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Perception on genetic testing in Korean medicine doctors: A mobile-based survey

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ABSTRACT

Background: Currently, genetic testing is widely used to understand individual characteristics. In Korea, genetic testing has been in use, but not actively in Korean Medicine (KM). To examine the perceptions of genetic testing, we performed online survey to Korean Medicine doctors (KMDs).
Methods: The survey was a mobile-based study that was developed by 6 survey specialists based on electronic database search results. The questionnaire consisted of 6 categories: general characteristics of respondents, understanding of genetic testing, demand for using genetic testing, application field and utilization level of genetic testing, limitations of genetic testing, and plans and necessary efforts to begin using genetic testing based on an 11-point Likert scale.
Results: With the response rate of 27.2% (n = 544), 46.9% of respondents answered that they understood the definition and mechanism of genetic testing. About 80% of KMDs responded that they would be willing to use genetic testing results; a notable reason for this was the need for more objective and evidence-based test results. KMDs recognized that genetic testing could not only provide personalized treatment and care, but also help communicate with patients.
Conclusions: This study observed KMDs' perceptions of the potential clinical benefits of genetic testing. We confirmed that development of genetic testing technology, knowledge of their use, and new technology-friendly policies are essential for expanding the genetic testing technology in Korean medicine.

1. Introduction

Since precision medicine can diagnose and treat patients more precisely, minimize adverse events, or prevent unnecessary payments based on the results of genetic testing, many healthcare providers are applying personalized treatments with genetic data or biomarkers.[1]

Since the completion of the Human Genome Project, the cost of sequencing a human genome has fallen from about $95 million in 2001 to $606 in May 2019.[2] As the cost of genetic testing has decreased and the usefulness of genetic variants has increased, genetic testing is being used in more medical fields, such as for predicting the risk of genetic disorders and other diseases in humans.[3–5]

Genetic testing has recently been used to determine the condition or risk of cancer patients[6,7] or to diagnose a congenital disease in a fetus.[6–8] It is also used to identify people with diabetes or who are at risk for diabetes, and to help patients make better treatment decisions. In addition, genetic testing results have also been applied to develop health policies or clinical practice guidelines with the advent of public health genomics.[9–11]

The market for precision medicine, including genetic testing is expected to grow to about $84 billion by 2026 in the United States.[12] There are about 75,000 genetic testing on the market, and about 14,000 new genetic testing came on the market between 2014 and 2017.[13] Among them, the global direct-to-consumer (DTC) genetic

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testing market was estimated at around $360 million in 2017 and expected to reach around $930 million by 2023.[14] DTC genetic testing allows consumers to directly discover their risk for common complex disorders, but for many reasons, expert advice is still essential in interpreting DTC genetic testing.[15]

In Korean Medicine (KM), treatment is provided considering the patient's overall symptoms or predisposition (mainly represented by the 'constitution').[16,17] Given that precision medicine tailors treatment to each patient's individual characteristics and plays a major role in predicting or treating diseases, basic diagnosis and treatment principles of KM are similar to those of precision medicine. Some studies tried to connect the constitutions classified by KM with genetic data, such as human leukocyte antigen (HLA-DR), angiotensin converting enzyme (ACE) type, and the obesity-risk variant of *FTO*.[18–21] Accordingly, the use and need of genetic testing have been increased in KM field, however, the perception and the demand of the actual user had not been explored. To develop the more effective and targeted genetic testing tool for KM, we had to identify the perspective of KM doctors (KMDs). Several studies have been conducted on DTC genetic testing in Korea,[22–24] including those that surveyed the public, consumers, and healthcare providers for genetic testing perceptions, experiences, or attitudes,[25–28] but they have not yet been studied from the perspective of KM doctors (KMDs).[25–28]

Using current science and technology to verify theories of traditional medicine or treating patients with the information collected from diagnostic tools commonly used in Western medicine contributes to the development of traditional medicine in harmony with modern medicine. To investigate the needs of both KMDs and patients for genetic testing, and to promote the development of KM with advanced precision medicine technology, it was necessary to conduct study on precision medicine in KM. As a first step, this study aimed to study KMDs' perceptions and the demands of genetic testing through online survey.

2. Methods

2.1. Study design

The survey was a mobile-based cross-sectional study to determine KMDs' perceptions about the need for and activation plans of genetic testing. All participants participated voluntarily with mobile-based informed consent. The survey was conducted once between October 12 and 27, 2018.

