of scientific evidence, the recent Dutch guideline contains a practical
advice. It recommends genetic testing in patients below the age of 60 who have ten or more metachronous colorectal adenomas, but, for patients between age 60 and 70, only when they have 20 or more adenomas. Genetic testing in patients with multiple adenomas above the age of 70 is not routinely recommended. Referral should also be considered for those with less than ten adenomas at a very young age and/or those with a positive family history.

Patients with adenomatous polyposis without an identified germline mutation, as well as their first-degree relatives, are recommended to undergo surveillance endoscopies. However, more knowledge is needed to obtain better evidence for this guideline. Future research should help to distinguish between patients with a non-genetic polyposis syndrome (MCRA) and those with multiple sporadic polyps. For patients with at least ten adenomas without an identified germline mutation, the variables age, sex, polyp number, extra-colonic findings, and family history of CRC and polyposis could be evaluated as potential risk factors for developing metachronous adenomas. One should also consider whether multiple polyps are detected during one endoscopy or over the course of several colonoscopies. Subsequently, all relevant factors could be combined in a risk model to determine which patients have MCRA rather than sporadic adenomas, and who would profit from surveillance.

**Characteristics, screening and surveillance of extra-colonic manifestations**

Screening and surveillance guidelines are ideally based on evidence on the risk of colonic and extra-colonic disease manifestations for each syndrome and the benefit of surveillance programs. For most polyposis syndromes, the risk of colonic adenomas and CRC is identified and clear and colonoscopy surveillance recommendations are provided. However, now that these patients survive much longer due to colonoscopy surveillance, extra-colonic manifestations become more clinically relevant. Little is known on the prevalence and outcome of most extra-colonic manifestations, and knowledge needs to be improved. In this thesis, both duodenal adenomas and adrenal lesions were evaluated. The risk of other extra-colonic manifestations, such as gastric adenomas and thyroid cancer, should also be further evaluated but are beyond the scope of this discussion.

- **Duodenal adenomas:**
  Duodenal adenomas are among the most commonly diagnosed and well-described extra-colonic manifestations in FAP. In patients with MAP and MCRA, only limited data are available on their prevalence and cancer risk and therefore similar surveillance recommendations as for patients with FAP are given. To increase the knowledge on the risk of duodenal adenomas in patients with MAP and MCRA, we studied the prevalence of duodenal adenomas in these patients. Based on our findings, we provide suggestions for adjusted upper gastrointestinal surveillance recommendations.
For MAP we recommend starting upper gastrointestinal surveillance at age 35 instead of 25, as is now usually recommended. Although the window of opportunity to identify or intervene in those with significant duodenal disease should not be missed, it is unlikely that a significant lesion would develop prior to this: 9% of patients in our study underwent an endoscopic intervention and none of them was younger than 38. The two cancers that occurred were in patients beyond 60 years who had not undergone surveillance prior to their cancer diagnosis. Currently surveillance intervals are determined by the Spigelman staging system, taking into account lesion number, size, histological type and dysplasia of all duodenal adenomas, including the ampulla. We demonstrated that those MAP patients with an increasing Spigelman stage, had increased in lesion size and/or villous changes, rather than lesion number or dysplasia. As only those two of the four criteria seem particularly relevant for MAP, the rationale for using the Spigelman scoring system to determine surveillance intervals can be questioned. It might be time for a modified staging system for more accurate assessment of duodenal polyposis severity and surveillance intervals, based on lesion size and histology type only, instead of the Spigelman classification.

This new staging system might even be more useful and needed for decision-making in patients with FAP and AFAP and duodenal polyposis. Due to prolonged survival of polyposis patients and improvements in endoscopic imaging, more patients will be identified with duodenal adenomas and develop an advanced Spigelman stage. As not all will ultimately develop duodenal cancer and treatment options are generally more invasive than for the colon, we need accurate assessment of the chance that the patient develops duodenal cancer in due time. Using the Spigelman classification, a person with many small tubular adenomas with low-grade dysplasia is now scored as having stage III or IV disease, the same as a person with a small number of large high-grade dysplastic adenomas. Therefore, surveillance and treatment options are similar in both those cases, which does not seem right. Another disadvantage of the Spigelman classification is the routine performance of taking biopsies of duodenal polyps, resulting in fibrosis, potentially making polyp removal more difficult once indicated.

A new staging system providing a more balanced view, with more specified indications for biopsies, (prophylactic) polyp removal and duodenal surgery is needed. Instead of only intervening at an advanced stage, a strategy based on the removal of duodenal adenomas when still relatively small and of non-advanced histology might prevent the need for large polypectomies or duodenal surgery, both with considerable morbidity and mortality rates as well. This strategy, without performing multiple biopsies, seems reasonable but has not yet been evaluated. Besides, in this staging system we suggest to score the ampulla of Vater as a separate entity. Whereas Spigelman staging is meant to determine when duodenal adenoma resection needs to take place, an ampullary resection might be indicated when an ampullary adenoma is increasing in size, which can occur even at a low Spigelman stage.
For MCRA, we advise to deviate from the current recommendations to follow the guidelines for FAP. Based on our data, we suggest upper gastrointestinal screening at the time of MCRA diagnosis, then again from the age of 45 and every 5 years thereafter until the age of 65. If at the age of 65, or older, no duodenal adenomas are identified, further surveillance is not expected to improve life-expectancy. Unfortunately, our follow-up data were insufficient to describe the natural course of duodenal adenomas. We therefore suggest to apply the Spigelman classification system once duodenal adenomas are identified, as is done in classical FAP.30

Future multicenter prospective long-term cohort studies in MCRA patients, who have preferentially undergone multigene testing, are needed for developing evidence-based upper gastrointestinal screening and surveillance guidelines, and results should be compared with patients with an attenuated phenotype and a germline mutation to evaluate if these are really two distinct syndromes. These studies could also identify risk factors for duodenal adenomas, which could be used to optimize surveillance strategies. A next step would be to evaluate if and how often first-degree relatives of MCRA patients should be screened.

To enhance duodenal surveillance while avoiding the need for a side-viewing endoscopy in patients with adenomatous polyposis syndromes, we suggest forward-viewing, cap-assisted endoscopy, to reduce burden, time, and costs of an additional side-viewing endoscopy. With the reported success rate and in the absence of adverse events it seems reasonable to consider that the costs of a cap outweigh the costs and burden of an additional side-viewing endoscopy. In cases where the ampulla cannot be fully identified using this approach, a subsequent side-viewing endoscopy should be performed, but this seems only necessary in a minority of cases.

### Adrenal lesions:

In this thesis, we also described data on the risk of adrenal lesions in patients with FAP, AFAP and MAP, confirming an increased risk. To fill the remaining gaps in our knowledge, more long-term follow-up studies are needed in patients with adrenal lesions, representing all polyposis subtypes, including MCRA. The role of familial clustering should also be assessed. Until then, active screening for these lesions does not seem indicated.

We believe that the findings from our work, as well as from other recent studies, have contributed to our understanding of identification strategies, clinical characteristics and surveillance methods for patients at risk of familial and hereditary CRC. The remaining gaps in our understanding discussed here should be addressed in the years to come, eventually resulting in further facilitating the identification of these persons at risk, and in appropriate screening and surveillance strategies to prevent cancer.
REFERENCES


