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Korean patients with hereditary cancer: A prospective multicenter cohort study

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1 Korean patients with hereditary cancer: A

2 prospective multicenter cohort study

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페이지 **1 / 24**

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페이지 **2** / **24**

53 **ABSTRACT**

54 **Introduction**

55 Although genetic testing for hereditary cancers is increasing, data on health attitudes based on genetic

56 pathogenicity are limited. This cohort study aims to establish three sub-cohorts based on genetic testing

57 results to assess the health impact of genetic variations. This study evaluates changes in participant

58 quality of life, unmet needs, and mental health over time based on their genetic variant status.

59 **Methods and analysis**

60 This prospective cohort study will recruit 1,435 patients with suspected hereditary cancer who have

61 undergone *BRCA1/2* or next-generation sequencing (NGS) testing. The study began in July 2023 and

62 will continue until December 2027. By 2026, participants will be surveyed up to four times annually

63 during their outpatient visits. The survey consists of 342 items across five domains: comorbidities (96),

64 health behaviors (80), quality of life (QoL) (41), unmet needs (75), and mental health (50). Data were

65 collected using 11 validated surveys. In addition, information on the chronic diseases, cancer diagnoses,

66 medical history, and treatment history of participants will be extracted from their electronic medical

67 records to analyze their health status and cancer treatment experiences. Genetic variant data from

68 *BRCA1/2* and NGS will be used to classify participants into three sub-cohorts: pathogenic variants,

69 variants of uncertain significance, and undetectable mutations. A three-generation pedigree that

70 includes details such as the year of cancer diagnosis, age at diagnosis, cancer type, survival status of

71 family members, and age at death will be constructed for each participant. the collected data will be

72 linked to secondary sources such as cancer registries and National Health Insurance Service data to

73 provide a comprehensive analysis of the impact of hereditary cancer on health and survival.

74 **Ethics and dissemination**

75 The study protocol was approved by the Research Ethics Committees of the participating institutions.

76 The study outcomes will be disseminated through conference presentations, peer-reviewed publications,

77 and social media.

78 **Keywords**: Genetic testing, Genetic predisposition to disease, Genetic variation, High-throughput

79   nucleotide sequencing, Health behavior

80

81   **STRENGTHS AND LIMITATIONS OF THE STUDY**

82   1. The Korean hereditary cancer cohort study is a large-scale multicenter study conducted at five major

83   university hospitals in Korea, targeting 1,435 patients.

84   2. The study is designed to track participants through annual surveys over five years, analyzing long-

85   term health outcomes, changes in quality of life, and unmet healthcare needs based on genetic variant

86   status. This will help understand the evolving healthcare needs of hereditary cancer patients.

87   3. Participants are classified into three sub-cohorts based on pathogenic variants(PV), variants of

88   uncertain significance (VUS), and undetectable variants(ND), allowing for a precise analysis of

89   differences in health outcomes according to genetic status.

90   4. The participating hospitals are concentrated in metropolitan areas, the study does not include patients

91   from rural regions, which may limit the external validity of the results.

92   5. There may be challenges in achieving statistical significance when analyzing smaller subgroups

93   with rarer genetic mutations or specific conditions.

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페이지 **4 / 24**

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103 **INTRODUCTION**

104 The diagnosis of hereditary cancers has steadily increased, primarily owing to the introduction of

105 *BRCA1/2* genetic testing and advancements in next-generation sequencing (NGS) [1-4] (Figure 1).

106 Hereditary cancers account for 5–10% of all cancer cases and are mostly inherited in an autosomal-

107 dominant manner [5]. This often results in the sharing of identical genetic variants among family

108 members, which significantly affects familial health management.

109 Hereditary cancers generally occur at a younger age and pose a higher cancer risk compared to sporadic

110 cancers. Individuals with pathogenic variants (PV) in the *BRCA1* and *BRCA2* genes have a 65–80% and

111 45–85% risk of developing breast cancer, respectively, and a 37–62% and 11–23% risk of developing

112 ovarian cancer, respectively [6]. However, the genetic variants that cause hereditary cancer are often

113 unidentifiable during genetic testing on individuals suspected of hereditary cancer. Variants of uncertain

114 significance (VUS) are detected in many cases. A VUS is defined as a genetic variant for which the

115 association with the disease has not been clearly established. Current scientific knowledge and available

116 data cannot classify these variants as pathogenic or benign. Additionally, no known mutations or

117 variants have been identified in some cases [7, 8].

118 Uncertainty and confusion regarding various genetic test results and their management can lead to

119 severe psychological stress in patients with hereditary cancer, including anxiety, depression, and fear

120 of cancer recurrence [9]. In addition, sharing genetic information with family members can cause

121 tensions and conflicts within families. Moreover, the lack of genetic counseling makes it difficult for

122 individuals to make informed decisions regarding health management and preventive measures [10].

123 Living with the risk of hereditary cancer has long-term effects, including continuous health surveillance,

124 lifestyle adjustments, and the possibility of preventive surgeries, which substantially affect the overall

125 quality of life in patients and family members who share genetic components [11]. In addition, clinical

126 management becomes ambiguous when a personal or family history of hereditary cancer is suspected

127 but an uncertain variant is detected [12]. Given the limited research on uncertain variants, it is necessary

128 to conduct additional data analyses on these variants [13]. Therefore, it is crucial to prioritize patients

129 with detailed family histories, including pedigrees, and to incorporate a wide range of pathogenic

130 genetic variants when planning clinical studies targeting patients with hereditary cancer [14].

131 Furthermore, efforts should be made to include cohorts of patients with VUS and those whose test

132 results are inconclusive in establishing valuable control groups and evaluating consistency in result

133 interpretation [15].

134 Despite the rapid increase in hereditary cancer, the exact number of hereditary cancers is small. Thus,

135 it is essential to establish a multi-institutional cohort to collect substantial data and systematically study

136 the health problems of patients with hereditary cancer and those who are suspected to have hereditary

137 cancer without established causative variants. Previous studies have highlighted the unmet needs of

138 healthcare providers concerning hereditary cancers, including the lack of clinical guidelines, need for

139 reduced testing costs, and necessity for additional testing for undiagnosed hereditary cancers [16]. The

140 provision of tailored healthcare may address unmet healthcare needs, improve health outcomes, and

141 enhance quality of life. Therefore, the present study aimed to identify long-term health impacts of

142 genetic variations. This study further aimed to evaluate changes in quality of life, unmet needs, and

143 mental health according to genetic variant status to promote health improvement and quality of life.

144 This approach will also support the development and validation of personalized healthcare technologies.

145

METHODS AND ANALYSIS

Study aim

148 In this study, we established a prospective cohort of Korean patients with hereditary cancer. Three sub-

149 cohorts will be formed based on the genetic test variant results: patients with PV, VUS, and no

150 detectable mutations (ND).

Table 1 Project research question and hypotheses

Questions	Hypotheses

How do the long-term health impacts differ among patients with hereditary cancer characterized by pathogenic variants (PV), variants of uncertain significance (VUS), and undetected (ND) variants?	Patients with PV will experience higher cancer incidence rates and more health complications over the long term than those with VUS and ND variants.
What is the relationship between genetic variant status and changes in quality of life among patients with hereditary cancer over time?	Patients with PV will experience greater stress and anxiety than those with VUS and ND variants, leading to a more considerable decline in quality of life scores over time.
How do unmet healthcare needs and mental health outcomes differ based on genetic variant status in patients with hereditary cancer?	Patients with PV will require more healthcare services and psychological support, and will have higher rates of mental health issues, such as anxiety and depression, than those with VUS and ND variants.

151

Study design

153 This study is a prospective multicenter cohort study conducted in five hospitals: National Cancer Center,

154 Samsung Medical Center, Severance Hospital, Hanyang University Guri Hospital, Keimyung

155 University Dongsan Hospital. The research protocols are as follows:

156   **1. Participant registration**: Researchers at each participating institutions explained the study

157   objective, research procedures and methods, potential risks and discomfort associated with

158   participation, and the right of patients suspected of having hereditary cancer to voluntarily

159   withdraw from the study at any time. Informed consent was obtained from the participants for

160   study participation and the use of human biological materials. Relevant data, including family

161   history, clinical data, genetic test results, and blood samples are collected after enrolling the

162   participants. Blood samples stored in the Department of Laboratory Medicine were collected

163   as specified in the informed consent form. Specifically, residual blood samples of at least 4

164   mL in EDTA bottles were collected. Next, plasma and buffy coat were separated and stored at

165   -80 °C. These residual blood samples were used to identify the risk factors and prognostic

166   predictors of hereditary cancer.

167   **2. Survey:** The survey is conducted over a five-year period, with four annual follow-up surveys

168   after the baseline. The survey consists of 342 items across five domains: comorbidities, health

169   behaviors, quality of life, unmet needs, and mental health.

170   **3. Expected cohort output:** The data collected in this study will provide foundational

171   information for clinical and genetic research on hereditary cancers in Korea. These data will

172   help establish clinical guidelines for patients with hereditary cancer, propose policies for

173   patient management and support, and promote clinical advancements through detailed and

174   practical clinical research on hereditary cancer.

175   **4. Short-term outcome:** The short-term goals of this study are to evaluate changes in QoL,

176   identify unmet needs, and assess mental health and health behaviors. QoL encompasses the

177   overall patient well-being, including physical, mental, and social health. Unmet needs refer to

178   the demands of patients not currently met by existing healthcare services. Survey tools

179   validated for patients with cancer are used to evaluate how the QoL of the participants changes.

