# Improving the overall diagnostic rate of early gastric cancer by managing family members with hereditary cancer syndromes (Review)

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**Abstract.** The 5-year survival rate of early gastric cancer (EGC) is significantly higher compared with that of advanced gastric cancer; however, the general diagnostic rate of EGC remains low in certain regions. The discovery of novel methods for diagnosing EGC will be beneficial for the general population. Among all gastric cancers, ~90% are sporadic, 10% are characterized as familial aggregation, and 3-5% of gastric cancer is attributed to genetic predisposition. Compared with sporadic cancer types, hereditary cancer syndromes (HCS) are usually characterized by the development of cancer at an early age. The present study proposes an approach for promoting the diagnostic rate of EGC in the general population by managing individuals with a family history of HCS and germline mutations of susceptibility genes. The proposed management strategy has three steps: i) Establish family history archives of the general population to screen families with individuals who have HCS; ii) recommend genetic testing for the individuals among the selected families to screen for high-risk EGC, (i.e., with HCS family history and genetic mutations); and iii) perform active routine surveillance for selected individuals to improve the overall diagnostic rate of EGC in the general population. Individuals with a positive family history should undergo the process presented above early in life, while those with a negative history may undergo routine inspection when necessary. With advances in the medical field and reductions in the cost of genetic testing, the diagnostic rate of EGC may be improved.

**Contents**



## 1. Introduction

Gastric cancer remains a major cause of cancer-associated mortality worldwide (1), and the morbidity and mortality from this disease often rank in the top three in China (2). The seventh American Joint Committee on Cancer states that the highest 5-year survival rate of early gastric cancer (EGC) is 95.1% in three Eastern countries and America, while that of late gastric cancer is only 58.4% (3). Therefore, it is important to identify gastric cancer in the early stage. To date, the diagnosis of EGC mostly depends on endoscopic screening, the *Helicobacter pylori* test, pepsinogen analysis, long-term surveillance, and follow-up for chronic atrophic gastritis. These methods may improve the diagnostic rate of EGC in a proportion of patients with routine physical examinations; however, the general population does not routinely visit clinics unless they are experiencing some discomfort. A retrospective study, which was undertaken by 10 hospitals and medical agencies in 2009, showed that the diagnostic rate of EGC was <10% in China (4). However, these data exceeded 50% in Korea and 80% in Japan at the same time (3,5). By contrast, by 2017, this diagnostic rate was merely up to 20% (6). Therefore, it is necessary to identify a novel method for diagnosing gastric cancer in the early stage to improve the diagnostic rate of EGC in regions with poor rates of EGC. In recent years, the number of studies on hereditary gastric cancer (HGC) has increased. Due to the strong specificity and germline mutation, HGC may bring significant psychosomatic pressure to family members of patients with, although the percentage of HGC is low in the general population. However, the management of patients with HGC is feasible because germline mutations in these patients are carried throughout life. Therefore, establishing management strategies for families with HGC may improve the

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*Abbreviations:* EGC, early gastric cancer; HGC, hereditary gastric cancer; HCS, hereditary cancer syndromes; HDGC, hereditary diffuse gastric cancer; ODR, overall diagnostic rate; LS, Lynch syndrome; JPS, juvenile polyposis syndrome PJS, Peutz-Jeghers syndrome; HBC, hereditary breast cancer; LFS, Li-Fraumeni syndrome

*Key words:* hereditary gastric cancer, hereditary cancer syndromes, early gastric cancer, overall diagnostic rate

early-warning effect of EGC and increase the diagnostic rate of EGC in the general population, which may be considered a practical approach in the diagnosis of EGC.

Among all gastric cancers worldwide, ~90% are sporadic, 10% are familial, and 3-5% have a genetic predisposition (7-9). Generally, HGC is accompanied by multiple cancers of different organs, including breast cancer and colon cancer, which mostly represent hereditary cancer syndromes (HCS) with their corresponding susceptibility genes (10). Compared with sporadic cancers, HCS are usually characterized by an early age of cancer onset, which may be a reason to perform screening for EGCs in the clinic. Jones (11) reported that gastric cancer occurred in a New Zealand Maori family for generations in 1964, and the genetic factors were first presumed to serve a key role in the occurrence of malignant disease. In 1998, Guilford *et al* (12) demonstrated that hereditary diffuse gastric cancer (HDGC) was associated with *CDH1* (encoding E-cadherin) germline mutations for the first time after analysing the family history of 25 gastric cancers in three families. Since then, studies on the genetic susceptibility of gastric cancer have been conducted.