2.2. Participants

The survey was conducted on about 2000 KMDs who were members of Haniplanet (https://www.haniplanet.com). Haniplanet is an online community in Korea for KMDs, and about 10% of all KMDs (24,627 KMDs, as of 2017) that have licenses in Korea are registered on this site. To achieve high response rate, we selected the most highly response online community. All KMD who had license were allowed to answer the survey.

2.3. Survey questionnaire

The questionnaire was developed by 6 survey specialists (3 KMDs and 3 genetic researchers) based on electronic database search results about investigating perceptions of genetic testing.[13,25] The items were fixed by consensus method between the specialists. Next, three clinical KMDs who did not participate in the questionnaire developing process reviewed the survey draft and pilot-tested the mobile-based questionnaire.

The questionnaire consisted of 6 categories: 1) general characteristics of respondents, 2) understanding of genetic testing, 3) demand for using genetic testing, 4) application field and utilization level of genetic testing, 5) limitations of genetic testing, and 6) plans and necessary efforts to begin using genetic testing. Each question in each category was designed to be answered on an 11-point Likert scale to identify the strength of agreement (from 0: strongly disagree or unaware ~ to 10: strongly agree or aware) (Supplement 1). The results were described in mode.

2.4. Statistical analysis

Frequency analyses were performed with SPSS Statistics ver.18.0 (IBM; Armonk, NY). Data were shown by descriptive statistics with frequencies and percentages. For ease of interpretation, the scores were classified into 5 levels: extreme high level (score 10), high level (7~9 scores), moderate level (4~6 scores), low level (1~3 scores), and extreme low level (score 0) level. The mean score was calculated by the following formula:

$$\frac{\{10 \times (NRS\,10)\} + \{9 \times (NRS\,9)\} + \ldots\{2 \times (NRS\,2)\} + \{1 \times (NRS\,1)\}}{sum\ of\ all\ respondents}$$

NRS X: number of respondents for score X

The results were reported according to the STROBE guideline.

2.5. Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Daejeon University (No. 1040647-201809-HR-001) in October 2018.

3. Results

3.1. General characteristics of participants

Among all KMDs (n = 2000) on the Haniplanet website, 544 KMDs responded to the survey with a response rate of 27.2%. Table 1 presents the general characteristics of the survey respondents.

3.2. Understanding of genetic testing

Nearly half (n = 255, 46.9%) of the respondents answered that they understood well the definition and mechanism of genetic testing (sum of answers from scores 6 to 10). Almost one-fifth (17%) of respondents selected a score of 5 (n = 95). There were 194 respondents who answered with a score from 0 to 4.

3.3. Demand for genetic testing

Of the 544 respondents, 79.2% (n = 431) answered that they were willing to use a genetic testing in their practice. For those who answered 'yes' (n = 431), the reasons for willing to use the test are shown in Table 2. Among the six reasons, the respondents answered strongly positive for 'for personalized treatment and care', "to conduct accurate medical examination based on objective testing", and "easy to explain to the patients".

The modes for each item in the question asking the reason for willingness to use a genetic testing were as follows: "for personalized treatment and care", score 8 (27.1%); "to conduct accurate medical examination based on objective tests", score 10 (26.2%); "easy to explain to the patients", score 8 (26.9%); "non-covered items", score 5 (17.2%); "use in other clinics", score 5 (18.8%); and "patient's request", score 3 (18.3%) (data not shown).

The reasons for saying "no" to using genetic testing were "unnecessary", "expensive cost", "inconvenient", "difficult to interpret", "non-covered item", "insufficient knowledge", "complexity of the

Table 1
General characteristics of survey participants (n = 544).

Characteristics		n	%
Work region	Seoul Special City	149	27.4
	Metropolitan city and Sejong Special Self-Governing City	151	27.8
	Middle city and Jeju Special Self-Governing Province	187	34.4
	County	57	10.5
Age (years)	< 40	383	70.4
	40–49	134	24.6
	50–59	23	4.2
	> 60	4	0.7
Sex	Male	365	67.1
	Female	179	32.9
Clinical experience (years)	< 5	242	44.5
	5-9	159	29.2
	10-14	91	16.7
	≥ 15	52	9.6
Highest level of education	Bachelor's degree	374	68.8
	Master's degree	82	15.1
	Doctoral degree	75	13.8
	Doctor course completion	12	2.2
	No response	1	0.2
Medical license	Both MD and KMD	30	5.5
	Only KMD	514	94.5
Training	Specialized Practitioner	99	18.2
	General Practitioner	445	81.8
Workplace	KM hospital	80	14.7
	General hospital	11	2.0
	Nursing hospital	40	7.4
	KM clinic	298	54.8
	University and research institute	35	6.4
	Others	82	15.1
Terms of clinic opening (total years)	<5	283	52.0
	5–9	138	25.4
	10–14	69	12.7
	15–19	33	6.1
	≥20	21	3.9
Mean time spent on patient care (hours/day)	<5	43	7.9
	5–9	440	80.9
	≥10	43	7.9