180   Baseline QoL scores and changes will be analyzed at each follow-up.

181   Additionally, the study annually tracks changes in participant mental health by evaluating

182   depression, suicidal thoughts, anxiety, fear of cancer recurrence, and disease awareness using

183   standardized survey tools. It also analyzes how knowledge of genetic status affects lifestyle

184   choices and preventive health measures through the annual monitoring of health behaviors.

185   Unmet needs are assessed using comprehensive survey tools designed to capture general and

186   hereditary cancer-specific requirements, helping identify the most common unmet needs

187   among patients.

188   **5. Long-term outcome:** The long-term objectives of this study are as follows: 1) To track cancer

189   incidence and analyze causes of death. This will involve the monitoring of new cancer cases

190   and systematic analysis of the causes of death through annual follow-ups, including medical

191   records, self-reports, and official death records; 2) We use secondary data linkages to track

192   cancer incidence and analyze the causes of death. This involves utilizing the system of data

193   integration established by authorized institutions to protect personal information and link

194   secondary data sources, such as the cancer registry and National Health Insurance Service data.

195   This approach aims to obtain more accurate and comprehensive data on cancer incidence and

196   causes of death.

197

Inclusion criteria

199   The high risk of cancer among patients with suspected hereditary cancer is attributed to genetic factors,

200   such as family history, age at cancer onset, and the occurrence of specific cancer types in multiple

201   family members [17, 18].

202   According to the 2012 National Health Insurance (NHI) coverage guidelines in Korea, *BRCA1/2*

203   pathogenic variant testing is recommended for patients with breast cancer and ovarian cancer who meet

204   the following criteria: a family history of breast or ovarian cancer within second-degree relatives, early

205   onset breast cancer (diagnosed at age ≤ 40 years), bilateral breast cancer, concurrent breast and ovarian

206   cancer, male breast cancer, or multiple primary cancers. The NHI coverage guidelines revised in 2020

207   further recommended *BRCA1/2* pathogenic variant testing for patients with breast cancer with a family

208   history of the disease, ovarian cancer, male breast cancer, metastatic prostate cancer, or pancreatic

209   cancer within third-degree relatives; early-onset breast cancer (diagnosed at age ≤ 40 years); triple-

210   negative breast cancer diagnosed at age ≤ 60 years; bilateral breast cancer; concurrent breast cancer

211   with ovarian or pancreatic cancer; male breast cancer; or epithelial ovarian cancer (including fallopian

212   tube and primary peritoneal cancer), excluding histologically pure mucinous ovarian cancer.

213   Additionally, NGS has been conditionally covered with 50% co-payment since March 2017, and the

214   co-payment rate increased to 80% in December 2023. This study included patients who underwent

215   genetic testing regardless of insurance coverage status, including minors aged 13 years or older who

216   underwent genetic counseling and related genetic testing for suspected hereditary cancer.

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Study population estimate

페이지 **9 / 24**

219 The extent to which patient-centered decision-making is implemented in clinical settings in South Korea

220 remains largely understudied. Consequently, evidence on this topic often relies on international

221 literature. A study conducted at a tertiary university hospital in South Korea reported that 37.4% of

222 orthopedic patients engaged in patient-centered decision making. Additionally, a national survey of the

223 general population indicated that 33.5–44.3% of individuals prefer shared decision-making between

224 patients and healthcare providers [19, 20].

225 In this study, we hypothesized that the rate of patient-centered decision-making without intervention

226 would be approximately 30%. We further assumed that using a tailored decision-making tool would

227 increase this rate by 10%, increasing it to a total of 40%. A two-proportion test with a significance level

228 (α) of 5% and a power (1-β) of 85% was performed based on these assumptions. The required sample

229 size was calculated to be 405 patients in each group. When the power was set to 80%, the required

230 sample size was 354 patients per group, resulting in a total of 708 patients.

231 Considering an estimated dropout rate of 20% and the fact that the number of patients with PV was

232 expected to be lower than that of those with VUS or negative variants, the target sample size was

233 adjusted. The final target sample size was set at 1,435 patients to ensure equal enrollment of patients

234 with PV and those with VUS or negative variants. Sample size estimation was conducted to establish a

235 cohort of Korean patients with hereditary cancer.

236

Data collection items

238 This study collected clinical, survey, genetic variant, and pedigree data from the participants.

239   1. **Clinical data**: Clinical data were directly extracted by researchers with access to electronic

240   medical records. These data included histories of chronic diseases (e.g., hypertension,

241   diabetes, and heart disease), cancer diagnosis (year of diagnosis, age at diagnosis, and type

242   and stage of cancer), and surgeries related to cancer treatment (date of surgery, type, and

243   outcome). Treatment history included the current and past types, duration, and outcomes of

244   anticancer therapies (chemotherapy, radiotherapy, and hormone therapy), including related

245   side effects and complications. The test results include health assessment outcomes, such as

246   general blood tests, cancer marker tests, ECGs, and pulmonary function tests. Imaging data

247   include the results and interpretations of imaging tests conducted during cancer diagnosis and

248   treatment, such as CT, MRI, PET, and ultrasonography. Anthropometric data include patient

249   weight, height, BMI, and other measurements. Obstetric, menstrual, breastfeeding, and

250   hormone use histories are also included for female patients.

251   **2.   Surveys:** The surveys were designed to be completed within 20 minutes to facilitate ease of

252   response for the participants and were structured to be administered as interviewer-

253   administered questionnaires. The survey tools were tailored to different time points: at the

254   time of cancer diagnosis; during treatment (typically four months post-diagnosis); and at 1-,

255   2-, 3-, and 4-year intervals post-diagnosis. These surveys collect detailed information on

256   lifestyle factors, environmental exposures, and other health-related data.

257   3.   **Genetic variants:** Genetic mutation data were obtained using *BRCA1/2* or NGS panel testing.

258   Based on these results, patients were classified into three sub-cohorts: PV, VUS, and ND.

259   4.   **Family history and pedigree:** Pedigree data were collected by the participants after they

260   were educated on how to construct a pedigree chart encompassing three generations. This

261   includes information on the years of cancer diagnosis, age at diagnosis, and type of cancer

262   among family members, as well as whether the family member is deceased and their age at

263   death. This structured approach ensures comprehensive data collection and analysis suitable

264   for the research objectives.

265   5.   **Biospecimen collection**: Biological samples are collected from the blood of participants in

266   accordance with protocols outlined in the informed consent documentation, with storage

267   facilitated by the Department of Laboratory Medicine. Specifically, we use residual blood

268   samples collected following clinical blood collection. A minimum of 4 mL of residual blood

269   is collected in EDTA tubes. Post-collection, the plasma and buffy coat are separated and

페이지 **11 / 24**

270   stored in an ultra-low temperature freezer at -80 °C. These residual blood samples will be

271   used to identify risk factors and prognostic predictors associated with hereditary cancer. This

272   approach is integral for improving the accuracy of assessing genetic risk factors and clinical

273   prognoses related to hereditary cancer.

274

275   **Survey tools and data collection**

276   Data were collected as follows: Baseline surveys are initially conducted with participants following

277   receipt of their genetic test results. Subsequently, annual follow-up surveys will be conducted for four

278   years from the baseline survey date. Surveys were self-administered through questionnaires or

279   telephone interviews. Participants were provided with explanations by well-trained nurses who assisted

280   them in completing the questionnaires or in conducting telephone surveys to record their responses.

281   In this study, data were collected from participants using 11 different survey tools (Table 2).

Table 2 An overview of survery questionnaire

Area	N of items	Subarea	Survey tool
Comorbidities	96	-	Korea National Health and Nutrition Examination Survey (KNHANES)
Health behavior	80	Obesity and Weight Management	
		Alcohol Consumption	
		Mental Health	
		Smoking/Secondhand Smoke/Smoking Cessation	
		Oral Health	
		Physical Activity	
		Sleep Health	
		Dietary Habits	

페이지 **12 / 24**

Quality of life	41	Quality of Life in Cancer Patients	EORTC-QLQ-C30
		General Quality of Life	EQ-5D-5L
Unmet needs	75	Comprehensive Needs Assessment	CNAT
		Hereditary Cancer Specific Needs Assessment	Development of additional items
Mental health	50	Depression	PHQ-9
		Suicide	MINI
		Anxiety	GAD-7
		Fear of Cancer Recurrence	QOL-CS
		Disease Awareness	BIPQ

282

283   1. **Comorbidities:** The current medical diagnostic status of the study participants was

284   recorded using the Korea National Health and Nutrition Examination Survey [21]. Major

285   chronic conditions included hypertension, diabetes, cardiovascular diseases. In addition,

286   the presence of malignant tumors such as gastric cancer, liver cancer, colorectal cancer,

287   and other conditions was noted. Detailed information on comorbidities, including age at

288   diagnosis and current treatment status, was collected to comprehensively assess the health

289   status of participants and to analyze the occurrence and treatment status of comorbidities.

290   2. **Health behaviors:** The Korea National Health and Nutrition Examination Survey consists

291   of eight detailed items for evaluating health-related behaviors [21, 22]. 1) Obesity and

292   weight management were assessed using self-reported weight changes and weight

293   management methods over the previous year. 2) Alcohol consumption was evaluated by

294   measuring the frequency and quantity of alcohol consumption to assess the health risk

295   factors related to alcohol consumption. 3) General mental health status was assessed using

296   standardized questions. 4) Smoking status, passive smoking exposure, as well as cessation

페이지 **13** / **24**

297   attempts and intention were evaluated to assess smoking-related health risks. 5) Oral

298   health status was assessed through self-reporting of dental hygiene habits and oral health

299   problems. 6) Physical activity was assessed by measuring the frequency, duration, and

300   intensity of physical activity. 7) Sleep health was assessed by evaluating sleep duration,

301   quality, and disturbances to identify sleep-related issues. 8) Finally, dietary habits were

302   evaluated by assessing the frequency and diversity of food intake. A comprehensive

303   evaluation of individual health habits and lifestyles was conducted through responses to

304   each item used as foundational data for health promotion.

