**Challenges and Framework of the Taiwan Biobank in Returning “Incidental Findings”**

*Abstract*

**Background:** Due to ground-breaking developments in medical imaging techniques, researchers and biobanks are expected to encounter clinically relevant incidental findings (IF) more frequently. The World Medical Association *Declaration of Taipei* (2016) also highlights the possibility of encountering IF and requires research on biospecimens from stored in biobanks addressing their feedback policies in their informed-consent process. This development demonstrates that the issue of IF has become a global and pragmatic issue in bioethics governance. Nevertheless, law and practice in Taiwan have not responded to this issue in a systematic way. Thus, there is a need for a change.

**Discussion:** This article will first briefly illustrate the essence of IF and the obligation and disputes of returning IF. Second, the difficulties and challenges associated with returning IF will be discussed. Third, reflections and the corresponding measures should be made on Taiwanese current regulations and practice. A workable and ethical framework on the return of IF needs to be built according to each research project and the unique features Taiwanese biobanks (e.g. size, research scope, resources and funding, etc.), as the researchers involved in these research projects cannot wait passively for governmental regulations. Thus, establishing an endurable and horizontal connection among biobanks and clinical institutions within the health care system of Taiwan is recommended since working separately may be not only risky but also a waste of time and resources. Thus, in order to comply with law and fit with current trends, we provide an overview of contemporary concerns over the return of IF, and then propose a framework for the Taiwan biobank, based on a limited responsibility to disclose.

**Summary:** By drawing upon their own experiences and knowledge about research using biospecimens, the Taiwan biobank can implement a standardized practice on the return of IF that will provide better and more comprehensive protection for their rights of participants.

**Keywords:** *bioethics; biobanks; incidental finding; altruism; individual feedback; re-contact; reidentification; ethic governance; ethics, legal, and social impact; the WMA Declaration of Taipei*.

**Background**

Advances in medical technology are always associated with on-going ethical debates. As a result of recently developed medical technologies and methods, researchers (secondary users) using biospecimens from biobanks have a greater chance of encountering incidental findings (IF) more frequently then they have done in the past.1-2 However, the IF addressed in this paper are not unexpected breakthroughs or exciting findings in medical field. Rather IF in this context raises issues regarding the responsibility of researchers on returning potential and important health information to participants.3

How to effectively treat cancer is a critical issue that every country around the world urgently needs to face. To this end, the national academy of Taiwan - Academia Sinica and the National Cancer Institute (NCI) signed a memorandum in 2016 to join “Cancer Moonshot 2020”, which was proposed by US President Obama in January 2016. The goal of this collaboration is to accelerate the process of cancer-related prevention, diagnosis, and treatment from 10 years to 5 years. The Taiwan Biobank, established under Academia Sinica, will work with biobanks found in many other countries to use new strategy of Proteogenomics to conduct large-scale analysis of cancerous models. It will also help to understand the mechanisms of cancerous diseases and accelerate the implementation of new guidelines for precision medicine. In addition, the Taiwan Biobank is a member of “The Public Partnership Project in Genomics and Society (P3G)”, which is an international nonprofit consortium dedicated to the development and management of multi-disciplinary policy infrastructures and research consortia.

Since 2012, the Taiwanese government has funded the Taiwan Biobank to establish national genetic data of Taiwanese people. The Taiwan Biobank plans to conduct both a large-scale community-based cohort and several patient cohorts on local chronic diseases from medical centers (the hospital-based cohorts). The community-based cohort study plans to recruit 200,000 volunteers between 30 and 70 years of age with no history of cancer, and the hospital-based cohort study will recruit 100,000 patients affected by the most common chronic diseases in Taiwan, including lung, breast, oral cavity and colorectal cancers, hepatitis, cardiovascular disease, diabetes, chronic kidney disease, stroke, Alzheimer’s disease, endometriosis, and asthma. The establishment of the Taiwan Biobank is an incredible resource for biomedical research, and can help shed light on the complicated relationship between genes and environmental factors in disease causation. Thus, these studies will enable the Taiwan Biobank to identify the disease-causing factors and mechanisms of common diseases to facilitate the development of better treatment and prevention, reduce the cost of medical treatment and make it possible to achieve the goal of improving our nation’s health. Furthermore, the Taiwan Biobank has long-term tracking and comprehensive data, integrating high-quality medical resources, such as the National Health Insurance system. At present, the Taiwan Biobank has 100,229 cases of volunteers and 19,642 cases of tracking patients.