MD, Medical doctor.
KMD, Korean Medicine doctor.

laws, systems, and regulations", and "negative effect to patients of misleading interpretation" (data not shown).

3.4. Application field and utilization level of genetic testing

In Table 3, KMDs (N = 431) reported fields to which genetic testing could be applied and the utilization level for each disease.

In the question asking about application fields for genetic testing, the respondents replied positively to all 5 questions (Table 3). The modes of items were score 8 in 4 items except for "check adverse events" (score 7, 18.4%). The modes were 8 for "predict future diseases" (24.8%), "predict efficacy based on personalized medicine" (27.2%), "predict prognosis" (25.9%), "examine Sasang constitution" (24.8%).

For the utilization level of genetic testing for diseases, the KMDs thought that the genetic testing is very useful for internal diseases such as autoimmune disease, endocrine, nutritional, and metabolic disease, neoplasms, circulatory system diseases, mental and behavioral diseases, nervous system diseases, and respiratory diseases. However, they thought the utilization level was moderate for musculoskeletal system and connective tissue system diseases (Table 3).

The modes for 3 diseases were score 10: "autoimmune diseases" (36.9%), "endocrine, nutritional and metabolic diseases" (31.1%), and "neoplasms (cancers)" (33.1%). The modes for 4 diseases were score 8: "diseases of circulatory system" (26.8%), "mental and behavioral disorders" (25.2%), "diseases of the nervous system" (24.3%), and "diseases of digestive system" (24.4%). The modes for "diseases of the respiratory system" and "diseases of musculoskeletal system and connective tissue" were score 7 (23.0%) and score 5 (23.7%), respectively (not shown).

3.5. Barriers of genetic testing

The results of the question on limitations of genetic testing are presented in Table 4. The KMDs replied that test accuracy, interpretation accuracy, personal information protection, providing latest knowledge, and laws and related regulations are strongly important to solve out to spread the use of genetic testing. The modes for all 5 items were score 10: "test accuracy" (43.8%), "interpretation accuracy" (41.9%), "personal information protection" (47.1%), "providing latest knowledge" (34.2%), and "laws and regulations" (31.1%).

3.6. Plan and necessary efforts to begin using genetic testing

Table 5 shows the results of KMDs' responses to the plans and necessary efforts to begin using genetic testing. For all 6 items presented, the modes were score 10: "development of test interpretation guideline" (48.5%), "research activation and evidence backup" (47.1%), "improve test accuracy" (46.0%), "strengthening related training" (38.1%)", "improve law, system and regulation" (37.3%), and "strengthening protection of personal information and human rights" (38.1%).

4. Discussion

We conducted this study to investigate KMDs' perceptions of genetic testing and to understand how KM will prepare for changes in the healthcare system that will utilize various precision medicine-based tools, like genetic testing, in the future.

According to our results, about 80% of KMDs responded that they would be willing to use genetic testing results. A notable reason for this was to provide personalized treatment and care and to conduct more objective and evidence-based test results. KMDs recognized that genetic testing could not only, but also help communicate with patients. Whether the testing is 'noncovered-items', 'other clinics' use', and 'patients' request' were not relatively important (Table 2).

They thought that genetic testing could be applied to predict outcomes such as future diseases, efficacy, and prognosis. In addition, KMDs replied that genetic testing could be used for diagnosis ('examine Sasang constitution', Korean diagnosis system based on individual constitution) and checking adverse events. The results of this survey suggest a positive perception among KMDs that genetic testing may enable KM to be applied clinically based on more objective data. Regarding the diseases to which genetic testing can be applied, KMDs responded that they are likely to be used mainly for incurable and chronic diseases such as autoimmune diseases, endocrine and metabolic diseases, or neoplasms (Table 3). The application of genetic testing is expected to contribute to expanding the field for clinical use of KM.