305   3. **Quality of Life**: The general and cancer-specific QoL were assessed using the EQ-5D-

306   5L questionnaire to measure five dimensions: mobility, self-care, usual activities,

307   pain/discomfort, and anxiety or depression [23]. Each dimension was evaluated on a 5-

308   point scale scored from 1 (no problem) to 5 (severe problem). The responses were

309   subsequently combined to express a 5-digit number representing health status. This

310   facilitated a comprehensive assessment of general QoL levels. The QoL of patients with

311   cancer was assessed using the EORTC-QLQ-C30, which consists of functional (physical,

312   role, emotional, cognitive, and social functioning), symptom (fatigue, nausea, vomiting,

313   pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties),

314   an overall health status, and single-item scales [24]. Each item was evaluated on a Likert

315   scale ranging from 1 (not at all) to 4 (very much), with higher scores indicating better

316   functional status and worse symptom burden.

317   4. **Unmet needs:** This assessment comprised comprehensive and hereditary cancer-specific

318   needs. Comprehensive needs were assessed using the CNAT to evaluate the following

319   subdomains: information and education, psychological issues, medical staff, physical

320   symptoms, hospital facilities and services, family/interpersonal issues, religious/spiritual

321   issues, and social support [25]. Each item was rated from 0 (not at all needed) to 3

322   (extremely needed). Specific needs related to hereditary cancer were assessed using the

323   Study for HeredItary questionnaire Development (SHIELD) questionnaire developed by

324   the research team, with a focus on information and education, psychological issues,

325   medical services, and social support [26]. Each item was rated on a scale of 0 (not at all

326   needed) to 3 (extremely needed). Scores for each item were calculated to determine the

327   level of need, with higher scores indicating a greater need.

328   5.   **Mental health:** This evaluation comprises five detailed areas: depression, suicide risk,

329   anxiety, fear of cancer recurrence, and illness perception. The depression domain was

330   assessed using the PHQ-9 to evaluate nine depressive symptoms, with each item scored

331   from 0 (not at all) to 3 (nearly every day). This yielded a total score of 0–27, with higher

332   scores indicating higher levels of depression [27]. Furthermore, suicide risk was assessed

333   using the MINI questionnaire to evaluate the suicide risk levels of respondents based on

334   their thoughts, plans, and attempts. Each item was scored as yes (1 point) or no (0 points)

335   [28]. The anxiety domain was assessed using the GAD-7 questionnaire to evaluate seven

336   anxiety symptoms. Each item was scored from 0 (not at all) to 3 (nearly every day),

337   yielding a total score of 0–21; higher scores indicate higher anxiety levels [29]. Moreover,

338   fear of cancer recurrence was assessed using the QOL-CS questionnaire to measure the

339   concerns of cancer survivors about recurrence from various aspects. Each item was scored

340   from 0 (not at all) to 3 (very much), with higher scores indicating greater fear of cancer

341   recurrence [30]. Illness perception was assessed using the BIPQ to measure the

342   perceptions and attitudes of patients toward the disease. The BIPQ consists of nine items

343   that are each scored on a scale of 0–10, with higher scores indicating stronger negative

344   perceptions of the disease [31]. The scores for each item are summed to calculate the

345   overall illness perception score, with higher scores indicating stronger negative

346   perceptions of the disease.

347

348 **Study plan**

349 The study commenced in July 2023. Following participant enrollment and discussions among the

350 research team, 11 survey instruments were used to comprehensively collect baseline data in the first

351 year. Subsequent follow-up surveys are scheduled annually, with the scope and items to be determined

352 based on an analysis of the first year's results.

353

354 **Data management**

355 The data were collected by well-trained nurses who directly interacted with the participants to

356 administer the survey. The nurses provided detailed explanations of the survey questions and content

357 to ensure that the participants responded completely and accurately. Each participant was assigned a

358 unique research identification number to anonymize the data. These identifiers were used to enter data

359 into a de-identified database, thereby protecting personal information and maintaining privacy.

360 The collected data were reviewed and validated monthly. To enhance the accuracy and completeness,

361 an automated system was employed to identify and correct out-of-range values, missing fields, and

362 input errors, ensuring the integrity of the data. Monthly meetings were held with all researchers to

363 discuss issues arising during data collection and seek solutions, facilitating protocol adherence and

364 continuous improvement.

365 Access to the database was strictly controlled; the analytical database was encrypted and restricted to

366 essential members of the research team. These procedures were established to maintain high standards

367 of data integrity, privacy, and security while promoting continual protocol compliance and

368 improvement through regular oversight and discussions.

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페이지 **16 / 24**

370   **Data linkage**

371   This study initially collected baseline data through annual surveys over the first four years. From the

372   fifth year onwards, we will conduct a long-term follow-up study by linking secondary data sources,

373   including the cancer registry, National Health Insurance Service (NHIS), and mortality data from

374   Statistics Korea. This approach will facilitate a systematic analysis of cancer incidence, secondary

375   cancers, the onset of other diseases, and causes of mortality among participants.

376   Pseudonymized data were used to ensure the protection of personal information. Data linkage will be

377   performed securely and reliably through a pseudonym information integration system provided by the

378   NHIS, Health Insurance Review and Assessment Service, and Korea Health Industry Development

379   Institute.

380   The linked data will be utilized for various analyses, including the tracking of cancer incidence,

381   analysis of mortality causes, examination of secondary cancer occurrences, and investigation of

382   comorbid chronic diseases.

383

384   **Ethics and dissemination**

385   The protocol for this study has been approved by the Institutional Review Boards of each participating

386   institution, which have taken responsibility for supervising all aspects of the study. All participants who

387   agree to take part in the study will sign an informed consent form. The study protocol has been registered

388   with the Clinical Research Information Service (CRIS) in Korea, and the study results will be presented

389   at both national and international conferences. The research data will be linked with related institutions

390   and deposited at the National Cancer Data Center. Personal identifiable information will be encrypted

391   and stored separately from other research data.

392

DISCUSSION

394 Most studies on hereditary cancer have been conducted in Western populations, with only small-scale

395 studies focusing on Korean populations [32]. Previous multi-ethnic Asian cohort studies involving 1056

396 patients with suspected hereditary breast cancer have provided insight into the prevalence of genetic

397 variants across various Asian ethnicities, including Chinese, Malay, Indian, and Middle Eastern

398 populations [33]. These studies highlighted the genetic diversity and risk variations among these groups

399 and demonstrated the feasibility and effectiveness of guideline-based panel testing in Asians with

400 suspected hereditary breast cancer. *BRCA1/2* and multi-gene panel tests have been covered by health

401 insurance since 2018 in Japan [34]. However, there remains a need for medical staff and patient

402 education to improve access to genetic testing and counseling. Risk-reducing mastectomy and bilateral

403 salpingo-oophorectomy are performed at rates of 19.3% and 24.1%, respectively in Japan, with many

404 institutions considering their introduction. These studies emphasize the specific needs for and genetic

405 diversity in the management of hereditary cancers across various Asian populations. Furthermore, they

406 demonstrate the need for tailored genetic testing panels, comprehensive risk assessments, and

407 development of region-specific guidelines for effective management and prevention strategies.

408 Research on Korean populations is insufficient compared to Western studies, and Korea lacks integrated

409 management of patients with hereditary cancer [35]. Some variability has been observed in the risk

410 assessment for secondary cancers, preventive surgeries, and screening recommendations across medical

411 institutions. Additionally, there is a need for comprehensive studies on genetic testing and management

412 of families.

413 Our study aims to establish a cohort of patients with hereditary cancer in Korea by collecting substantial

414 data to address the unmet healthcare needs of these patients. This will enable tailored medical

415 interventions and support services that consider the genetic, environmental, and cultural characteristics

416 of the Korean population.

417 This study has some limitations. First, the participating hospitals are concentrated in metropolitan areas.

418 This limits the collection of data from patients with hereditary cancer who reside in rural areas. This

419 restriction reduces the external validity of the study and increases the risk of overlooking important

420 information related to characteristics of hereditary cancers in patients residing in rural areas. Second,

421 the accuracy of the survey data has limitations. Respondents may not accurately report their health

422 status or may rely on memory when answering questions about comorbidities or family histories,

423 leading to a recall bias that can undermine the reliability of the study results. Therefore, it is essential

424 to use objective data sources, such as electronic medical records, and to collect data through multiple

425 verification processes to enhance data reliability.

426 This study aims to elucidate the practical issues and challenges faced by Koreans during the diagnosis

427 and treatment of hereditary cancer. We formed three cohorts: patients with PV, VUS, and negative

428 variants. We aim to identify the specific needs of each variant group and propose a comprehensive care

429 plan. This approach will support genetic counseling and testing accessibility, communication with

430 healthcare providers, psychological support, and decision-making regarding treatment and preventive

431 measures.

432 Our study will contribute to a better understanding of the genetic and environmental factors involved

433 in hereditary cancers. The collection of survey data from participants will provide insights into their

434 health behaviors, QoL, and unmet needs, and elucidate differences among the cohorts. We will also

435 collect genomic data and biospecimens to secure samples for future research and develop a variant risk

436 assessment model using pathogenic variant prediction. This will further reveal the factors influencing

437 the onset and progression of hereditary cancers and facilitate the development of personalized treatment

438 and prevention strategies.

