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Mini Review

# Managing “incidental findings” in biobank research: Recommendations of the Taiwan biobank

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ABSTRACT

**Background:** In this article, incidental findings (IF) refer to unforeseen findings made possible through biobanking research and advances in medical diagnostic technologies that raise issues regarding the obligation and/or responsibility of biobank-users and biobanks to return clinically significant information to participants. The World Medical Association (WMA) Declaration of Taipei (2016) highlights the possibility of encountering IF and requires that research on biospecimens address biobank feedback policies in their informed consent process, leaving open the possibility that the policy may be “no return”. As clinicians and researchers begin to use these “resources”, the possibility of finding clinically significant IF is becoming a reality.

**Discussion:** In line with the WMA's Declaration of Taipei, a pragmatic approach is needed to deal with the issue of returning IF in biobank governance. Indeed, the impacts and concerns associated with the return of IF differ across different stakeholder groups and jurisdictions. Therefore, the framework governing IF return needs to be custom-built, taking into account the nature of each research project and the unique features of biobanks. To this end, in addition to facilitating biobank transparency, establishing an enduring and horizontal connection among biobanks and clinical institutions under a public health system will improve efficiency and effectiveness. Hence, subject to contemporary Taiwanese ethical and/or legal regulations, this article argues for the establishment of an updated framework for imaging-related and genetic-related IF return within the Taiwan Biobank (TWB), mainly based on a limited obligation to disclose life-threatening information revealed by imaging, but not genetic information.

**Summary:** After discussing some of the ethical, legal and social issues encountered by the TWB and accounting for the experiences of other international biobanks, we propose a systematic framework for returning IF, mainly on a “limited obligation” basis, which offers better and more comprehensive protection for biobank-participants' rights and health.

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Abbreviations: IF, Incidental Findings; WMA, World Medical Association; GP, General Practitioners; GNC, German National Cohort; UNESCO, United Nations Education Scientific and Cultural Organization; TWB, Taiwan Biobank; ESC, European Society of Cardiology; EGF, Ethical Governance Framework; P<sup>3</sup>G, Public Population Project in Genomics and Society; NHI, National Health Insurance; NIH, National Institutes of Health; MRI, Magnetic Resonance Imaging; IRBs, Institutional Review Boards; ELSI, Ethical, Legal and Social Implications.

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## 1. Background

Advances in medical technologies are always associated with on-going ethical debates and legal challenges. As a result of recently developed medical technologies and methods, researchers or secondary users that draw upon biospecimens from biobanks (hereinafter referred to as “biobank-users”) have a greater chance of encountering incidental findings (IF) more frequently than they have done in the past [1,2]. However, the IF addressed in this article are not unexpected breakthroughs or exciting findings in the medical field, which have been defined in previous literature as information relating to “...an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study...” [3]. Rather, IF in this context refer to clinically significant information made possible through biobanking practices and evolving medical diagnostic technologies that raise issues regarding the obligation and/or responsibility of biobank-users and biobanks to return potentially important health related findings to participants [4].

To this date, the “Human Subjects Research Act (2011),” and the “Human Biobank Management Act (2012)” of Taiwan have not yet explicitly addressed the issue of returning IF [5]. Neither has the 2013 “World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.” Obviously, the rapid development of biomedical technology and the ethical governance that accompanies it are well beyond the reach of external individuals, political departments or legal norms. Therefore, it becomes an unavoidable necessity for relevant research institutions to actively identify and address problems, rather than passively wait for external governance or even deliberately ignore ethics-related issues. Nevertheless, in point 4 of Article 12, the 2016 “WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks” 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.” [6] More specifically, the WMA Declaration of Taipei provides the ethical directive that participants must be informed of the procedures for the return of IF if consent is to be valid [6]. Hence, this would guide researchers or biobanks in protecting participants' best interests, while also resolving the dilemma of ethical obligations and legal obligations/responsibilities of returning IF.

This article, taking into account the Taiwan Biobank (TWB)'s seven years of experience in processing medical imaging and genomic data, tries to propose a feedback policy, together with a systematic approach for the return of IF, that might fit with the guidance of WMA Declaration of Taipei, mentioned above. It should be noted that this article does not aim to resolve all the ethical and/or legal debates over the obligation to return IF. This is because the practices of returning IF remain complex, as extensive variation exists among jurisdictions and research contexts, and disagreement persists over whether or not researchers and biobanks are obligated to return IF. Thus, in this article, ethical issues

and logistical difficulties surrounding the return of IF encountered by biomedical researchers in Taiwan will first be reviewed in a general way. Then, current trends regarding the return of IF will be compared with international initiatives in this area so as to substantiate the main arguments about the IF return policy. Finally, a governance framework for the return of IF proposed by the TWB is introduced. This framework is meant to better and more comprehensively protect biobank-participants' rights and/or benefits by taking the equitable principle that underpins Taiwan's national insurance program into consideration.

## 2. Discussion

Since 2012, the Taiwanese government has overseen the project of the TWB under Academia Sinica to collect national genetic data of Taiwanese people [7]. The TWB plans to conduct a large-scale population-based cohort and several clinical-based cohorts on local chronic diseases from medical centers across the country. The population-based cohort plans to recruit 200,000 volunteers between the ages of 30 and 70 with no history of cancer, and the clinical-based one will recruit 100,000 patients of the most common chronic diseases in Taiwan [7]. The establishment of the TWB has laid a solid foundation for Taiwan's further pursuance of biomedical industry and/or precision medicine developments.