On the other hand, it was observed that overcoming the technical limitations of current genetic testing technology (test and interpretation accuracy), a system for protecting personal information, and knowledge of utilizing it in the care of their patients are essential for efforts to expand genetic testing in the future (Table 4). This is consistent with the results of a recent study conducted on primary care providers in the United States.[25]

Table 2
Demand for genetic testing (N = 431).

	Score level (5 level)* n (%)										Mean score†
	Extreme low (0)		Low (1∼3)		Moderate (4∼6)		High (7∼9)		Extreme high (10)		
For personalized treatment and care	3	(0.7)	5	(1.2)	39	(9.0)	278	(64.5)	106	(24.6)	8.17
To conduct accurate medical examination based on objective testing	1	(0.2)	6	(1.4)	54	(12.5)	257	(59.6)	113	(26.2)	8.16
Easy to explain to the patients	8	(1.9)	16	(3.7)	72	(16.7)	270	(62.6)	65	(15.1)	7.41
Noncovered items	38	(8.8)	115	(26.7)	145	(33.6)	120	(27.8)	13	(3.0)	4.75
Use in other clinics	53	(12.3)	139	(32.3)	138	(32.0)	93	(21.6)	8	(1.9)	4.15
Patients' request	52	(12.1)	157	(36.4)	129	(29.9)	82	(19.0)	11	(2.6)	4.06

(0: Strongly disagree ∼ 10: Strongly agree).
* Scores of 11-point Likert scale were classified into 5 levels, except the both extremes (score 0, 10).
† The mean score was calculated by following formula: {10×(number of respondents for 10 score)}+{9×(number of respondents for 9 score)}+ . . . +{1×(number of respondents for 1 score)} / total number of respondents.

Table 3
Application field and utilization level of genetic testing (N = 431).

	Score level (5 level)* n (%)										Mean score†
	Extreme low (0)		Low (1-3)		Moderate (4-6)		High (7-9)		Extreme high (10)		
3-1. Application field of genetic testing											
Predict future diseases	9	(1.7)	18	(3.3)	79	(14.5)	335	(61.6)	103	(18.9)	7.67
Predict efficacy based on personalized medicine	14	(2.6)	16	(2.9)	110	(20.2)	322	(59.2)	82	(15.1)	7.31
Predict prognosis	12	(2.2)	22	(4.0)	121	(22.2)	316	(58.1)	73	(13.4)	7.18
Examine Sasang constitution	23	(4.2)	47	(8.6)	126	(23.2)	289	(53.1)	59	(10.8)	6.66
Check adverse events	17	(3.1)	82	(15.1)	159	(29.2)	227	(41.7)	59	(10.8)	6.19
3-2. Utilization level of genetic testing for diseases											
Autoimmune diseases	2	(0.4)	9	(1.7)	35	(6.4)	297	(54.6)	201	(36.9)	8.58
Endocrine, nutritional, and metabolic diseases	4	(0.7)	6	(1.1)	50	(9.2)	315	(57.9)	169	(31.1)	8.33
Neoplasms (cancers)	4	(0.7)	12	(2.2)	51	(9.4)	297	(54.6)	180	(33.1)	8.32
Diseases of the circulatory system	6	(1.1)	11	(2.0)	76	(14.0)	333	(61.2)	118	(21.7)	7.84
Mental and behavioral disorders	10	(1.8)	42	(7.7)	121	(22.2)	279	(51.3)	92	(16.9)	7.15
Diseases of the nervous system	7	(1.3)	31	(5.7)	141	(25.9)	289	(53.1)	76	(14.0)	7.06
Diseases of the digestive system	7	(1.3)	36	(6.6)	161	(29.6)	283	(52.0)	57	(10.5)	6.82
Diseases of the respiratory system	7	(1.3)	33	(6.1)	178	(32.7)	272	(50.0)	54	(9.9)	6.73
Diseases of the musculoskeletal system and connective tissue	17	(3.1)	119	(21.9)	252	(46.3)	131	(24.1)	25	(4.6)	5.21

(0: Strongly disagree - 10: Strongly agree).
* Scores of 11-point Likert scale were classified into 5 levels, except the both extremes (score 0, 10).
† The mean score was calculated by following formula: {10×(number of respondents for 10 score)}+{9×(number of respondents for 9 score)}+ . . . +{1×(number of respondents for 1 score)} / total number of respondents.