439 Finally, establishing a cohort of Korean patients with hereditary cancer will lead to further research in

440 the field of hereditary cancer in Korea. This will consequently address the specific medical needs of

441 this population. Moreover, our findings will highlight the importance of equitable healthcare access and

442 support for the development of medical and health policies aimed at ensuring a healthy life for all

443 individuals.

444

Author contributions

446 JKK drafted the manuscript. MAJ, JEP, DJW, JSH, KBK, BYP, and SYK contributed to the study

447 design and conception, as well as the overall study planning. JKK, BYP, and SYK critically revised the

448 manuscript and prepared the final version. All authors contributed to the revision of the manuscript and
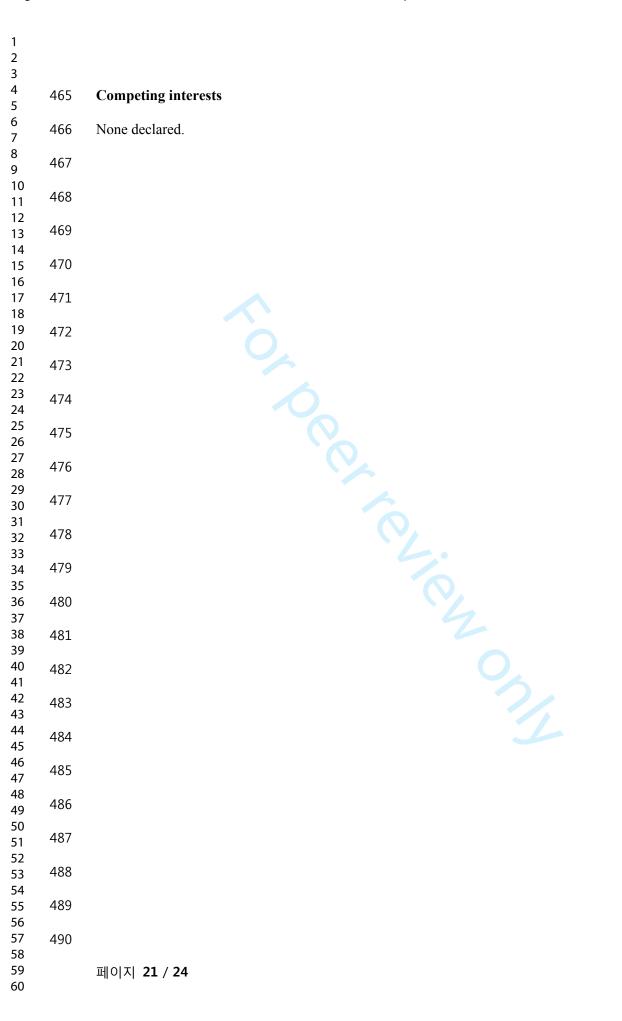
449 approved the final version for submission.

450

465 **Competing interests**

466 None declared.

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페이지 **21 / 24**

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579   **FIGURE LEGENDS**

580   **Figure 1**. **Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022.** The data for
581   this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open
582   Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests
583   conducted annually to diagnose hereditary diseases in Korea.

584   **Figure 2. Establishing a protocol logic for the hereditary cancer cohort.**
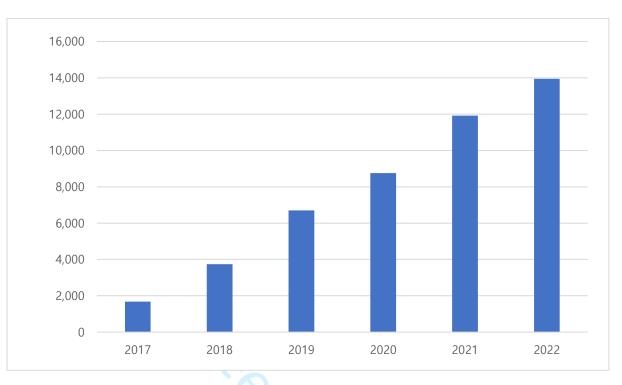
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Figure 1. **Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022.** The data for this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests conducted annually to diagnose hereditary diseases in Korea.
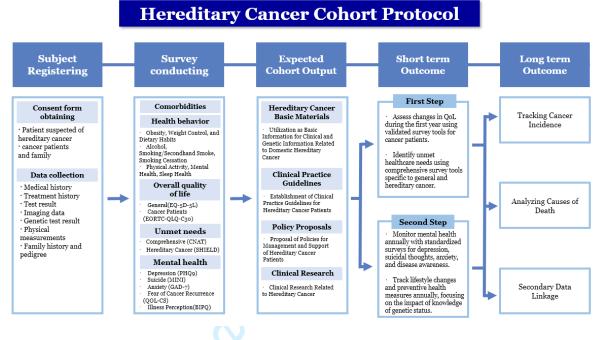
Hereditary Cancer Cohort Protocol

| Subject Registering | Survey conducting | Expected Cohort Output | Short term Outcome | Long term Outcome |

Subject Registering

Consent form obtaining
· Patient suspected of hereditary cancer
· cancer patients and family

Data collection
· Medical history
· Treatment history
· Test result
· Imaging data
· Genetic test result
· Physical measurements
· Family history and pedigree

Survey conducting

Comorbidities

Health behavior
· Obesity, Weight Control, and Dietary Habits
· Alcohol, Smoking/Secondhand Smoke, Smoking Cessation
· Physical Activity, Mental Health, Sleep Health

Overall quality of life
· General(EQ-5D-5L)
· Cancer Patients (EORTC-QLQ-C30)

Unmet needs
· Comprehensive (CNAT)
· Hereditary Cancer (SHIELD)

Mental health
· Depression (PHQ9)
· Suicide (MINI)
· Anxiety (GAD-7)
· Fear of Cancer Recurrence (QOL-CS)
· Illness Perception(BIPQ)

Expected Cohort Output

Hereditary Cancer Basic Materials
· Utilization as Basic Information for Clinical and Genetic Information Related to Domestic Hereditary Cancer

Clinical Practice Guidelines
· Establishment of Clinical Practice Guidelines for Hereditary Cancer Patients

Policy Proposals
· Proposal of Policies for Management and Support of Hereditary Cancer Patients

Clinical Research
· Clinical Research Related to Hereditary Cancer

Short term Outcome

First Step
· Assess changes in QoL during the first year using validated survey tools for cancer patients.
· Identify unmet healthcare needs using comprehensive survey tools specific to general and hereditary cancer.

Second Step
· Monitor mental health annually with standardized surveys for depression, suicidal thoughts, anxiety, and disease awareness.
· Track lifestyle changes and preventive health measures annually, focusing on the impact of knowledge of genetic status.

Long term Outcome

Tracking Cancer Incidence

Analyzing Causes of Death

Secondary Data Linkage

Figure 2. Establishing a protocol logic for the hereditary cancer cohort.

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Korean patients with hereditary cancer: A prospective multicenter cohort study protocol exploring psychosocial and health outcomes

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Korean patients with hereditary cancer: A

prospective multicenter cohort study protocol

exploring psychosocial and health outcomes

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53 **ABSTRACT**

54 **Introduction**

55 Although genetic testing for hereditary cancers is increasing, data on health attitudes based on genetic

56 pathogenicity are limited. This cohort study aims to establish three sub-cohorts based on genetic testing

57 results to assess the health impact of genetic variations. This study evaluates changes in participant

58 quality of life, unmet needs, and mental health over time based on their genetic variant status.

59 **Methods and analysis**

60 This prospective cohort study will recruit 1,435 patients with suspected hereditary cancer who have

61 undergone *BRCA1/2* or next-generation sequencing (NGS) testing. The study began in July 2023 and

62 will continue until December 2027. By 2026, participants will be surveyed up to four times annually

63 during their outpatient visits. The survey consists of 342 items across five domains: comorbidities (96),

64 health behaviors (80), quality of life (QoL) (41), unmet needs (75), and mental health (50). Data were

65 collected using 11 validated surveys. In addition, information on the chronic diseases, cancer diagnoses,

66 medical history, and treatment history of participants will be extracted from their electronic medical

67 records to analyze their health status and cancer treatment experiences. Genetic variant data from

68 *BRCA1/2* and NGS will be used to classify participants into three sub-cohorts: pathogenic variants,

69 variants of uncertain significance, and undetectable mutations. A three-generation pedigree that

70 includes details such as the year of cancer diagnosis, age at diagnosis, cancer type, survival status of

71 family members, and age at death will be constructed for each participant. the collected data will be

72 linked to secondary sources such as cancer registries and National Health Insurance Service data to

73 provide a comprehensive analysis of the impact of hereditary cancer on health and survival.

74 **Ethics and dissemination**

75 The study protocol was approved by all the Ethics Committees: the National Cancer Center IRB

76 (NCC2023-0179), the Samsung Medical Center IRB (SMC2023-09-057), the Yonsei University Health

77 System, Severance Hospital IRB (4-2023-0627), the Hanyang University Guri Hospital IRB

78 (GURI2023-08-021), and the Keimyung University IRB (DSMC IRB 2024-05-048). The study

79 outcomes will be disseminated through conference presentations, peer-reviewed publications, and

80 social media.

81 **Trial registration number** KCT0009460

82 **Keywords**: Genetic testing, Genetic predisposition to disease, Genetic variation, High-throughput

83 nucleotide sequencing, Health behavior

84

85 **STRENGTHS AND LIMITATIONS OF THE STUDY**

86 1. The Korean hereditary cancer cohort study is a large-scale multicenter study conducted at five major

87 university hospitals in Korea, targeting 1,435 patients.

88 2. The study is designed to track participants through annual surveys over five years, analyzing long-

89 term health outcomes, changes in quality of life, and unmet healthcare needs based on genetic variant

90 status. This will help understand the evolving healthcare needs of hereditary cancer patients.

