A Strategic Plan for the Second Phase (2013–2015) of the Korea Biobank Project

Ok Park a,*, Sang Yun Cho a, So Youn Shin a, Jae-Sun Park a, Jun Woo Kim a, Bok-Ghee Han b

aDivision of Biobank for Health Sciences, Korea National Institute of Health, Osong, Korea. bCenter for Genome Science, Korea National Institute of Health, Osong, Korea.

Abstract

The Korea Biobank Project (KBP) was led by the Ministry of Health and Welfare to establish a network between the National Biobank of Korea and biobanks run by university-affiliated general hospitals (regional biobanks). The Ministry of Health and Welfare started the project to enhance medical and health technology by collecting, managing, and providing researchers with high-quality human bio-resources. The National Biobank of Korea, under the leadership of the Ministry of Health and Welfare, collects specimens through various cohorts and regional biobanks within university hospitals gather specimens from patients. The project began in 2008, and the first phase ended in 2012, which meant that there needed to be a plan for the second phase that begins in 2013. Consequently, professionals from within and outside the project were gathered to develop a plan for the second phase. Under the leadership of the planning committee, six working groups were formed to formulate a practical plan. By conducting two workshops with experts in the six working groups and the planning committee and three forums in 2011 and 2012, they have developed a strategic plan for the second phase of the KBP. This document presents a brief report of the second phase of the project based on a discussion with them. During the first phase of the project (2008–2012), a network was set up between the National Biobank of Korea and 17 biobanks at university-affiliated hospitals in an effort to unify informatics and governance among the participating biobanks. The biobanks within the network manage data on their biospecimens with a unified Biobank Information Management System. Continuous efforts are being made to develop a common standard operating procedure for resource collection, management, distribution, and personal information security, and currently, management of these data is carried out in a somewhat unified manner. In addition, the KBP has trained and educated professionals to work within the biobanks, and has also carried out various publicity promotions to the public and researchers. During the first phase, biospecimens from more than...
The planning committee for the second phase evaluated that the first phase of the KBP was successful. However, the first phase of the project was meant to allow autonomy to the individual biobanks. The biobanks were able to choose the kind of specimens they were going to collect and the amount of specimen they would set as a goal, as well as being allowed to choose their own methods to manage their biobanks (autonomy). Therefore, some biobanks collected resources that were easy to collect and the resources needed by researchers were not strategically collected. In addition, there was also a low distribution rate to researchers outside of hospitals, who do not have as much access to specimens and cases as those in hospitals. There were also many cases in which researchers were not aware of the KBP, and the distribution processes were not set up to be convenient to the demands of researchers.

Accordingly, the second phase of the KBP will be focused on increasing the integration and cooperation between the biobanks within the network. The KBP plans to set goals for the strategic collection of the needed human bioresources. Although the main principle of the first phase was to establish infrastructure and resource collection, the key objective of the second phase is the efficient utilization of gathered resources. In order to fully utilize the gathered resources in an efficient way, distribution systems and policies must be improved. Vitalization of distribution, securing of high-value resource and related clinical and laboratory information, international standardization of resource management systems, and establishment of a virtuous cycle between research and development (R&D) and biobanks are the four main strategies. Based on these strategies, 12 related objectives have been set and are planned to be executed.

1. Introduction

1.1. Importance of a biobank as an infrastructure for biomedical research to realize personalized medicine

Recently, there has been a shift in patient treatment, i.e., a shift from treating patients after contracting diseases to personalized medicine, in which diseases are prevented and treated according to individual genetic differences. Following the trend, biobanks have been stressed as an important basic infrastructure for biomedical research and the way to open up a new era of personalized medicine. In the past 10 years, there have been continuous researches and studies in Korea on various related topics, such as relationships between genes and diseases, health behaviors, and interactions with environmental factors. Such researches have been carried out in large scales through research consortiums, and various cohorts have been established to study the incidence and causes of chronic diseases. Accordingly, it has become necessary to establish a biobank to collect and supply large amounts of samples to researchers or effectively manage the collected specimens. In addition, many medical professionals have come to realize that biobank and its biobank network would be essential to support specified researches pertaining to the analytic study of Korean genetic material, especially because such research is needed to make personalized medicine in Korea. The biobank network would also collect high-quality human biospecimens and related clinical, epidemiological, and laboratory information, making such information more accessible for researchers.