The present review provides an overview of HCS and its susceptibility genes and further proposes an idea for improving the overall diagnostic rate (ODR) of EGC in the general population by managing individuals with family histories of HCS and germline mutations of susceptibility genes.

## 2. Hereditary cancer syndromes

This section describes HCSs that have been commonly studied clinically to date. HDGC, characterized by autosomal dominant inheritance, is a type of HCS with a large number of studies and accounts for ~1-3% of gastric cancers (9). Furthermore, ~25-40% of HDGC family members carry germline mutations of *CDH1* (13-15). Other susceptibility genes, including *CTNNA1*, *DOT1L*, *FBXO24*, *PRSS1*, *MAP3K6*, *MSR1* and *INSR*, which encode alpha-E-catenin, histone methyltransferase, f-box protein, trypsinogen, a serine/threonine protein kinase, the class A macrophage scavenger receptors and receptor tyrosine kinase, respectively (16), are rare but are detected in HDGC in a minority of cases (9). Generally, patients with HDGC also have colon cancer and breast cancer (17-19), with a mean onset age of 38 years (20) and most cases occurring before the age of 40 years, while the youngest age reported is 14 years (12). Chun and Ford (21) suggested that individuals in families with HDGC who have *CDH1* mutations should perform regular surveillance for stomach and breast cancer from the age of 25 years. In addition, van der Post *et al* (22) recommended that colonoscopy surveillance should be performed at the age of 40 years or earlier for individuals with a positive familial history, and routine surveillance for breast cancer should be performed at 30 years of age for *CDH1* germline mutation carriers. Secondly, the susceptibility genes of Lynch syndrome (LS), also termed hereditary nonpolyposis colorectal cancer, are *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* (21,23). The patients diagnosed with this syndrome usually have a mean age of onset of gastric cancer at 56 years, colon cancer at 44-61 years, and endometrial cancer at 48-62 years (21). Surveillance of patients with this syndrome includes screening at 30-35 years of age for stomach and 20-25 years of age for colon (24). Thirdly, juvenile polyposis syndrome (JPS) presents with multiple gastric polyps in juveniles, and its susceptibility genes are *SMAD4* and *BMPR1A* (21,24). Jasperson *et al* (24) suggested that surveillance for this disease should begin when symptoms occur or in the late teens if no symptoms occur. Fourthly, Peutz-Jeghers syndrome (PJS) is characterized by a germline mutation in *STK11* in 30-80% of patients with this syndrome (21,24). Previous studies have recommended that surveillance for this syndrome be initiated from the age of 20, at 8 years for gastroscopy, 20 years for colonoscopy and 25 years for breast screening (21,24). Furthermore, the susceptibility gene for familial adenomatous polyposis is *APC*, and surveillance should be performed at 10-12 years of age for colonoscopy and 20-25 years of age for gastroscopy for patients who meet the criteria (21,24). Additionally, breast surveillance for hereditary breast cancer (HBC) is recommended for patients who fulfilled the criteria of HBC after the age of 35 years, and the susceptibility genes of this syndrome are *BRCA1* and *BRCA2* (25). Furthermore, Li-Fraumeni syndrome (LFS) is a significant cancer syndrome with a high risk of multiple cancer types, including gastric cancer, with a frequency of up to 2.8% in LFS families, and the mean age of diagnosing gastric cancer is 43 years (21) (Table I).

Generally, the age of onset of malignant diseases in patients with a familial history of HCS and positive mutations is earlier than that of sporadic cancers. The youngest age of onset of gastric cancer in a family with HDGC is 14 years (21), and JPS and PJS were also found in malignant diseases in clinical patients with juvenile onset. Therefore, the family members with HCS with germline mutations have a higher risk of early-onset cancer. Therefore, the individuals with HCS with germline mutations begin routine surveillance at a young age to detect malignant diseases, which is recommended in the National Comprehensive Cancer Network guidelines and the aforementioned studies (Table II). Consequently, screening for a positive family history and germline mutations in these patients will contribute toward confirming malignant diseases. These diseases developed in the early stage, which may aid the general population in identifying the onset of EGC from this management system. Notably, the ODR in EGC may be improved by managing the family members of HCS.