91 3. Participants are classified into three sub-cohorts based on pathogenic variants(PV), variants of

92 uncertain significance (VUS), and undetectable variants(ND), allowing for a precise analysis of

93 differences in health outcomes according to genetic status.

94 4. The participating hospitals are concentrated in metropolitan areas, the study does not include patients

95 from rural regions, which may limit the external validity of the results.

96 5. There may be challenges in achieving statistical significance when analyzing smaller subgroups

97 with rarer genetic mutations or specific conditions.

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103 **INTRODUCTION**

104 The diagnosis of hereditary cancers has steadily increased, primarily owing to the introduction of

105 *BRCA1/2* genetic testing and advancements in next-generation sequencing (NGS) [1-3] (Figure 1).

106 Hereditary cancers account for 5–10% of all cancer cases and are mostly inherited in an autosomal-

107 dominant manner [4]. This often results in the sharing of identical genetic variants among family

108 members, which significantly affects familial health management.

109 Hereditary cancers generally occur at a younger age and pose a higher cancer risk compared to sporadic

110 cancers. Individuals with pathogenic variants (PV) in the *BRCA1* and *BRCA2* genes have a 65–80% and

111 45–85% risk of developing breast cancer, respectively, and a 37–62% and 11–23% risk of developing

112 ovarian cancer, respectively [5]. However, the genetic variants that cause hereditary cancer are often

113 unidentifiable during genetic testing on individuals suspected of hereditary cancer. Variants of uncertain

114 significance (VUS) are detected in many cases. A VUS is defined as a genetic variant for which the

115 association with the disease has not been clearly established. Current scientific knowledge and available

116 data cannot classify these variants as pathogenic or benign. Additionally, no known mutations or

117 variants have been identified in some cases [6, 7].

118 Uncertainty and confusion regarding various genetic test results and their management can lead to

119 severe psychological stress in patients with hereditary cancer, including anxiety, depression, and fear

120 of cancer recurrence [8]. In addition, sharing genetic information with family members can cause

121 tensions and conflicts within families. Moreover, the lack of genetic counseling makes it difficult for

122 individuals to make informed decisions regarding health management and preventive measures [9].

123 Living with the risk of hereditary cancer has long-term effects, including continuous health surveillance,

124 lifestyle adjustments, and the possibility of preventive surgeries, which substantially affect the overall

125 quality of life in patients and family members who share genetic components [10]. In addition, clinical

126 management becomes ambiguous when a personal or family history of hereditary cancer is suspected

127 but an uncertain variant is detected [11]. Given the limited research on uncertain variants, it is necessary

128 to conduct additional data analyses on these variants [12]. To enhance clinical studies targeting

129 hereditary cancer, it is essential to prioritize patients with detailed family histories, including pedigrees,

130 and to incorporate a broad range of pathogenic genetic variants [13]. Establishing cohorts that include

131 patients with VUS or inconclusive test results can provide valuable control groups and aid in the

132 consistent interpretation of genetic findings [14].

133 Existing research on hereditary cancer patients has primarily focused on White women, neglecting the

134 diverse racial and cultural contexts of patients worldwide [15-17]. Studies involving Asian populations

135 are relatively rare, and large-scale investigations targeting Koreans are almost non-existent [18, 19].

136 Consequently, there is a critical lack of systematic data on the quality of life, mental health, and medical

137 needs of Korean hereditary cancer patients. This study aims to bridge this gap by establishing a multi-

138 institutional cohort of hereditary cancer patients in Korea to analyze long-term changes in health status,

139 quality of life, and mental health.

140 Despite the rapid increase in hereditary cancer, the exact number of hereditary cancers is small. Thus,

141 it is essential to establish a multi-institutional cohort to collect substantial data and systematically study

142 the health problems of patients with hereditary cancer and those who are suspected to have hereditary

143 cancer without established causative variants. Previous studies have highlighted the unmet needs of

144 healthcare providers concerning hereditary cancers, including the lack of clinical guidelines, need for

145 reduced testing costs, and necessity for additional testing for undiagnosed hereditary cancers [20]. The

146 provision of tailored healthcare may address unmet healthcare needs, improve health outcomes, and

147 enhance quality of life. Therefore, the present study aimed to identify long-term health impacts of

148 genetic variations. This study further aimed to evaluate changes in quality of life, unmet needs, and

149 mental health according to genetic variant status to promote health improvement and quality of life.

150 This approach will also support the development and validation of personalized healthcare technologies.

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페이지 **6** / **26**

153 **METHODS AND ANALYSIS**

154 **Study aim**

155 In this study, we established a prospective cohort of Korean patients with hereditary cancer (Table 1).

156 Three sub-cohorts will be formed based on the genetic test variant results: patients with PV, VUS, and

157 no detectable mutations (ND).

Table 1 Project research question and hypotheses

Questions	Hypotheses
How do the long-term health impacts differ among patients with hereditary cancer characterized by pathogenic variants (PV), variants of uncertain significance (VUS), and undetected (ND) variants?	Patients with PV will experience higher cancer incidence rates and more health complications over the long term than those with VUS and ND variants.
What is the relationship between genetic variant status and changes in quality of life among patients with hereditary cancer over time?	Patients with PV will experience greater stress and anxiety than those with VUS and ND variants, leading to a more considerable decline in quality of life scores over time.
How do unmet healthcare needs and mental health outcomes differ based on genetic variant status in patients with hereditary cancer?	Patients with PV will require more healthcare services and psychological support, and will have higher rates of mental health issues, such as anxiety and depression, than those with VUS and ND variants.

158

159 **Study design**

160 This study is a prospective multicenter cohort study conducted in five hospitals: National Cancer Center,

161 Samsung Medical Center, Severance Hospital, Hanyang University Guri Hospital, Keimyung

162 University Dongsan Hospital. The research protocols are as follows (Figure 2):

163 **1. Participant registration**: Researchers at each participating institutions explained the study

164 objective, research procedures and methods, potential risks and discomfort associated with

165 participation, and the right of patients suspected of having hereditary cancer to voluntarily

166 withdraw from the study at any time. Informed consent was obtained from the participants for

167 study participation and the use of human biological materials. Relevant data, including family

168 history, clinical data, genetic test results, and blood samples are collected after enrolling the

169 participants. Blood samples stored in the Department of Laboratory Medicine were collected

170   as specified in the informed consent form. Specifically, residual blood samples of at least 4

171   mL in EDTA bottles were collected. Next, plasma and buffy coat were separated and stored at

172   -80 °C. These residual blood samples were used to identify the risk factors and prognostic

173   predictors of hereditary cancer.

174 **2. Survey:** The survey is conducted over a five-year period, with four annual follow-up surveys

175   after the baseline. The survey consists of 342 items across five domains: comorbidities, health

176   behaviors, quality of life, unmet needs, and mental health.

177 **3. Expected cohort output:** The data collected in this study will provide foundational

178   information for clinical and genetic research on hereditary cancers in Korea. These data will

179   help establish clinical guidelines for patients with hereditary cancer, propose policies for

180   patient management and support, and promote clinical advancements through detailed and

181   practical clinical research on hereditary cancer.

182 **4. Short-term outcome:** The short-term goals of this study are to evaluate changes in QoL,

183   identify unmet needs, and assess mental health and health behaviors. QoL encompasses the

184   overall patient well-being, including physical, mental, and social health. Unmet needs refer to

185   the demands of patients not currently met by existing healthcare services. Survey tools

186   validated for patients with cancer are used to evaluate how the QoL of the participants changes.

187   Baseline QoL scores and changes will be analyzed at each follow-up.

188   Additionally, the study annually tracks changes in participant mental health by evaluating

189   depression, suicidal thoughts, anxiety, fear of cancer recurrence, and disease awareness using

190   standardized survey tools. It also analyzes how knowledge of genetic status affects lifestyle

191   choices and preventive health measures through the annual monitoring of health behaviors.

192   Unmet needs are assessed using comprehensive survey tools designed to capture general and

193   hereditary cancer-specific requirements, helping identify the most common unmet needs

194   among patients.

195   **5. Long-term outcome:** The long-term objectives of this study are as follows: 1) To track cancer

196   incidence and analyze causes of death. This will involve the monitoring of new cancer cases

197   and systematic analysis of the causes of death through annual follow-ups, including medical

198   records, self-reports, and official death records; 2) We use secondary data linkages to track

199   cancer incidence and analyze the causes of death. This involves utilizing the system of data

200   integration established by authorized institutions to protect personal information and link

201   secondary data sources, such as the cancer registry and National Health Insurance Service data.

202   This approach aims to obtain more accurate and comprehensive data on cancer incidence and

203   causes of death.

204

205   **Inclusion criteria**

206   The high risk of cancer among patients with suspected hereditary cancer is attributed to genetic factors,

207   such as family history, age at cancer onset, and the occurrence of specific cancer types in multiple

208   family members [21, 22].

209   According to the 2012 National Health Insurance (NHI) coverage guidelines in Korea, *BRCA1/2*

210   pathogenic variant testing is recommended for patients with breast cancer and ovarian cancer who meet

211   the following criteria: a family history of breast or ovarian cancer within second-degree relatives, early

212   onset breast cancer (diagnosed at age ≤ 40 years), bilateral breast cancer, concurrent breast and ovarian

213   cancer, male breast cancer, or multiple primary cancers. The NHI coverage guidelines revised in 2020

214   further recommended *BRCA1/2* pathogenic variant testing for patients with breast cancer with a family

215   history of the disease, ovarian cancer, male breast cancer, metastatic prostate cancer, or pancreatic

216   cancer within third-degree relatives; early-onset breast cancer (diagnosed at age ≤ 40 years); triple-

217   negative breast cancer diagnosed at age ≤ 60 years; bilateral breast cancer; concurrent breast cancer

218   with ovarian or pancreatic cancer; male breast cancer; or epithelial ovarian cancer (including fallopian

219   tube and primary peritoneal cancer), excluding histologically pure mucinous ovarian cancer.