Table 4
Barriers for using genetic testing (N = 544).

	Score level (5 level)* n (%)										Mean score**
	Extreme low (0)		Low (1-3)		Moderate (4-6)		High (7-9)		Extreme high (10)		
Test accuracy	2	(0.4)	4	(0.7)	39	(7.2)	261	(48.0)	**238**	**(43.8)**	8.65
Interpretation accuracy	2	(0.4)	3	(0.6)	36	(6.6)	275	(50.6)	**228**	**(41.9)**	8.64
Personal information protection	3	(0.6)	11	(2.0)	57	(10.5)	217	(39.9)	**256**	**(47.1)**	8.51
Providing latest knowledge	1	(0.2)	7	(1.3)	57	(10.5)	293	(53.9)	**186**	**(34.2)**	8.34
Laws and regulations	3	(0.6)	16	(2.9)	115	(21.1)	241	(44.3)	**169**	**(31.1)**	7.81

(0: Strongly disagree - 10: Strongly agree).
Bolds are mode.
* Scores of 11-point Likert scale were classified into 5 levels, except the both extremes (score 0, 10).
** The mean score was calculated by following formula: {10×(number of respondents for 10 score)}+{9×(number of respondents for 9 score)}+ . . . +{1×(number of respondents for 1 score)} / total number of respondents.

Table 5
Plan and necessary efforts to activate the use of genetic testings (N = 544).

	Score level (5 level)* n (%)										Mean score**
	Extreme low (0)		Low (1-3)		Moderate (4-6)		High (7-9)		Extreme high (10)		
Development of testing interpretation guideline	2	(0.4)	3	(0.6)	22	(4.0)	253	(46.5)	**264**	**(48.5)**	8.91
Research activation and evidence backup	1	(0.2)	4	(0.7)	28	(5.1)	255	(46.9)	**256**	**(47.1)**	8.85
Improve testing accuracy	2	(0.4)	5	(0.9)	35	(6.4)	252	(46.3)	**250**	**(46.0)**	8.76
Strengthen related training	2	(0.4)	5	(0.9)	44	(8.1)	286	(52.6)	**207**	**(38.1)**	8.52
Improve law, system, and regulation	3	(0.6)	6	(1.1)	70	(12.9)	262	(48.2)	**203**	**(37.3)**	8.30
Strengthen protection of personal information and human rights	2	(0.4)	15	(2.8)	86	(15.8)	234	(43.0)	**207**	**(38.1)**	8.13

(0: Strongly disagree - 10: Strongly agree).
Bolds are mode.
* Scores of 11-point Likert scale were classified into 5 levels, except the both extremes (score 0, 10).
** The mean score was calculated by following formula: {10×(number of respondents for 10 score)}+{9×(number of respondents for 9 score)}+ … +{1×(number of respondents for 1 score)} / total number of respondents.

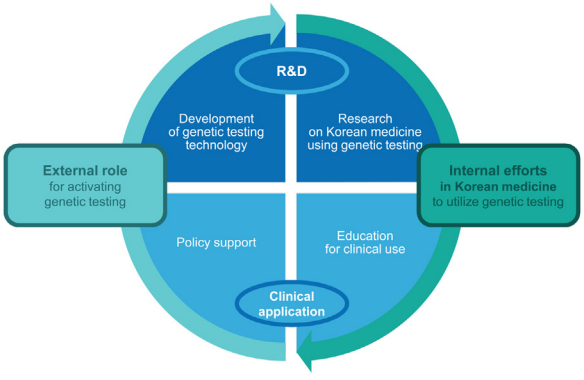

Fig. 1. Internal and external efforts required to activate genetic testing in Korean medicine.

Considering various external and internal changes, it is clear that precision medicine based on genetic testing is the path for future medicine. Based on the results of this study, it was confirmed that KMDs share a deep understanding of these environmental changes. In addition, we observed that further internal and external efforts are required to keep pace with changes in the medical system using various precision medicine-based tools such as genetic testing (Fig. 1).