 However, to date, the "Act on Human Subjects Research (2011)”, and the "Human Biobank Management Act (2012)” still do not explicitly address the issue of returning IF in Taiwan. Even the 2013 “WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects” did not discuss this issue. The pace of development of biomedical technology and the corresponding ethical governance are well beyond the reach of external individuals, political departments or legal norms. Therefore, it is necessary that relevant research institutions actively raise problems, rather than passively wait for external governance or even deliberately ignore related issues.

In October, 2016, the World Medical Association (WMA) released the “Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks”. In point 4 of Article 12, the Declaration requests that “if the data or biological material are collected and stored in a Health Database or a Biobank for multiple and indefinite uses, [informed] consent is only valid if the concerned individuals have been adequately informed about the procedures for return of results including incidental findings.” 4 Thus, the return of IF raised a big concern throughout the biobanking research system on how any such obligations might apply to users of biobanks. The feedback procedures such as assessment, re-identification, and re-contact should be implemented in the informed consent form of Taiwan Biobank.\*

This paper describes a new implementation framework for the return of IF to participants, based on our experience developing a feedback policy for imaging and genomic research at the Taiwan Biobank. Our framework is suited to similar personalized research projects, though it may offer a practical guideline to any research project or biobank for returning IF. Note that this paper does not aim to resolve the debate over what types of information should return to participants. The practices of returning IF still remain complex, as extensive variation exists among jurisdictions and research contexts and disagreement persists over whether or not researchers have an obligation to return IF. Thus, in this paper, we will first briefly discuss obligations and disputes for deciding if information should be returned in the context of a population-based biobanking research system. We will then discuss the difficulties and challenges when returning IF is put into practice. Finally, this paper will describe how the corresponding measures and policies will be implemented within the Taiwan Biobank for returning IF.

**Discussion**

**Most current practices do not return “incidental findings”**

First and foremost, it is quite legitimate to ask: “Should users of biobanks bare responsibilities to inform medical information of IF to participants?” The debate has spanned this issue from recommending limited disclosure all requested information through clinical/medical research.5 When an informed consent is a broad consent, the consent has been obtained for unspecified future research. Participants have no way of knowing whether their biospecimens have been released or tested. 6 Thus, it is difficult to exercise their rights to request relevant information. In fact, most European and U.S. human biobanks currently do not return any research results, including incidental findings; however, this trend is changing.3,7 For example, in All of Us, the UK Biobank imaging pilot project has already started to offer feedbacks of IF, and will involve re-identification and re-contact of participants in an existing anonymous state.\* However, the procedure of returning IF will result in an increased cost of research budgets; thus, it makes users less interested in the return of IF. The aim of biobanks is to promote health and wellbeing at no individual cost or risk.23 Thus, if a delayed treatment of a participant is caused by the policies of non-return of IF, it will undermine the public’s trust in these institutions and and will lose public support on the question: “why set up a biobank?" In turn, it will also affect the willingness of participants to provide biospecimens to a biobank.8 In fact, regardless of whether the result of IF is positive or negative, a study showed that most people were still willing to know relevant personal health information.9 Therefore, it is imperative and ethical that there are feasible procedures and arrangements associated with returning IF.3 The current discussion of this issue usually revolves around “establishing standards for assessing the return of IF” and “arranging appropriate feedback procedures of IF”, rather than addressing the issue of whether to inform or not.

**Conditions of returning “incidental findings”**

Based on the limited obligations of users for returning IFs, the following three conditions, as the current cumulative consensus, should be followed: (1) decisions associated with returning IF must be made based on validity; (2) procedures for returning IF must be established for a substantial risk; and (3) returning IF must be expected to be of clinical significance and actionable meanings to a serious health of participants.10-12 However, these three issues are still worth discussing.3

First of all, full compliance with ethical, legal, and social implications in informed consent is not always justified.24 In the informed consent; thus, “agree to be informed IF in advance” might constitute an ethical issue, with respect to the autonomy of participants.1 However, even when all of the three above-mentioned conditions are fulfilled, it means that users has already fallen into an ethnical risk of practice before validation of the findings. The ethical principles, such as “beneficence”, “reciprocity” and “respect for persons”, constitute a strong ethical responsibility and obligation for users to return IFs. The nature of these ethical principles do not establish in consolidating autonomy of participants, but accomplish the obligation of users on returning IFs. Therefore, it would definitely be the right thing to do for users of biobanks to fulfill their ethical obligations to inform IF to participants.12