220 Additionally, NGS has been conditionally covered with 50% co-payment since March 2017, and the

221 co-payment rate increased to 80% in December 2023.

222 This study included patients suspected of hereditary cancer who underwent genetic counseling and

223 related genetic testing, regardless of insurance coverage status. Based on the results of genetic testing,

224 patients were categorized into three groups: Pathogenic Variant (PV or Likely PV), Variant of Uncertain

225 Significance (VUS), and Not Detected (Likely Benign or Benign).

226 According to the American College of Medical Genetics and Genomics (ACMG) guidelines, genetic

227 variants are classified into five categories: Pathogenic, Likely Pathogenic, Uncertain Significance,

228 Likely Benign, and Benign [23]. However, this study categorized patients into three groups—PV,

229 VUS, and ND—to systematically evaluate the clinical and psychological indicators of hereditary cancer

230 patients. This classification established a group of patients with clinically significant variants closely

231 associated with the disease, while also including groups of patients with VUS and those with no detected

232 variants as comparative cohorts. These groups served as valuable control cohorts for future clinical

233 research. By doing so, the study aimed to provide a detailed evaluation of the clinical and psychological

234 characteristics of each group and to better understand the impact of genetic testing results on the health

235 and quality of life of hereditary cancer patients.

236

237 **Study population estimate**

238 The extent to which patient-centered decision-making is implemented in clinical settings in South Korea

239 remains largely understudied. Consequently, evidence on this topic often relies on international

240 literature. A study conducted at a tertiary university hospital in South Korea reported that 37.4% of

241 orthopedic patients engaged in patient-centered decision making. Additionally, a national survey of the

242 general population indicated that 33.5–44.3% of individuals prefer shared decision-making between

243 patients and healthcare providers [24].

244   In this study, we hypothesized that the rate of patient-centered decision-making without intervention

245   would be approximately 30%. We further assumed that using a tailored decision-making tool would

246   increase this rate by 10%, increasing it to a total of 40%. A two-proportion test with a significance level

247   (α) of 5% and a power (1-β) of 85% was performed based on these assumptions. The required sample

248   size was calculated to be 405 patients in each group. When the power was set to 80%, the required

249   sample size was 354 patients per group, resulting in a total of 708 patients.

250   Considering an estimated dropout rate of 20% and the fact that the number of patients with PV was

251   expected to be lower than that of those with VUS or negative variants, the target sample size was

252   adjusted. The final target sample size was set at 1,435 patients to ensure equal enrollment of patients

253   with PV and those with VUS or negative variants. Sample size estimation was conducted to establish a

254   cohort of Korean patients with hereditary cancer.

255

256   **Data collection items**

257   This study collected clinical, survey, genetic variant, and pedigree data from the participants.

258   1.   **Clinical data**: Clinical data were directly extracted by researchers with access to electronic

259   medical records. These data included histories of chronic diseases (e.g., hypertension,

260   diabetes, and heart disease), cancer diagnosis (year of diagnosis, age at diagnosis, and type

261   and stage of cancer), and surgeries related to cancer treatment (date of surgery, type, and

262   outcome). Treatment history included the current and past types, duration, and outcomes of

263   anticancer therapies (chemotherapy, radiotherapy, and hormone therapy), including related

264   side effects and complications. The test results include health assessment outcomes, such as

265   general blood tests, cancer marker tests, ECGs, and pulmonary function tests. Imaging data

266   include the results and interpretations of imaging tests conducted during cancer diagnosis and

267   treatment, such as CT, MRI, PET, and ultrasonography. Anthropometric data include patient

페이지 **11 / 26**

268   weight, height, BMI, and other measurements. Obstetric, menstrual, breastfeeding, and

269   hormone use histories are also included for female patients.

270   **2. Surveys:** The surveys were designed to be completed within 20 minutes to facilitate ease of

271   response for the participants and were structured to be administered as interviewer-

272   administered questionnaires. The survey tools were tailored to different time points: at the

273   time of cancer diagnosis; during treatment (typically four months post-diagnosis); and at 1-,

274   2-, 3-, and 4-year intervals post-diagnosis. These surveys collect detailed information on

275   lifestyle factors, environmental exposures, and other health-related data.

276   3. **Genetic variants:** Genetic mutation data were obtained using *BRCA1/2* or NGS panel testing

277   (S1 table). Based on these results, patients were classified into three sub-cohorts: PV, VUS,

278   and ND.

279   4. **Family history and pedigree:** Pedigree data were collected by the participants after they

280   were educated on how to construct a pedigree chart encompassing three generations. This

281   includes information on the years of cancer diagnosis, age at diagnosis, and type of cancer

282   among family members, as well as whether the family member is deceased and their age at

283   death. This structured approach ensures comprehensive data collection and analysis suitable

284   for the research objectives.

285   5. **Biospecimen collection**: Biological samples are collected from the blood of participants in

286   accordance with protocols outlined in the informed consent documentation, with storage

287   facilitated by the Department of Laboratory Medicine. Specifically, we use residual blood

288   samples collected following clinical blood collection. A minimum of 4 mL of residual blood

289   is collected in EDTA tubes. Post-collection, the plasma and buffy coat are separated and

290   stored in an ultra-low temperature freezer at -80 °C. These residual blood samples will be

291   used to identify risk factors and prognostic predictors associated with hereditary cancer. This

292   approach is integral for improving the accuracy of assessing genetic risk factors and clinical

293   prognoses related to hereditary cancer.

페이지 **12** / **26**

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294   **Survey tools and data collection**

295   Data were collected as follows: Baseline surveys are initially conducted with participants following

296   receipt of their genetic test results. Subsequently, annual follow-up surveys will be conducted for four

297   years from the baseline survey date. Surveys were self-administered through questionnaires or

298   telephone interviews. Participants were provided with explanations by well-trained nurses who assisted

299   them in completing the questionnaires or in conducting telephone surveys to record their responses.

300   In this study, data were collected from participants using 11 different survey tools (Table 2).

Table 2 An overview of survey questionnaire

Area	N of items	Subarea	Survey tool
Comorbidities	96	-	Korea National Health and Nutrition Examination Survey (KNHANES)
Health behavior	80	Obesity and Weight Management	
		Alcohol Consumption	
		Mental Health	
		Smoking/Secondhand Smoke/Smoking Cessation	
		Oral Health	
		Physical Activity	
		Sleep Health	
		Dietary Habits	
Quality of life	41	Quality of Life in Cancer Patients	EORTC-QLQ-C30
		General Quality of Life	EQ-5D-5L
Unmet needs	75	Comprehensive Needs Assessment	CNAT
		Hereditary Cancer Specific Needs Assessment	Development of additional items
Mental health	50	Depression	PHQ-9

페이지 **13 / 26**

		Suicide	MINI
		Anxiety	GAD-7
		Fear of Cancer Recurrence	QOL-CS
		Disease Awareness	BIPQ

301

302   1. **Comorbidities:** The current medical diagnostic status of the study participants was

303   recorded using the Korea National Health and Nutrition Examination Survey [25]. Major

304   chronic conditions included hypertension, diabetes, cardiovascular diseases. In addition,

305   the presence of malignant tumors such as gastric cancer, liver cancer, colorectal cancer,

306   and other conditions was noted. Detailed information on comorbidities, including age at

307   diagnosis and current treatment status, was collected to comprehensively assess the health

308   status of participants and to analyze the occurrence and treatment status of comorbidities.

309   2. **Health behaviors:** The Korea National Health and Nutrition Examination Survey consists

310   of eight detailed items for evaluating health-related behaviors [25, 26]. 1) Obesity and

311   weight management were assessed using self-reported weight changes and weight

312   management methods over the previous year. 2) Alcohol consumption was evaluated by

313   measuring the frequency and quantity of alcohol consumption to assess the health risk

314   factors related to alcohol consumption. 3) General mental health status was assessed using

315   standardized questions. 4) Smoking status, passive smoking exposure, as well as cessation

316   attempts and intention were evaluated to assess smoking-related health risks. 5) Oral

317   health status was assessed through self-reporting of dental hygiene habits and oral health

318   problems. 6) Physical activity was assessed by measuring the frequency, duration, and

319   intensity of physical activity. 7) Sleep health was assessed by evaluating sleep duration,

320   quality, and disturbances to identify sleep-related issues. 8) Finally, dietary habits were

321   evaluated by assessing the frequency and diversity of food intake. A comprehensive

322   evaluation of individual health habits and lifestyles was conducted through responses to

323   each item used as foundational data for health promotion.

324   3. **Quality of Life**: The general and cancer-specific QoL were assessed using the EQ-5D-

325   5L questionnaire to measure five dimensions: mobility, self-care, usual activities,

326   pain/discomfort, and anxiety or depression [27]. Each dimension was evaluated on a 5-

327   point scale scored from 1 (no problem) to 5 (severe problem). The responses were

328   subsequently combined to express a 5-digit number representing health status. This

329   facilitated a comprehensive assessment of general QoL levels. The QoL of patients with

330   cancer was assessed using the EORTC-QLQ-C30, which consists of functional (physical,

331   role, emotional, cognitive, and social functioning), symptom (fatigue, nausea, vomiting,

332   pain, dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial difficulties),

333   an overall health status, and single-item scales [28]. Each item was evaluated on a Likert

334   scale ranging from 1 (not at all) to 4 (very much), with higher scores indicating better

335   functional status and worse symptom burden.