1.2. Background of the Korea Biobank Project

Over the recent decades, the Korean government has increasingly noticed the growing importance of biospecimens. The Ministry of Education and Science Technology, the Ministry of Environment, and the Ministry of Health and Welfare have been working together to build biobanks to catch up with the government’s intent. In 1995, the Ministry of Education and Science Technology established the Korea National Research Resource Centers for collecting various bioresources including specimens from plants and animals. Five of the 36 research centers that are part of the network collect human biospecimens. However, the scale and variety of the collections were small because collections were made on an individual research project level. The Ministry of Environment established biobanks through cohorts to study the effect of harmful environmental substances on the human body, but their samples were limited to specimens needed for researching environmentally induced diseases. Therefore, there was a necessity to establish a biobank that is centered on hospitals, and not just on individual research-level studies, especially within general hospitals run by universities. In 2008, the Ministry of Health and Welfare started the Korea Biobank Project (KBP)
and led the effort to establish biobanks within university-affiliated general hospitals as well as creating a network among these biobanks [1,2].

1.3. Changes in biobanks within and outside of Korea

Over the last two decades, many biobanks and international collaborations have been installed to obtain the needed critical mass of a certain of biospecimen to commence biomedical researches. Especially the number of population biobanks and projects (i.e. UK biobank (3), Estonian Genome Project (4), Chinese Kadoorie study (5) and others) has significantly increased on the completion of the Human Genome Project. The international trend has also recently spread to developing countries (Table 1) [3]. In March 2009, the Time Magazine chose biobanks as one of the “10 Ideas Changing the World Right Now,” stressing the biobank’s prospective influence on future significance in medicine [4]. The UK biobank has secured biospecimens from 500,000 people between 2006 and 2010, and has made it official that they would be supplying their specimens to researchers starting from March 2012 [5,6]. Over the years, many biobanks have been established and are moving from a phase of sample collection to provide their samples for researches. It can be predicted that biobanks will continue to greatly influence biomedical research and medical treatment in the future.

In Korea, The Bioethics and Safety Act has been completely revised to reinforce research ethics within the country and will be effective in 2013. Based on the newly revised law, it can be predicted that the number of biobanks within university-affiliated hospitals will grow. Laws pertaining to bioethics and safety encourage biobanks to reinforce ethical use of biospecimens. In addition, the law underlines biobanks’ responsibility to obtain informed consent from donors and oversight by institutional review boards. The law also encourages individual researchers to deposit and use biospecimens at any biobanks instead of collecting their own samples.

Biobanks are also included as obligatory criteria in the “research-centered hospital” program initiated by the Ministry of Health and Welfare for enhancing clinical researches at hospitals. In order for hospitals to qualify as a ministry-listed “research-centered hospital” and receive financial support from the government body for researches, they must have a biobank. This program is another reason the number of biobanks is likely to increase in Korea in the coming years.

Until now, the biospecimens collected by the KBP are provided to researchers free of charge, but do not provide samples for industrial use. However, recently, many pharmaceutical companies and venture enterprises have begun to request distribution of samples for their own research. In the future, it looks likely that the regulations will change to also provide samples to industries, though systemic changes, such as charging fees for the samples, will be necessary.

2. Major Achievements and Limitations of the First Phase of the KBP

2.1. Main achievements

The KBP was initiated in 2008 to cooperate with the National Biobank of Korea and eight biobanks of university-affiliated hospitals. The number of registered biobanks in the network has increased every year, and in 2012, there were 17 biobanks of university-affiliated hospitals, in addition to the National Biobank of Korea, as part of the network (Figure 1). The biobanks that are within the Korea Biobank Network (KBN) use the single Biobank Information Management System (BIMS) to manage information on biospecimens they collect (Figure 2). The objective of the first phase of the KBP was to collect specimens from 500,000 people and to provide samples for 500 or more research projects [1]. This objective was achieved in 2012. Specimens from 300,000 people have been collected by population-based cohorts established by the government, and the remaining specimens have been collected from 200,000 people who came to the university-affiliated hospitals [7]. In April 2012, the National Biobank of Korea opened its dedicated building, which means that a better infrastructure has been established for stable storage, management, and distribution of biospecimens for related researches (Figure 3) [8]. It has enough space to store biospecimens from 1,000,000 people (i.e., approximately 30 million vials). The National Biobank of Korea has been constructed to allow for renovation and expansion. Another achievement of the KBP is that