## 3. Promoting the diagnostic rate of EGC by managing the family members of patients with HCS

The diagnostic rate of EGC and the overall survival rate of gastric cancer in the general population will be improved by managing the family members of patients with HCS due to the germline mutations being carried throughout the lives in every patient with HCS. Therefore, individuals belonging to a family with a history of HCS are recommended to undergo a susceptibility genetic test to identify those who possess a positive family history and germline mutations. Furthermore, individuals with both indications, namely, a population with a high risk of cancer, should undergo routine surveillance to confirm the risk level of early cancer as well as to improve their prognosis. This process may be implemented as follows (Fig. 1).

Table I. The acronyms or aliases of genes and their associated information.

| Gene | Corresponding acronym or alias | Corresponding protein | Corresponding HCS | (Refs.) |
|---|---|---|---|---|
| *CDH1* | *Cadherin 1* | E-cadherin | Gastric cancer, including HDGC | (9,13-17,19,21) |
| *CTNNA1* | *Catenin α 1* | α-E-catenin | HDGC, colorectal cancer | |
| *INSR* | *Insulin receptor* | Receptor tyrosine kinase | HDGC | |
| *FBXO24* | *F-box protein 24* | F-box protein | HDGC | |
| *DOT1L* | *Disruptor of telomeric silencing 1-like* | Histone methyltransferase | HDGC | |
| *MAP3K6* | *Mitogen-activated protein kinase kinase kinase 6* | Serine/threonine protein kinase | HDGC | |
| *PRSS1* | *Serine protease 1* | Trypsinogen | HDGC | |
| *MSR1* | *Macrophage scavenger receptor 1* | Class A macrophage scavenger receptor | HDGC | |
| *MLH1* | *MutL homolog 1 gene* | Mismatch repair system component | LS | (21,23) |
| *MSH2* | *MutS homolog 2* | Mismatch repair system component | LS | |
| *MSH6* | *MutS homolog 6* | Mismatch repair system component | LS | |
| *PMS2* | *PMS1 homolog 2* | Mismatch repair system component | LS | |
| *EPCAM* | *Epithelial cell adhesion molecule* | Carcinoma-associated antigen | LS | |
| *SMAD4* | *SMAD family member 4* | Signal transduction protein | JPS | (21,24) |
| *BMPR1A* | *Bone morphogenetic protein receptor type 1A* | Transmembrane serine/threonine kinase | | |
| *STK11* | *Serine/Threonine Kinase 11* | Serine/threonine kinase | PJS | (21,24) |
| *APC* | *Adenomatous polyposis coli* | Tumor suppressor protein | FAP | (21,24) |
| *BRCA1*, *BRCA2* | *BRCA1/BRCA2 DNA repair-associated* | Corresponding proteins encoded by these genes | HBC | (25) |

HCS, hereditary cancer syndrome; HDGC, hereditary diffuse gastric cancer; LS, Lynch syndrome; JPS, Juvenile polyposis syndrome; PJS, Peutz-Jeghers syndrome; FAP, familial adenomatous polyposis; HBC, hereditary breast cancer.

Table II. Susceptibility genes and recommended starting ages for surveillance of hereditary cancer syndromes.

| Syndrome | Susceptibility genes | Recommended age for surveillance, years | (Refs.) |
|---|---|---|---|
| HDGC | *CDH1* | 25 (stomach, breast), 40 (colon) | (8,11-20) |
| LS | *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM* | 30-35 (stomach), 20-25 (colon) | (17,21,22) |
| JPS | *SMAD4*, *BMPR1A* | Beginning with symptoms or in late teens if no symptoms occur | (17,22) |
| PJS | *STK11* | 20 or 8 (stomach), 20 (colon), 25 (breast) | (17,22) |
| FAP | *APC* | 10-12 (colon), 20-25 (stomach) | (17,22) |
| HBC | *BRCA1/BRCA2* | 35 (breast) | (23) |

HDGC, hereditary diffuse gastric cancer; fLS, Lynch syndrome; JPS, juvenile polyposis syndrome; PJS, Peutz-Jeghers syndrome; FAP, familial adenomatous polyposis; HBC, hereditary breast cancer.