Second, the context of “a potential and serious risk to participants” should be defined clearly,11 especially when it is of reproductive importance. The research team led by the University of Minnesota, in their consensus paper of 2008, considered that some IF of reproductive importance should be included to offer feedback to participants; however, in their 2012 report, they debated that reproductive importance does not reach an agreement in the“must return” category, so it should put in the“should return” category.12,13

Third, the current procedural guidelines for the return of IF in an informed consent are not often followed. With the different sizes, attributes and social environments of various biobanks, the guidelines should remain somewhat flexible, but the establishment of general guidelines can save the cost and risk of individual biobanks.3 However, studies have reported that the actual operators of many European biobanks state that the guidelines should be more specific, or they will be too abstract to define criteria of“must return” and “should retrun”.7 In addition, the ambiguity of guidelines can also easily lead to different standards for returning IF among different biobanks, resulting in a big mess.7

**“Limited obligation” for returning of “incidental findings”**

In the discussion of biomedical ethics in Europe and North America, the guidelines have gradually formed a consensus of “limited obligation” for returning IFs.1,11,13 The limited obligation is based on the ethical principles of “beneficence,” “reciprocity,” and “respect for people.”12 First, returning might indeed personally benefit participants, especially in clinically urgent circumstances, but biobanks can also operate under the assumption that it is a privilege for participants to contribute to public health, as altruism. Many arguments against providing feedback to the individual participant are based on “altruism.”23 The main reason for this is to avoid the ethical considerations for selling human samples to biobanks. However, for example, in Taiwan, after the passage of “Regulations of Benefit Sharing for Commercial Use of Human Biobanks”, it is legal of establishing any commercial use of biobanks in Taiwan. Compared to it, receiving feedback to avoid major health risks for participants seems even more legitimate rather than being profitable.

Whether it is an external normative prohibition, or a decision made on the level of individual biobanks not to inform the participants might create serious ethical issues, as we discussed previously.3 A recent trend in research is to respect participants and view biomedical encounters as a research partnership. 13 It is generally believed that the principle of reciprocity is very important for the establishment of mutual trust. The implementation of reciprocity can balance the existence of a stable relationship of trust and support among users of biobanks and participants.15

In the “Universal Declaration on Bioethics and Human Rights” published by United Nations Education Scientific and Cultural Organization (UNESCO) in 2005, In Article 15(1) advocates that benefits resulting from any scientific research and its applications should be shared with the whole society and the international community. In addition, Article 15(2) further advocates that such benefits should not form “improper inducements” for research participants. However, many scholars have argued that the principle of reciprocity under the context of biomedical research not only benefits a “group”, but also may be inferred to benefit an “individual”.16 In addition, as far as UNESCO's official information is concerned, there is no further explanation to define “inappropriate.”17 Meanwhile, it should be noted that in Article 15(1)(i) benefits may take special and sustainable assistance to the groups and individuals that have participated in the research. Obviously, it is clear that not all positive benefits are "improper." An individual should not be excluded from the feedback of IF. In other words, the personal benefit of receiving IF does not violate ethical requirements.

In brief, the study of the focus group as an empirical method also pointed out that when there is the use of personally-provided biospecimens in medical research, the public generally has a strong awareness of the right to know the result.18-19 The study indicates that such feedback is indeed attractive, and may change the general public’s decision to participate in a biobanking research. Furthermore, it is impossible to determine if the return of IF will become an act of exploiting or infringing any vulnerable groups or individuals. Thus, there is no reason to prohibit the research results from returning IF to a particular individual, or to conclude it as categorically ambiguous for ethical standards applying in the context of a particular situation.

**Difficulties for returning “incidental findings”**

1. **Procedure of returning “incidental findings”**

The procedure for the return of IF can be divided into three steps: (1) assessment: to assess whether returning IFs is necessary; (2) re-identification: de-identify and later re-identify the participant's identity; (3) communication: to notify participants and, in some cases, their families.11

However, such a logical and sound arrangement actually has its difficulties in practice. For example, in the first-step of assessment, the participant might not want to be informed of IF.20 To solve this problem, we can design a specific code to the participant who is willing or unwilling to accept the feedback (the person who is willing to be xxxxx-1, the person who is unwilling to be xxxxx-0). The code (1 or 0) can tell whether the return of IF process should be continued.11 In addition, we can also set up trusted intermediary to secure more private information.6