Table 1. Biobanks with sample sizes ≥200,000 (2010)

| Name of biobank                          | Size (age group) | Start-up cost | Chronic Disease | Infectious Disease |
|------------------------------------------|------------------|---------------|-----------------|--------------------|
| UK Biobank                               | 500,000*(40-69 yr) | $120 million | Yes             | No                 |
| Estonian Genome Project                  | ~ 1 million      | $2.5 million | Yes             | No                 |
| Icelandic deCode Biobank                 | ~ 250,000        | $212 million | Yes             | No                 |
| Kadoorie Study of Chronic Diseases in China | 500,000 (35-74 yr) | $22 million | Yes             | Some               |
| The Mexico City Prospective Study        | 160,000 (35+ yr)  | Not available | Yes             | Some               |
| The Indian National Biobank              | ~ 2-3 million (18+ yr) | $20-30 million | Yes             | Yes                |

Note. Sgaier SK, et al. (2007) Biobanks in Developing Countries: Needs and Feasibility. Science 318:1074–5 [3].
it has successfully educated and trained personnel to have a clear understanding as well as technical skills necessary for the successful management of biobanks.

2.2. Limitations
The first phase just focused on resource collection, and therefore there were not many distribution routes to researchers. In particular, the project was not able to meet the demand of researchers outside of the project. So far, samples were provided to approximately 600 research projects, but the rate of distribution to researchers outside of the university hospitals who have less access to biospecimens is comparatively less (only one in three researchers had access and utilized

Figure 1. Nationwide distribution of biobanks participating in the Korea Biobank Project in 2012. KCDC = Korea Centers for Disease Control and Prevention; NUH = National University Hospital.

Figure 2. A screen shot of the Biobank Information Management System.
samples) [7]. Therefore, in the future, it will be necessary to increase the rate of distributions to such researchers.

Another issue is that there is not enough related clinical and laboratory data on specimens within affiliated biobanks. A few of the biobanks use the electronic medical record system (EMRS) to synchronize their clinical databases with the BIMS database, but most of the biobanks are not automatically linked to the electronic medical record, and therefore, it is difficult to compile comprehensive clinical information. In addition, during the first phase, the KBP respected the autonomy of individual biobanks, allowing them to collect whatever specimens and data they had wished for, but from now on it may be more effective for the government to select and rate the most needed specimens and set goals for better coordinated specimen collection.

In the first phase, the KBP secured budgets to purchase storage facilities such as deep freezers and liquid nitrogen tanks as well as cover labor costs for the biobank personnel. However, research funding for using the collected specimens was scarce, and so it was not possible to put the gathered samples to use in researches. High-quality specimen can be collected much more efficiently when collected through research projects, which is why systemization of virtuous cycle between research projects and the biobanks would be beneficial for both parties. Specimens collected through research projects can be stored in biobanks, and therefore be available for further projects; research results can also disclose useful information on the provided biospecimens, which can then be used as secondary resources.

Another problem is that even though there have been various publicity promotions for the KBP to researchers, awareness of the KBP and the KBN is relatively low. According to an online survey on the demand for bio-resources in research (2012), only approximately 7% of the participating researchers responded that they had experience using the KBN website (http://kbn.cdc.go.kr/) [9]. Furthermore, 65.5% of the participants were not even aware that they could acquire bioresources through the KPB-affiliated biobanks [9]. This highlights that there must be constant publicity for the KBN.

### 3. Vision and Mission of the Second Phase of the KBP

The vision and mission will be the same as set in the first phase of the KBP and are as follows:

- **Vision:** “Realizing biobanks for a healthy future society”
- **Mission:** “Promoting public health through enhancing biomedical researches”
- **Objective:** “Distributing biospecimens to more than 1000 studies”

Based on the discussions, four strategies and 12 objectives were identified (Figure 4).
4. Strategy and Objectives of the Second Phase of the KBP

4.1. Strategy 1: To establish a demand-centered distribution system

4.1.1. Objective 1: To establish a one-stop distribution system

The KBN website (http://kbn.cdc.go.kr) provides its introduction, a search engine functionality, and a list of available biospecimens at the moment. However, the search function is not sufficient enough to get diverse information. Regarding the biospecimens stocked in the National Biobank of Korea, there are approximately 2000 variables of data that are linked to each specimen and it is possible to search through them by filling out certain required fields. However, it still needs to improve its efficient search function for researchers. Data gathered from the 17 regional biobanks participating in the KBN are not easy to standardize, and the BIMS has only 18 variables filled out on the form, making a search through them almost insufficient for researchers.