To begin with, the archives of the family history of the general population should be established in clinics and hospitals/medical institutions to screen families for HCS. Monahan and Hopkins (26) reported that the cancer risk of individuals with first-degree relatives with gastric cancer is increased by 1.3-3.5 times. Choi and Kim (27) also stated that first-degree relatives in a family with a positive history have a strong and consistent risk of being diagnosed with gastric cancer. Slavin *et al* (28) reported that germline genetic syndromes, similar to HDGC, PJS and LS, are associated with

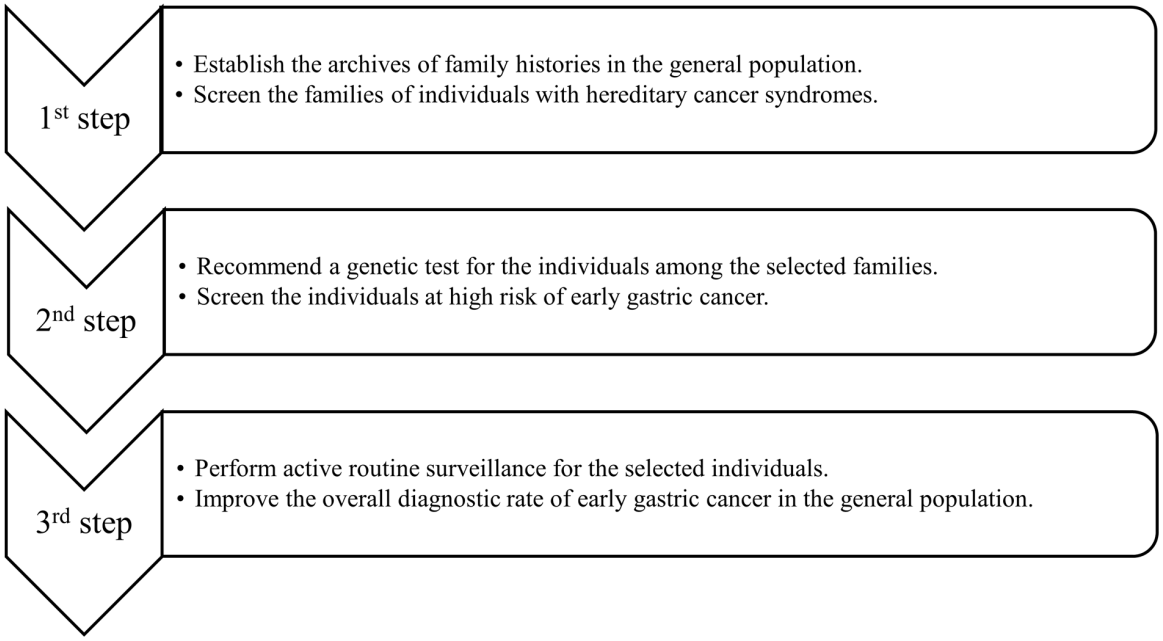


Figure 1. Process for improving the overall diagnostic rate of early gastric cancer in the general population.

gastric cancer predisposition. Therefore, a detailed family history is important for the diagnosis of HCS. Karimi *et al* (29) reported that numerous factors may serve a role in gastric cancer progression, including age, male sex, tobacco smoking, physical activity, family history and hereditary syndromes. The more detailed the family history is, the better the outcomes. However, the most significant point that should be emphasized is the impact on families with HCS, particularly those with positive first-degree relatives (27,29,30). Therefore, detailed family histories, including multiple individuals in a family identified as having HCS, should be established for statistical analysis in clinics and hospitals/medical institutions, which may provide basic data for screening the population with high-risk cancer types and may be used to gradually establish a systematic database of hereditary cancers. If the database were to be established across multiple hospitals/medical institutions, more epidemiological and clinical features of gastric cancer would be available for statistical analysis.