1. **Difference between Clinical Practice and Research**

Most research using materials from biobanks is quite different from clinical care. This gap not only makes it easy for the users of biobanks to ignore the clinically meaningful information, but also creates a problem of how to “interpret” the IF. Most participants do not have a background in medicine; thus, if there is misinterpretation of IF, it might cause the research participants’ psychological, social, and economic harm.21

To solve this problem, biobanks must secure the help of health professionals (such as general practitioner (GP) or family physicians) to assist in the return of IF; however, in some countries, this solution also has practical difficulties. For example, in Taiwan, there is no family physician healthcare system for integrating research and clinical resources. Generally speaking, it is better for biobanks to cooperate with relevant hospitals to form a consulting team; or provide medical information to participants for further medical diagnosis or treatment.7

1. **Funding problem**

Returning of IFs is very costly: from the process of assessment whether there is a need for returning IFs, re-contacting the original sample provider, and hiring consultants. But most of the users of biobanks do not have a portion of their budgets allocated for this purpose.7 In addition, IF has high degree of uncertain probability for allocating the budget. Therefore, it increases the difficulty of raising funds and might affect the biobanks research goals.

One possible approach to this problem is that the fees can be borne by participants. According to a study, a participant can expect to pay about $445 for returning IFs.22 This approach allows direct beneficiaries to spend more than other non-beneficiaries, but reduces the idle costs of biobanks. However, under principles of "beneficence" and "reciprocity", these fees should not be fully borne by participants. Thus, another possible approach is funded by the National Health Care System. In the case of returning IFs, the results are able to reduce public health expenditures; thus, it is reasonable to fund returning IF to individual participants, as a part of health care.

**Taiwan Biobank's Reflections and Framework**

In Taiwan, the regulations do not explicitly address the issue. The current legal system in Taiwan and the most directly relevant legislation for returning IFs should be the "Act on Human Subjects Research," (2011) which regulates specific research projects and the "Human Biobank Act" (2012), which regulates the collection, storage, and release of human biological specimens. However, these Acts have not dealt with the issues of Ifs as part of the research output. However, according to the "Personal Information Protection Act" (2015), in Article 3, participants may request the following: (1) inquiry or read; (2) a duplicated copy; (3) add or modify; (4) stop collecting, processing or utilization; (5) delete. However, in the “Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks”, the procedures for return of results including IF should be implemented in an informed consent to give IF information to participants in order to protect participants’ best interests, and resolve the dilemma of ethical obligations and legal responsibilities of IF.

At present, in Taiwan, 30 biobanks have been established and registered in accordance with the law, 24 and most of them use the template of informed consent provided by the Ministry of Health and Welfare in Taiwan, which does not include a return of IF. So far, only the biobank of Hualien Tzu Chi Hospital incorporates returning IF procedure in their informed consent. Taiwan Biobank is a national biobank funded by the Taiwanese government. The informed consent form of the Taiwan Biobank only lists whether a participant is willing to receive the physical examination report. However, it does not include a return of incidental findings. Thus, the Taiwan Biobank, the largest population-based biobank among 30 biobanks established in Taiwan,should set up general criteria, or develop consensus-generating procedures in the Taiwanese research community

First, for returning IF related to imaging, we realize that the UK Biobank also does not inform participants of the measurement results in the past. However, in the image pilot study of the UK Bank, based on their past experience, about 2% of participants have an abnormality that a radiologist agrees is potentially serious. Therefore, for imaging scanning, the UK Biobank later decided to inform participants of IF that could have a major effect on participant’s body functions or quality of life, or could be life-threatening. The radiographers mainly look at the images to ensure their quality, rather than look into any evidence of health problems. However, if the radiographers find a serious and unusual problem, they will pass along the image to a radiologist for review. If the radiologist also determines that it is a serious abnormal problem (regardless of whether it can be treated), the relevant procedures will be arranged within a few weeks. The radiographers will inform participants of the relevant abnormal problems and will contact the participants’ GP (general practitioner). However, there is often no GP or family practitioner in the Taiwanese health care system. Thus, once IF are identified, the Taiwan Biobank will contact the participant and refer them to see a specialist doctor for review.