Furthermore, samples are distributed at both the National Biobank of Korea and the 17 regional biobanks. Researchers in need of specimens must find a biobank, contact the bank in person, and request to receive it. During the second phase, one of the objectives of the KBP is to set up an online one-stop distribution system that would allow researchers to search for resources, request, and receive specimen as well as upload the results of their research, all through a single system. In order to achieve this, each biobank in the network must compile standardized data on their biospecimens according to the condition or disease the specimens pertain to. In addition, a center for biospecimen distribution must be set up to manage operation, coordinate requests, and connect researchers to the biobank, so as to allow them to get what they need.

4.1.1.1. Execution plan

- Develop an online portal for a demand-centered distribution: (1) improving database creation and search function through standardization of biobank specimen information; and (2) developing an online system to register requests for specimen distribution, view distribution confirmation/denial status of the requested specimen, and upload research results.
- Create distribution centers to better coordinate distributions of biospecimens by the 17 affiliated biobanks: (1) developing a single unified distribution system aided by professional coordinators with whom researchers can consult; and (2) developing objective distribution policies and a standardized distribution manual for a more fair and synchronized process.

4.1.2. Objective 2: To revise process and regulate distribution of biospecimens

At present, the KBP does not supply specimens to the industrial sector, but there have been requests for specimen distributions from various industries. Thus, in the second phase, the KBP will begin distribution of biospecimens to pharmaceutical companies and medical

Figure 4. Framework of the strategic plan for the second phase of the KBP.
industries. Because the amount of specimens requested by industries is relatively larger than other research projects and there are a lot more requests in general, it is difficult to distribute specimens to industries free of charge. Therefore, the policy for industrial distributions should include a fee.

It is also necessary for them to be a quicker process so as to aid in decision making of distributing biospecimens. Currently, there is a monthly committee meeting that deals with matters related to its distribution, but some less significant matters, such as simple period extensions at the time of research, use of distributed resources, or requests for additional data should be judged in a faster and simpler process. It will be necessary to introduce a simpler and faster working judging panel for less serious matters. Although biospecimens are only distributed to funded research projects at this time, there is an increasing demand to approve distribution of biospecimens to pilot studies that are without research funding.

4.1.2.1. Execution plan

- Improve policy for simplification of the distribution process: introduction of a simpler and faster working judging panel for less serious matters regarding the distribution of biospecimens.
- Promote policy for a larger distribution base: (1) extending the scope of distribution to pilot studies without research funding; and (2) enlargement of sectors including pharmaceutical and medical companies.

4.1.3. Objective 3: To expand types of biospecimen distribution

The National Biobank of Korea has stored specimens including DNA, plasma, serum, urine, whole blood, lymphoblastoid cell lines (LCLs), etc. of each donor. Currently, only DNAs are distributed. Because the DNA for distribution purpose is mounted on an automated working bank, so the DNA can be easily distributed. The other reason is that the policy decision for distribution of plasma, serum, urine, or LCLs has not yet been made. By contrast, many researchers are requesting that these resources are distributed extensively, and therefore a plan to allow such distributions must be formulated.

4.1.3.1. Execution plan

- Expand distribution of human biospecimen items from only DNA to plasma, serum, urine, and LCLs: (1) establishment of plans to distribute biospecimens other than DNA such as serum, plasma, urine, and LCLs; and (2) program for automatic working of serving information on plasma, serum, urine, etc.

4.2. Strategy 2: To secure and utilize high-value bioresources

4.2.1. Objective 1: To produce a panel of high-quality biospecimens

The National Biobank of Korea and regional biobanks participating in the KBN prepare data based on a request by a researcher and provide information he or she requested. In addition, a panel, immediately possible to use, can increase the utility of bioresources. Some researchers requested panels related to biospecimens and information analyzed with its previous use. For example, in the case of distribution of LCL, some researchers want to get preanalyzed genotype data together. Accordingly, it needs to produce a panel connected to supplementary data having clinical, epidemiological, and genetic information prior to providing them. It is also possible to produce a panel of DNA, plasma, serum, urine, etc. from a population considered “healthy.” Furthermore, biospecimen panels of case and control of target diseases in cohorts will be utilized efficiently. If a panel is produced by sets of clinical information on a whole set of biospecimens—serum, plasma, urine, cancer tissue, and DNA—of a patient, the quality of the biospecimens will be improved. Therefore, there is a need to survey the demand of researchers, and then the National Biobank of Korea can provide state-of-the-art information to researchers.