336   4. **Unmet needs:** This assessment comprised comprehensive and hereditary cancer-specific

337   needs. Comprehensive needs were assessed using the CNAT to evaluate the following

338   subdomains: information and education, psychological issues, medical staff, physical

339   symptoms, hospital facilities and services, family/interpersonal issues, religious/spiritual

340   issues, and social support [29]. Each item was rated from 0 (not at all needed) to 3

341   (extremely needed). Specific needs related to hereditary cancer were assessed using the

342   Study for HeredItary questionnaire Development (SHIELD) questionnaire developed by

343   the research team, with a focus on information and education, psychological issues,

344   medical services, and social support [30]. Each item was rated on a scale of 0 (not at all

345   needed) to 3 (extremely needed). Scores for each item were calculated to determine the

346   level of need, with higher scores indicating a greater need.

5. **Mental health:** This evaluation comprises five detailed areas: depression, suicide risk, anxiety, fear of cancer recurrence, and illness perception. The depression domain was assessed using the PHQ-9 to evaluate nine depressive symptoms, with each item scored from 0 (not at all) to 3 (nearly every day). This yielded a total score of 0–27, with higher scores indicating higher levels of depression [31]. Furthermore, suicide risk was assessed using the MINI questionnaire to evaluate the suicide risk levels of respondents based on their thoughts, plans, and attempts. Each item was scored as yes (1 point) or no (0 points) [32]. The anxiety domain was assessed using the GAD-7 questionnaire to evaluate seven anxiety symptoms. Each item was scored from 0 (not at all) to 3 (nearly every day), yielding a total score of 0–21; higher scores indicate higher anxiety levels [33]. Moreover, fear of cancer recurrence was assessed using the QOL-CS questionnaire to measure the concerns of cancer survivors about recurrence from various aspects. Each item was scored from 0 (not at all) to 3 (very much), with higher scores indicating greater fear of cancer recurrence [34]. Illness perception was assessed using the BIPQ to measure the perceptions and attitudes of patients toward the disease. The BIPQ consists of nine items that are each scored on a scale of 0–10, with higher scores indicating stronger negative perceptions of the disease [35]. The scores for each item are summed to calculate the overall illness perception score, with higher scores indicating stronger negative perceptions of the disease.

Study plan

The study commenced in July 2023. Following participant enrollment and discussions among the research team, 11 survey instruments were used to comprehensively collect baseline data in the first year. Subsequent follow-up surveys are scheduled annually, with the scope and items to be determined based on an analysis of the first year's results.

페이지 **16 / 26**

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372 **Data management**

373 The data were collected by well-trained nurses who directly interacted with the participants to

374 administer the survey. The nurses provided detailed explanations of the survey questions and content

375 to ensure that the participants responded completely and accurately. Each participant was assigned a

376 unique research identification number to anonymize the data. These identifiers were used to enter data

377 into a de-identified database, thereby protecting personal information and maintaining privacy.

378 The collected data were reviewed and validated monthly. To enhance the accuracy and completeness,

379 an automated system was employed to identify and correct out-of-range values, missing fields, and

380 input errors, ensuring the integrity of the data. Monthly meetings were held with all researchers to

381 discuss issues arising during data collection and seek solutions, facilitating protocol adherence and

382 continuous improvement.

383 Access to the database was strictly controlled; the analytical database was encrypted and restricted to

384 essential members of the research team. These procedures were established to maintain high standards

385 of data integrity, privacy, and security while promoting continual protocol compliance and

386 improvement through regular oversight and discussions.

387

388 **Data linkage**

389 This study initially collected baseline data through annual surveys over the first four years. From the

390 fifth year onwards, we will conduct a long-term follow-up study by linking secondary data sources,

391 including the cancer registry, National Health Insurance Service (NHIS), and mortality data from

392 Statistics Korea. This approach will facilitate a systematic analysis of cancer incidence, secondary

393 cancers, the onset of other diseases, and causes of mortality among participants.

394 Pseudonymized data were used to ensure the protection of personal information. Data linkage will be

395 performed securely and reliably through a pseudonym information integration system provided by the

페이지 **17** / **26**

396 NHIS, Health Insurance Review and Assessment Service, and Korea Health Industry Development

397 Institute.

398 The linked data will be utilized for various analyses, including the tracking of cancer incidence,

399 analysis of mortality causes, examination of secondary cancer occurrences, and investigation of

400 comorbid chronic diseases.

401

402 **Patient and public involvement**

403 Our study aims to integrate the needs of hereditary cancer patients into the research process and

404 effectively disseminate research findings to them. By collaborating with patient representatives, we

405 seek to actively incorporate the perspectives of both patients and the general public, ensuring that the

406 study is designed and conducted in alignment with their real-world needs and interests.

407 In this study, we will collect survey data on the health behaviors, quality of life, unmet medical needs,

408 and mental health of hereditary cancer patients. Based on this data and feedback from patient

409 representatives, we aim to identify additional research questions that reflect patient experiences and

410 perspectives. This approach will help ensure that the study addresses the actual needs of patients and

411 generates meaningful and practical results.We plan to invite groups of hereditary cancer patients to

412 share the study findings and evaluate how they interpret and perceive the results. This process will allow

413 us to refine the findings and present them in a way that is easily understandable to a broader audience.

414 We will further collaborate with patient representatives to develop strategies for effectively

415 disseminating research output, ensuring that the plain language summary is clear and accessible to all.

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418 **Ethics and dissemination**

419 The study protocol has been approved by the Ethics Committees of the participating institutions: the

420 National Cancer Center Institutional Review Board(IRB) (NCC2023-0179), the Samsung Medical

421 Center IRB (SMC2023-09-057), the Yonsei University Health System, Severance Hospital IRB (4-

422 2023-0627), the Hanyang University Guri Hospital IRB (GURI2023-08-021), and the Keimyung

423 University IRB (DSMC IRB 2024-05-048). Each IRB is responsible for overseeing all aspects of the

424 study to ensure compliance with ethical standards. All participants who agree to take part in the study

425 will sign an informed consent form. The study protocol has been registered with the Clinical Research

426 Information Service (CRIS) in Korea under the registration number KCT0009460, and the study results

427 will be presented at both national and international conferences. The research data will be linked with

428 related institutions and deposited at the National Cancer Data Center. Personal identifiable information

429 will be encrypted and stored separately from other research data.

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DISCUSSION

441 Most studies on hereditary cancer have been conducted in Western populations, with only small-scale

442 studies focusing on Korean populations [36]. Previous multi-ethnic Asian cohort studies involving 1056

443 patients with suspected hereditary breast cancer have provided insight into the prevalence of genetic

444 variants across various Asian ethnicities, including Chinese, Malay, Indian, and Middle Eastern

445 populations [37]. These studies highlighted the genetic diversity and risk variations among these groups

446 and demonstrated the feasibility and effectiveness of guideline-based panel testing in Asians with

447 suspected hereditary breast cancer. *BRCA1/2* and multi-gene panel tests have been covered by health

448 insurance since 2018 in Japan [38]. However, there remains a need for medical staff and patient

449 education to improve access to genetic testing and counseling. Risk-reducing mastectomy and bilateral

450 salpingo-oophorectomy are performed at rates of 19.3% and 24.1%, respectively in Japan, with many

451 institutions considering their introduction. These studies emphasize the specific needs for and genetic

452 diversity in the management of hereditary cancers across various Asian populations. Furthermore, they

453 demonstrate the need for tailored genetic testing panels, comprehensive risk assessments, and

454 development of region-specific guidelines for effective management and prevention strategies.

455 Research on Korean populations is insufficient compared to Western studies, and Korea lacks integrated

456 management of patients with hereditary cancer [39]. Some variability has been observed in the risk

457 assessment for secondary cancers, preventive surgeries, and screening recommendations across medical

458 institutions. Additionally, there is a need for comprehensive studies on genetic testing and management

459 of families.

460 Korean guidelines for *BRCA* mutation carriers include screening recommendations for breast and

461 ovarian cancers in women and breast and prostate cancers in men [40]. Additionally, screening

462 principles for other cancers, such as pancreatic, gastric, and colorectal cancers, have been proposed.

463 However, there is a lack of clear evidence regarding the appropriate timing and methods for screening

464 these cancers, limiting their practical application. In contrast, the guidelines in the United States and

465   the United Kingdom provide more detailed and systematic strategies for managing hereditary cancers.

466   The NCCN guidelines in the United States emphasize regular monitoring and early detection for various

467   cancers, including breast, ovarian, pancreatic cancers, and melanoma, with specific and detailed

468   recommendations tailored to each cancer type [41]. Similarly, the NICE guidelines in the United

469   Kingdom adopt a broader approach, encompassing high-risk individuals with *BRCA1/2* or *TP53*

470   mutations. These guidelines provide tailored surveillance strategies and recommendations for

471   preventive surgeries based on family history and individual risk factors (S2 Table) [42].

472   Our study aims to establish a cohort of patients with hereditary cancer in Korea by collecting substantial

473   data to address the unmet healthcare needs of these patients. This will enable tailored medical

474   interventions and support services that consider the genetic, environmental, and cultural characteristics

475   of the Korean population.

476   This study has some limitations. First, the participating hospitals are concentrated in metropolitan areas.

477   This limits the collection of data from patients with hereditary cancer who reside in rural areas. This

478   restriction reduces the external validity of the study and increases the risk of overlooking important

479   information related to characteristics of hereditary cancers in patients residing in rural areas. Second,

480   the accuracy of the survey data has limitations. Respondents may not accurately report their health

481   status or may rely on memory when answering questions about comorbidities or family histories,

482   leading to a recall bias that can undermine the reliability of the study results. Therefore, it is essential

483   to use objective data sources, such as electronic medical records, and to collect data through multiple

484   verification processes to enhance data reliability.