Secondly, the individuals with a family history of HCS should undergo genetic testing to screen for those who belong to the high-risk cancer groups. Kim *et al* (31) reported that people with a family history of HCS have a 3-fold higher risk of being diagnosed with gastric cancer than those without. Individuals with a family history of HCS and susceptibility gene mutations should be considered high risk. Generally, each syndrome of HCS, including HDGC, LS and JPS, has corresponding criteria for diagnosis and genetic testing (32-34). For instance, the criteria for diagnosis and genetic testing of HDGC had a significant application in daily practice since they were implemented by the International Gastric Cancer Linkage Consortium in 1999 (35) and updated in 2010 and 2015 (32). The approach for the diagnosis of LS includes clinical criteria, computational models, and genetic testing, through which ~95.1% of LS cases could be identified, as reported by Bui *et al* (23). Therefore, if a family history database were to be established across medical institutions, particularly for HCS, methods to diagnose HCS could be applied in daily clinical routines to ensure that families with HCS are identified. All individuals in these families who meet the criteria for HCS could be encouraged to undergo testing for susceptibility genes (21,25,32), which may reveal cancer risks earlier. In addition, Sun *et al* (36) reported that the risk of breast cancer in gene mutation carriers was significantly different between non-carriers before the age of forty years in a large Chinese cohort. As HCS is usually associated with an early onset, genetic screening may disclose the cancer risk for individuals and their children, which may contribute toward improving the ODR of EGC. Furthermore, genetic testing has positive influences on the treatment, prognosis, and recurrence risk of gastric cancer.

Thirdly, routine surveillance for individuals with a high risk of gastric cancer should be performed to promote the diagnostic rate of EGC in the general population. The patients with susceptibility gene mutations in families with gastric cancer belong to the high-risk population and are encouraged to adopt routine surveillance and/or prophylactic surgery to detect gastric cancer at an early stage and/or treat it in a timely manner. The patients with HDGC with *CDH1* germline mutations were recommended to undergo prophylactic gastrectomy or endoscopic surveillance (37), and a 16-year-old female with several relatives with gastric cancer accepted a prophylactic gastrectomy following the detection that she was a positive carrier of a *CDH1* germline mutation (38). Furthermore, colectomy is recommended for LS patients, but the choice of a partial colectomy or total colectomy remains controversial due to its physical and social impact (23). Due to the young age at surgery and the irreversible process, prophylactic surgery will bring certain social and psychological pressures, and regular surveillance may be more easily accepted by patients. Mi *et al* (39) reported that routine surveillance may improve the participants' quality of life and mental wellbeing, and they may also benefit from the support of other medical researchers

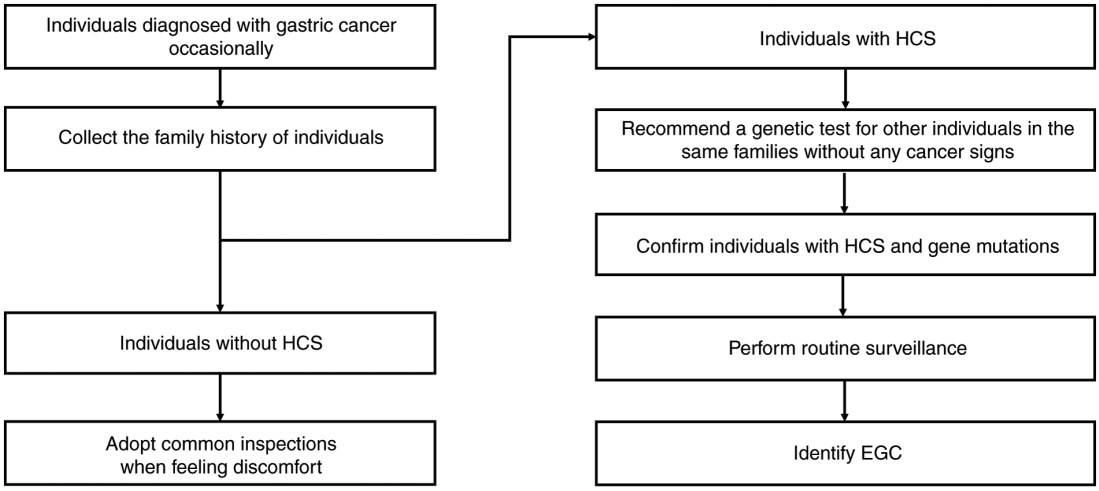


Figure 2. Recommended process for individuals to promote the overall diagnostic rate of EGC.

and continued counselling (39). Therefore, endoscopy surveillance accompanied by routine inspection should be conducted routinely for patients who are unwilling to accept prophylactic gastrectomy. More targeted clinical examination, more thorough biopsy and more frequent detection will contribute toward increasing the number of identified diagnoses of EGC for susceptibility gene mutation carriers and decreasing the number of missed cases. Routine surveillance for individuals with a high risk of gastric cancer in a family would aid in detecting the risk of gastric cancer in multiple individuals in this family. Consequently, as the detection efficiency of gastric cancer in the general population gradually improved on a large scale, the ODR of EGC in the general population may be increased.