4.2.1.1. Execution plan

- Utilize bioresources through a production of resource panel: (1) production of biospecimen panels having both personal information, such as tissue, plasma, serum, urine, and DNA, and clinical information; and (2) production of a panel in the level of cohort including target diseases or conditions between patients and control group.

4.2.2. Objective 2: To establish disease-collection system of specific biospecimens

During the first phase of the KBP, the collection of biospecimens in regional biobanks was centered on tissues, including solid cancer tissues, and collection of biospecimens from patients with highly prevalent diseases; however, there is not enough collection of tissues from patients with rare diseases, which individual doctors may find difficult to collect on their own. Such specimens must be collected through research projects or by establishing a network of medical doctors who specifically work with those diseases. In addition, certain biobanks should be registered as specialized...
banks to secure specimens that are usually difficult to collect in each hospital.

4.2.2.1. Execution plan

- Establish systemic methods to collect biospecimens related to rare diseases: (1) selection, categorization, and collection of specimens obtained from patients with rare diseases; and (2) establishing a network of medical professionals working with rare diseases or collecting rare-disease bioresources through research projects.
- Select and run specialized biobanks: establishing specialized biobanks focusing on the collection of certain bioresources that are difficult to find.

4.2.3. Objective 3: To revise BIMS for disease collection of specific biospecimens
The current BIMS is developed to generate ID numbers for each sample and then ask for information related to the sample to be inserted. However, the system needs to be improved to make it easier for long-term follow-ups on donor patients, whose information has been collected at periodic intervals, including information needed to fulfill Objective 1 and Objective 2, described previously. The BIMS must be made flexible, which allows for the customization of necessary clinical information according to the disease, and to allow for a long-term informational follow-up on patients.

4.2.3.1. Execution plan

- Improve the functions of BIMS: (1) enhancing the function of BIMS to be able to insert and manage information on resources will that need long-term tracking, information on specialized biobanks and their resources, as well as specific information on resources for certain diseases; and (2) development of a program to automatically synchronize clinical information of EMRS with BIMS.

4.3. Strategy 3: To advance a resource management system

4.3.1. Objective 1: To develop and operate a standardized resource management system
In the case of biobanks within the KBN, each biobank creates and uses their own standard operating procedure (SOP) according to the policy formulated by the KBN. However, biobanks have been asserting the need for developing a common SOP that biobanks can refer to. Although efforts have been made to develop a SOP, this task has not been completely fulfilled. In the future, there should be development and application of a common SOP that comprehensively compiles research results conducted up until now, as well as collects and stores resources, performs quality control, adheres to safety regulations, and secures personal information for privacy protection. In addition, international standards on resource management should be introduced [e.g., the International Society for Biological and Environmental Repositories’ (ISBER) Standard Pre-analytical Code (SPREC)] in order to provide information related to the processes of resource collection, storage, and quality control.

4.3.1.1. Execution plan

- Develop and apply the SOP: (1) introduction of an SOP according to the type of specimens and stage of management; (2) assigning SPREC to the National Biobank of Korea and other biobanks according to resource management and BIMS application; and (3) enhancement of training program for workers in regional biobanks on SOP.

4.3.2. Objective 2: To introduce a biobank certification policy
At present, the KBN-affiliated biobanks submit a yearly plan as well as a report of project results. The results, which are reviewed and evaluated, are used to decide the amount of government funding needed for the biobanks. However, the current evaluation methods are usually based on the amount of resources collected, the degree to which the biobanks are managed ethically, and the manner in which the biobanks are run. At this point, there are no direct assessments on actual resource collection, storage, and quality control. Evaluation is mainly based on the written reports submitted by the biobanks. Accordingly, an external quality control program should be introduced, and the quality of the biobank should be improved through a biobank certification process, which is evaluated through a peer review process. This certification process should later be extended to all the biobanks within the country, including those that are not part of the KBN.