485   This study aims to elucidate the practical issues and challenges faced by Koreans during the diagnosis

486   and treatment of hereditary cancer. We formed three cohorts: patients with PV, VUS, and negative

487   variants. We aim to identify the specific needs of each variant group and propose a comprehensive care

488   plan. This approach will support genetic counseling and testing accessibility, communication with

489 healthcare providers, psychological support, and decision-making regarding treatment and preventive

490 measures.

491 Our study will contribute to a better understanding of the genetic and environmental factors involved

492 in hereditary cancers. The collection of survey data from participants will provide insights into their

493 health behaviors, QoL, and unmet needs, and elucidate differences among the cohorts. We will also

494 collect genomic data and biospecimens to secure samples for future research and develop a variant risk

495 assessment model using pathogenic variant prediction. This will further reveal the factors influencing

496 the onset and progression of hereditary cancers and facilitate the development of personalized treatment

497 and prevention strategies.

498 Finally, establishing a cohort of Korean patients with hereditary cancer will lead to further research in

499 the field of hereditary cancer in Korea. This will consequently address the specific medical needs of

500 this population. Moreover, our findings will highlight the importance of equitable healthcare access and

501 support for the development of medical and health policies aimed at ensuring a healthy life for all

502 individuals.

503

504 **Author contributions**

505 JKK drafted the manuscript. MAJ, JEP, DJW, JSH, KBK, BYP, and SYK contributed to the study

506 design and conception, as well as the overall study planning. JKK, BYP, and SYK critically revised the

507 manuscript and prepared the final version. All authors contributed to the revision of the manuscript and

508 approved the final version for submission. SYK is responsible for the overall content as guarantor.

509

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518   for their meticulous efforts in ensuring the accuracy and integrity of the collected data.

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525   **Competing interests**

526   None declared.

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페이지 **23** / **26**

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637

FIGURE LEGENDS

638

639 **Figure 1**. **Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022.** The data for
640 this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open
641 Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests
642 conducted annually to diagnose hereditary diseases in Korea.

643 **Figure 2. Establishing a protocol logic for the hereditary cancer cohort.**
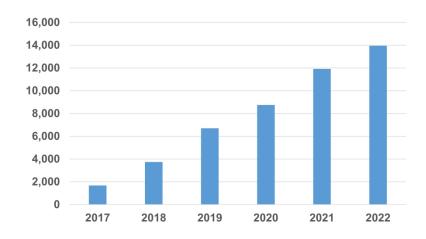
644

Figure 1. Trends in hereditary cancer diagnostic testing in Korea from 2017 to 2022. The data for this figure were sourced from the Health Insurance Review and Assessment Service Big Data Open Portal. It illustrates the increase in the number of next-generation sequencing-based genetic panel tests conducted annually to diagnose hereditary diseases in Korea.

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Figure 2. Establishing a protocol logic for the hereditary cancer cohort.

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Table S1. Gene lists included in next-generation sequencing (NGS) hereditary cancer panel

Panel	Updated date	Genes
Hereditary NGS panel (23 genes)	2018.02	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53*
Hereditary NGS panel (25 genes)	2018.10	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D*
Hereditary NGS panel (28 genes)	2019.11	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D, POLD1, POLE, SMAD4*
Hereditary NGS panel (73 genes)	2022.02	*APC, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MEN1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD50, RAD51C, RET, STK11, TP53, NF1, RAD51D, POLD1, POLE, SMAD4, BMPR1A, CDKN2A, FH, HRAS, MAX, MET, MRE11, NF2, RB1, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, TSC1, TSC2, VHL, WT1, AIP, AXIN2, BAP1, CDC73, CDK4, CDKN1B, CHEK1, CTNNA1, DICER1, EXT1, EXT2, FANCL, FLCN, GREM1, HOXB13, KIT, MSH3, NTHL1, PPP2R2A, PTCH1, RAD51B, RAD54L, SMARCA4, SMARCB1, SUFU*

*Abbreviation: NGS, next-generation sequencing

Table S2. Comparative Guidelines for Screening and Managing BRCA Gene Mutations: Korea, US, and UK

Guidelines	Country	Breast cancer	Ovarian cancer	Other cancers	Ref
10th Korean Breast Cancer Treatment Guidelines (2023)	Korea	Female carriers -Self-examination education from age 18. -Clinical breast examination every 6 months starting at age 25. -Annual MRI screening from age 25-29. -Annual MMG and MRI from age 30-75. Male carriers -Monthly self-examination and clinical breast examination every 12 months starting at age 35 -Annual MMG from age 50 for men with gynecomastia. Management -Bilateral RRM may be considered for BRCA1/2 carriers. -Contralateral mastectomy may be considered in carriers diagnosed with breast cancer.	Screening -Transvaginal ultrasound and CA125 blood test every 6 months starting at age 30. -Ultrasound is recommended between days 1-10 of the menstrual cycle; CA125 after day 5. Management -RRSO is recommended for BRCA1/2 carriers to lower ovarian and breast cancer risk. -RRSO is recommended at age 35-40 after family planning is complete. -Timing of RRSO should be individualized based on patient discussions.	**Prostate Cancer** -DRE and PSA blood test for early detection of prostate cancer from age 18. -Follow-up prostate cancer screening is recommended for *BRCA* carriers. **Pancreatic Cancer** -Initial screening with EUS, followed by alternating EUS and contrast-enhanced pancreatic MRI/MRCP, or annual MRI. **Gastric Cancer** -Endoscopy every 2 years starting at age 40, or 10 years earlier than the earliest age of onset in the family if there is a family history. **Colorectal Cancer** -Colonoscopy every 5 years starting at age 40, or 10 years earlier than the earliest age of onset in the family if there is a family history.	**[40]**
NCCN (2024)	US	Female carriers -Breast awareness from age 18. -Clinical breast examination every 6-12 months starting at age 25. -Annual MRI screening from age 25-29 (MMG if MRI unavailable). -Annual MMG and MRI from age 30-75. -Individualized management after age 75. Male carriers -Breast self-exam training and annual clinical breast examination starting at age 35 - Annual MMG from age 50 or earlier depending on family history. Management - RRM may be considered based on age, life expectancy, and residual breast cancer risk.	Screening -Undescribed Management -BRCA1 carriers: RRSO recommended at age 35-40. -BRCA2 carriers: RRSO can be delayed to age 40-45 unless family history suggests earlier intervention. -Pre-surgical CA125 testing and pelvic ultrasound recommended. -Combined OCP or hormonal IUDs can be considered to reduce ovarian cancer risk for women retaining their ovaries. -HRT may be considered post-RRSO, tailored to the presence or absence of the uterus.	**Prostate Cancer** -Screening should begin at age 40. -Screening may be considered for *BRCA1* PV/LPV carriers. -Screening is recommended for *BRCA2* PV/LPV carriers. **Pancreatic Cancer** -Screening for pancreatic cancer should be considered starting at age 50, or 10 years earlier than the earliest diagnosis of exocrine pancreatic cancer in a first- or second-degree relative with a germline PV/LPV, whichever comes first. -For individuals without a family history of exocrine pancreatic cancer, pancreatic cancer screening is not recommended for PV/LPV carriers in genes other than *ATM, BRCA2, STK11*, and *CDKN2A*.	**[41]**

					Melanoma	
					- There are no specific guidelines for melanoma; however, annual full-body skin examinations are recommended. - General melanoma risk management, such as minimizing UV exposure, is appropriate.	
NICE (updated 2023)	UK		Female carriers -MRI and MMG not recommended from age 20-29. -Annual MRI and consider annual MMG from age 30-39. -Annual MRI and MMG from age 40-49. -Annual MMG from age 50-59 (MRI only for dense breasts). -Annual MMG from age 60-69 (MRI only for dense breasts). -MMG as part of the population screening program after 70. Male carriers -Undescrbied Management -RRM available for *BRCA1* carriers, with detailed counseling on benefits and risks. Immediate or delayed breast reconstruction should be offered by specialized teams.	Screening - Serial CA125 testing every 4 months using validated algorithms - Annual consultations to discuss results and risk-reducing surgery. Management - *BRCA1* carriers: RRSO recommended after age 35. - *BRCA2* carriers: RRSO recommended after age 40. - Surgery should occur after family planning is complete. - Comprehensive discussion of benefits and risks is required. Surgery is not recommended for patients with significant comorbidities or limited life expectancy.	**Not Applicable**	[42]

* CA125: Cancer Antigen 125; DRE: Digital Rectal Examination; EUS: Endoscopic Ultrasound; LPV: Likely Pathogenic Variant; MMG: Mammogram; MRCP: Magnetic Resonance Cholangiopancreatography; MRI: Magnetic Resonance Imaging; NCCN: National Comprehensive Cancer Network; NICE: National Institute for Health and Care Excellence; OCP: Oral Contraceptives PV: Pathogenic Variant; RRM: Risk-Reducing Mastectomy; RRSO: Risk-Reducing Salpingo-Oophorectomy; UV: Ultraviolet

Correction: *Korean patients with hereditary cancer: a prospective multicentre cohort study protocol exploring psychosocial and health outcomes*

Kim J-K, Jang M-A, Park JE, *et al.* Korean patients with hereditary cancer: a prospective multicentre cohort study protocol exploring psychosocial and health outcomes. *BMJ Open* 2025;15:e093905. doi:10.1136/bmjopen-2024–0 93 905

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