Firstly, internal efforts are needed to utilize genetic testing in KM, including research on using genetic testing in KM (first quadrant, Fig. 1) and education for clinical use (fourth quadrant, Fig. 1). There have been several literature-based data-mining studies trying to link genetic data with KM-related diagnoses, pattern identification, constitution, or herbal medicine data, but it is still insufficient to interpret the results of genetic testing in connection with KM diagnoses.[19,21,26,29] To establish a scientific and objective basis that can actually link genetic testing results to KM diagnoses and treatments, research that can reveal the correlation between genetic testing results for various patient groups and KM's patient classification system (such as constitution or pattern identification) must be performed. For this to be possible, an environment capable of collecting data for research must be fostered, and technologies developed for accurate and efficient testing and analysis must be carried out in parallel. In addition, healthcare providers need to be able to accurately explain the meaning of genetic testing results to prevent mistranslation to patients. Similar to our findings, previous studies have recognized that healthcare providers, including primary care providers, were unable to interpret genetic testing results accurately and have not received sufficient training to interpret them correctly.[25,26] It is very important for clinicians to make internal efforts to utilize new technologies to keep up with changing medical trends.

Secondly, an external role for starting genetic testing is also important, which includes development of technology (second quadrant, Fig. 1) and policy support for genetic testing (third quadrant, Fig. 1). Policy support needs to be discussed primarily with regard to deregulating genetic testing and should be carefully handled under strict protection of personal information. Genetic testing regulations can avoid misuse of tests and ensure the quality of genetic testing, but they can be a barrier to technology development and active clinical use.

The Korean government introduced a 'regulatory sandbox' in 2019 to exempt or defer regulations on new products or businesses in certain fields, including DTC genetic testing.[30] Subsequently, on December 30, 2019, non-medical institutions were allowed to use DTC to start an empirical study related to obesity management. Although still a rudimentary challenge, it is expected that the Korean government will address the deadlocked regulation of DTC genetic testing and strengthen innovation. Along with this deregulation, it is essential to promote the development of the technology itself. Like other diagnostic tests, genetic testing also needs to focus on improving accuracy, sensitivity, and specificity. As shown in the results of this study, KMDs, who are subject to applying genetic testing directly to medical treatments at the front line of clinical fields, recognize the necessity of further developing the accuracy of tests and interpretation of results. Kim et al. showed that different genetic testing services use their own methods of calculation to estimate risks of diseases, and thus the relative risks of diseases may differ between services.[28,31] In addition, it has been reported

that interpretation results differ depending on who interprets DTC genetic testing results (general public or genetic counselors).[32] If the problem of a lack of objectivity in genetic testing is not technically resolved, distrust from the public and the medical community will result in negative effects on the genetic testing market.

For KMDs to finally utilize precision medicine tools, including genetic testing, various stakeholders contributing to these internal and external efforts will need to be involved. Researchers and clinicians should strive to establish and utilize reliable medical evidence. In a medical environment like that in Korea, the government needs to consider not only the improvement of the system for technology introduction, but also the close connection with the medical insurance system in Korea. Few legislative amendments have already been proposed or applied, but efforts to protect the privacy of the genetic information of the public should not be left behind in technological development. These efforts will lead to clinical validity of genetic testing results and reduce unnecessary payments (Table 5).[1,33]

Though our study was the first survey that investigated the perception and demands of genetic testing in KMDs, a representativeness of a sample is a limitation. As shown in Table 1, the relatively lower ages of respondents (those under 30) accounts for 70% of all respondents. Therefore, it requires caution to generalize. The results show that the main users will be the young groups of KMDs.

In conclusion, it was confirmed that the development of genetic testing technology, knowledge of their use, and new technology-friendly policies are essential for efforts to expand genetic testing technology. To meet the changing medical needs of patients and to promote the development of KM with advanced precision medicine technology, more studies have to be done to apply genetic testing to KM, the clinical effectiveness and cost-effectiveness of applying genetic testing, and the benefits to patients.

Author contribution

Conceptualization: SP. Methodology: SP. Software: SCW. Validation: SYK. Formal Analysis: SP, SCW, SYK. Investigation: SP. Resources: SP. Data Curation: SP, SCW, SYK. Writing – Original Draft: SP, SCW, SYK, HJJ. Writing – Review & Editing: SP, SWK. Visualization: SCW, SYK. Supervision: SP, SYK. Project Administration: HJJ, SL. Funding Acquisition: SJJ, SL, HJB.

Conflict of interest

The authors declare no conflict of interest.

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Ethical statement

This study was approved by the Institutional Review Board (IRB) of Daejeon University (No. 1040647-201809-HR-001). Mobile-based informed consent was obtained from all participants.

Data availability

The data will be made available upon request.

Supplementary material

Supplementary data related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imr.2020.100643.

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