4.3.2.1. Execution plan

- Establish external quality control policy: (1) establishment of a quality control committee and an external quality control program; (2) evaluating quality controls at individual biobanks; and (3) proficiency testing for biobanks regarding quality control.
- Execute biobank certification policy: (1) biobank certification policy evaluating the skill of the professional, operation of biobanks, privacy protection of donors, etc. should be implemented.

4.3.3. Objective 3: To strengthen collaboration with biobanks around the world
Since the 1990s, various countries around the world have been establishing large-scale biobanks. Approximately 70% of the biobanks are stand-alone, and 30%
are partnership banks. Internationally, many different biobanks are being established and there has been an increase in the number of cooperative research projects between biobanks across nations. At present, there are various standardizations such as the ISBER, Public Population Program in Genomics, and Biobanking and Biomolecular Resources Research Infrastructure for cooperative research projects. For the KBN to grow as an international biobank, there must be cooperation with other international biobanks.

4.3.3.1. Execution plan

- Encourage publicity for the KBP and efforts to increase international credit: (1) active publicity for the KBP; and (2) developing promotional materials (English leaflets, English website, or promotional videos).
- Collaborate foreign biobanks through a memorandum of understanding: (1) researcher exchange training; and (2) research cooperation, joint symposiums, etc.

4.4. Strategy 4: To systemize R&D biobanks virtuous cycle

4.4.1. Objective 1: To plan R&D-based human biosources collection and utilization

In the first phase of the KBP, biobanks focused on securing basic facilities, such as purchasing resource storage equipment as well as securing labor costs and management costs. Although research and development R&D funds for research that utilize the biobank resources were sought, they were not approved, which is why the collected biosources could not be fully utilized. However, such funds are necessary because more high-quality resources are secured through research, which increases the interest and participation in research among clinicians that allows for the gathering of high-quality resources with more information. Therefore, in the second phase, more researches that better utilize the current specimens will be planned, and more efforts will be made to secure necessary funding. In addition, there will be more R&D projects that support clinicians, so that it will be possible to gather resources with more information. For example, the National Biobank of Korea has collected and stored specimens from the National Health and Nutrition Examination Survey as well as from various cohorts to study chronic diseases, but there are not enough research funds for the researches to use these biosources. Therefore, it is necessary to find or develop more research projects and funds for the research projects in which these resources can be utilized.

4.4.1.1. Execution plan

- Plan and execute R&D research projects to better utilize specimens (biosources) stored in the KBN: (1) developing a plan for research projects that can make use of the regional biobanks’ specimens; (2) identifying funding source and subsequently securing funds for research projects that can make use of the specimens in the National Biobank of Korea, obtained from various cohorts and the Korea National Health and Nutrition Examination Survey; and (3) creation of high-value resources through attaching related research results to already existing specimens by making submission of research results using distributed specimens mandatory.
- Secure biosources through planned R&D projects: finding and funding planned R&D projects to collect biospecimens with information.

4.4.2. Objective 2: To co-plan and co-execute national-level research projects

There are many national-level research projects using biosources, but there is no official integration system that connects these national projects to the KBN. Large-scale national researches usually have their own systems of acquiring resources, so it may help to co-plan such research projects and use the biosources from the KBN to make way for prospective biospecimen collection.

4.4.2.1. Execution plan

- Establish a collaborative system with current national-level research projects: (1) collaborate with the National Research Foundation of Korea and the Korea Health Industry Development Institute to plan research projects that use biosources in the KBN; and (2) establishing prospective collection and provision of biospecimens to national-level research projects through the KBN.

4.4.3. Objective 3: To establish and execute public relations centered on possible consumers

Researchers are both the consumers and providers of the biosources. However, because many researchers’ awareness and interest in the KBP and the KBN are relatively low, collection and distribution of resources are still not completely established. Therefore, it is necessary to raise more awareness about the project and encourage participation and resource utilization. In addition, publicity directed toward the public is necessary to raise awareness and educate on the need for donating biosources.

4.4.3.1. Execution plan

- Establish advisory board for publicity: (1) establishment and operation of advisory board for publicity and systemic publicity schemes for the maximization of efficacy.
- Enhancement of publicity for experts: (1) operation of publicity booths at academic conferences and
presentation of research results related to biobanks; and (2) publicity through related portals, such as the Centers for Disease Control and Prevention website.

- Develop a publicity method directed toward the public to encourage donations: publication and distribution of promotional materials aimed at patients visiting hospitals.

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