Although individuals diagnosed with gastric cancer occasionally have no records of a familial history of HCS, a potential risk of cancer onset may be identified in other individuals of the same family without any cancer signs. In addition, the hereditary family history may be established for families with no prior record of cancer-related history. Consequently, their family history linked with HCS should be collected to differentiate the individuals with positive family history (i.e., HCS) from those with a negative family history (i.e., non-HCS). Individuals with a positive family history should undergo the flow process presented above early, which may eventually promote the ODR of EGC in the general population; however, individuals with a negative history may merely undergo routine inspection when they feel it is warranted (Fig. 2).

Genetic testing and genetic counselling have gradually becoming popular among the general population in recent years. To date, an increasing number of doctors have learned about this subject. By improving medical practitioners' knowledge and their familiarity with this subject, the individuals with HCS may be more efficiently diagnosed and treated, and appropriate and timely medical advice can be given to them. Family doctors who are familiar with this subject may be more likely to identify these asymptomatic individuals. In addition, as the patient information recording has improved in medical institutions, these individuals may be discovered timely through large-scale data analysis. Due to the recommendations of medical practitioners and the increased awareness of genetic diseases, the general asymptomatic population has shown an increasing acceptance of routine medical surveillance. Furthermore, people who accept regular medical monitoring tend to have healthier lifestyle habits (31), which has a positive effect on reducing the incidence of cancer in this group. As the cost decreases and the awareness increases, genetic testing should have a large space for expansion in general population. However, simple genetic testing has limited effects on the detection rate of EGC. It is necessary to combine the analysis of family history of HCS and genetic testing to give reasonable medical surveillance recommendations. This means that the individuals with gene mutations and a family history of HCS belong to high-risk group that requires intensive medical monitoring. Using this method, the diagnostic rate of EGC within the overall population may be improved.

The proportion of genetic diseases is very small, but if one positive case is detected, it will serve a clinical significance in the identification of HCS. Furthermore, it has a potential effect on the detection rate of other asymptomatic individuals in the family. Through improving patient record keeping in medical institutions, a patient's information management system is gradually formed and the family history of the general population can be obtained easily. Chen *et al* (2) performed numerous studies and analysis using the patient records collected by medical institutions. When the scope of HCS research is gradually expanded, the patients with genetic syndromes may be identified in a timely manner, and more targeted suggestions may be made for individuals who require genetic testing.

As this review recommends routine monitoring of asymptomatic individuals who have no signs of cancer, the potential cancer in these individuals may be detected as early as possible. Studies have demonstrated that routine surveillance has a positive effect on the detection of early gastric cancer (40). As the onset of HCS is often at an earlier age, this has an early warning effect on other asymptomatic individuals in the family, which may remind these people to commence regular medical monitoring at an early age. However, during the interval period of regular monitoring, an individual's gastric cancer may develop from early to advanced stage, and, once discovered, it is an advanced cancer. However,

this method may improve the detection rate of EGC in the overall population. The method mentioned in this article is different from traditional endoscopy monitoring, serum detection and other active detection methods for EGC. This method is based on complete medical information statistics and complete patient information registration, including the existing medical foundation and equipment; therefore, the recommendations often come from the statistics and analysis of big data, which can serve a positive role in the diagnosis of EGC.

## 4. Conclusions

The systematic and comprehensive archives of family history for the general population required improvement. Furthermore, the cost of genetic testing is expensive for certain people, but certain effective attempts could be made to gradually change this situation in certain areas. Due to the differences in ethnic and regional populations, the social environment and dietary habits, conducting large-sample and multi-centre studies is necessary to establish management strategies for family members of individuals with HCS and standards of genetic testing that will be compatible with populations from different regions. In the future, the diagnostic rate of EGC may benefit from the implementation of these methods.

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## Availability of data and materials

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## Authors' contributions

HZ conceived and designed the study, wrote and edited the manuscript.

## Ethics approval and consent to participate

Not applicable.

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## Competing interests

The authors declare that they have no competing interests.

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