Second, for the returning of IF related to genomic research, the next-generation sequencing technique massively parallel or deep sequencing as it first reads the short reads and then uses information technology to assist in the short-segment fragmentation and recombination to obtain the entire genome sequence. Thus, in addition to the relative increase in sequencing speed, the sequencing costs are greatly reduced. The probability of IF for a genetic disease will also increase dramatically. On March 22, 2013, American College of Medical Genetics and Genomics (ACMG) published a proposal entitled “ACMG for Accidental Discovery in Clinical Exons and Gene Sequencing”, which suggested that genetic professionals had extensive opinions on accidental findings.\* On one hand, the genetic libertarians believe that participants have the right to obtain sufficient and complete genetic information and their risk of diseases that may occur, and even the significance of new and unknown genetic diseases. On the other hand, genetic empiricists have expressed different opinions that the penetrance of most mutant genes is still insufficient for the pathogenic evidence. For example, a person with a disease-causing gene mutation may not always develop the disease, which often occurs in familial cancer. In addition, reduced penetrance may be related to many factors such as genes, environment and lifestyle, and there are still many factors that are still uncertain. Therefore, they believe that returning IF to participants might cause a psychological burden, making the participant feel as though they are "a patient in waiting". ACMG recommends a balance point between these two opinions to allow participants to obtain health benefits from the notification of mutated genes.

More recently, National Health Research Institute (NIH) launched the All of Us Research Program. on May 6, 2018. Participants are made available through participants' portals or a paper-based method. Educational information is also provided. Information on medical action obtained from physical examinations, including blood pressure and heartbeat, is sometimes flagged as emergency or urgency, and the staff will immediately advice participants or refer their biological sample analysis to a doctor. The results of the genome can be accessed by the participants and reviewed by Institutional Review Board (IRB). On the whole, the provision of access for results is still not yet clear, but it is in the direction of positive planning

Participants have the right to choose to know about the IF arising from their biological data and use this information to improve their health. However, participants do not have enough knowledge to interpret these findings—especially when they involve hereditary diseases caused by the genes. Although some studies have found that most people want to know relevant health information, some researchers think negative information may cause psychological harm or social risks for the participants. For example, only 15% of participants want to know if they have a gene disorder for Huntington disease.\* In practice, biobank research systems always include IRBs to examine these conditions. However, we agree that IRBs should not have the responsibility to assess the risks and benefits of returning individual IFs encountered in genomic research.\* Members in IRBs might not have enough clinical and scientific knowledge to assess IF arising from genomic research. Researchers, on the other hand, are more likely to have the expertise to assess IF. Therefore, the Taiwan Biobank currently does not provide IF of genomic research to participants. In the future, the Taiwan Biobank will form a clinical advisory committee including clinicians and psychologists to review IF arising from this kind of research on a case-by-case basis.

In brief, from the UK Biobank to All of Us research program, these programs show that the current trend of IF, the international trend seems to be no longer absolute not, but with a flexible approach to the relative issues.

**Summary**

Human biobanks ensure the large-scale and long-term collection of biological data for future research and development. However, in the post-genome era, personal biological or health information is gradually gaining attention as personal privacy information. We believe that, after sampling, biobanks that do not offer feedback to participants do not conform to current international IF trends.We should adopt a more flexible method, giving the general public and research participants appropriate health protection.

The “Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobank” recommends implementing procedure of returning IF into the informed consent, ensuring that the return of IF is gradually integrated into global ethical norms, as a trend. Although there is no clear instruction, researchers and biobanks should now consider changing from procedures of informed consent, communication, and to even resource allocation for "how to deal with the issue of a return of IF".

　　The active role of researchers and biobanks in the ethical governance of biomedicine is undoubtedly revealed. However, none of the official guidelines answer how to deal with a return of IF in Taiwan. If biobanks in Taiwan just ignore the issue and only follow the template given by the competent authority, they will ultimately confront a big crisis of public trust and support. Strictly speaking, it will also ruin the original intention of legislators to authorize various ethics committees in the field of biomedical science in Taiwan.

Of course, autonomy comes at a price. From the study of Ethical, Legal and Social Implications (ELSI) to the willingness of researchers and biobanks to implement compliance, it needs to invest a lot of resources to change the current situation. At this time, the development of the horizontal link among biobanks and medical institutes through the sharing of resources and exchanging of experiences can reduce the cost and risk associated with the return of IF. Furthermore, it is still necessary for the state (from legislative, executive, judicial, and even supervisory powers) to revise legislation or clarify the standards of legal interpretation in line with international ethical norms.

Returning of IF must integrate resources drawn from research and biobanks. How this will be done depends, to a large extent, on the object of research, funding sources and attributes of different researchers and biobanks. Therefore, it is difficult to enforce the mandatory provisions of the law. However, in the Taiwanese context, “National Health Insurance,” and the plethora of resources accompanying it, has the potential to support the expenses required for returning IF, as a part of health care, for raising health benefits of not only participants but also the rights of citizens.