At the present moment, the TWB has collected more than 100,000 participant's blood, urine and saliva, together with their personal health condition information. So far, 23,000 out of 100,000 participants have expressed their willingness to be examined using advanced imaging [7]. Although this data was collected for one purpose, technological advancement, enhanced algorithms, and new pathway control mechanisms have made it possible for researchers to reinterpret and use these materials in new ways. For example, Google's research team found a new way to screen patients for heart disease risk factors by using algorithm-driven technology to scan the retinas of more than 280,000 patients over 16 years and cross-referencing this information with their personal health data presented at the European Society of Cardiology (ESC) congress in 2017 [8]. Such an approach not only reveals new potential uses of biobank information in the era of Big-Data, but it also has a huge impact on the relationship between biobanks and their participants. With the advancement of IT technology, biobank participants' expectations of receiving feedback regarding their health data are rising. In turn, issues relating to the ever-expanding coverage of participants' consent, and the extent to which they should be informed of the results of analysis, and whether or not IF should be returned are emerging accordingly.

In Taiwan, prevailing ethical regulations and legal rules do not explicitly address issues associated with returning IF [9]. For instance, both the “Human Subjects Research Act (2011),” which regulates specific research projects and the “Human Biobank Management Act (2012),” which regulates the collection, storage, and release of human biological specimens, have been the most relevant legislation allowing biobanks to maintain the “irretrievability” of related data under the governance of the ethical code of “re-contact.” However, the issue of

returning IF related to research output is not covered by this legislation. On the other hand, subject to Article 3 of the “Personal Information Protection Act (2015),” participants have been given the right to make “(1) any inquiry and request for a review of the personal information; (2) any request to make duplications of the personal information; (3) any request to supplement or correct the personal information; (4) any request to discontinue collection, processing or use of personal information; and (5) any request to delete the personal information.” [10]. In principle, participants’ rights in this regard might imply that they are entitled to ask for the return of IF, providing that these rights are not waived in advance and/or limited by any specific agreement. However, the lack of sufficient legislative historical data or explicit legal context means that a pure “black letter” literal interpretation of this Act is not convincing.

Indeed, ever since the feasibility study stage of the TWB, the general ethical, legal, and social implications (ELSI) consideration concerning the “predictability” of genetic related disease in the so-called post genome era has been taken into consideration [11]. In turn, during the preparation of the Ethical Governance Framework (EGF) of the TWB, it was decided that, subject to the context of the Medical Law and Physician Law of Taiwan, researchers in the TWB were not in a position to inform and/or caution participants about any possible disease correlation inferred from the findings of genetic analysis [9]. However, as emphasized in WMA Taipei declaration, advanced biomedical technology has significantly changed the original belief and altruistic trust of participants. Theoretically speaking, to the extent that the participant’s autonomy has been fairly observed, the gift model of participant consent can be interpreted in a more equitable manner - with rationality and without the violation of legal rules. This is especially meaningful when the contemporary activities of the TWB not only include population-based cohort type of study, but also disease-oriented research. In Taiwan, the IF-related debate can be traced back to 2018 when the public called on Taiwan’s National Health Insurance (NHI) to cover the payment of genetic screening for cancer. This happened in the wake of the development of more sophisticated screening technology, which made cellular level diagnosis possible and thus significantly increased the effectiveness of target therapy. However, while the public’s claim was scientifically convincing, the mandatory and universal coverage characteristics of Taiwan’s NHI implied that this is not an affordable financial burden.

Following the same line of thinking, if we take further steps to actively inform participants of IF, “would Taiwan’s NHI be able to cover all of the subsequent claims for further disease examinations and/or treatments, especially at the costly cellular level?” In addition to those ethical and legal issues mentioned above, as a national biobank the TWB is obligated to take all of these social implications into consideration as well. In turn, the Public Population Project in Genomics and Society (P<sup>3</sup>G) initiatives were also taken into consideration when designing the TWB’s IF return policy [7]. P<sup>3</sup>G, in its 2012 Policy Statement, proposed that considerations associated with returning IF to participants should be based on, among other things, the principle of beneficence, i.e., the duty to maximize net benefit for research participants and for society as a whole, while advancing knowledge [12]. Thus, it is our belief that limiting the context of the return of IF within the boundary of “life threatening” as opposed to “curability” may better justify the ethical claim to grant participants fair beneficence, while also maintaining the sustainability of the IF returns policy.

At present in Taiwan, 30 biobanks have been established and registered in accordance with the law [7]. Most of these bodies use the informed consent template provided by the Ministry of Health and Welfare in Taiwan, which does not include the return of IF. So far, only the biobank of Hualien Tzu-Chi Hospital incorporates a relevant return of IF procedure in their informed consent form; however, their return policy is unclear. Therefore, as the only national biobank in Taiwan, it is the TWB’s responsibility to develop a workable IF return policy that can serve as a model for similar facilities.

The inquiry concerning the willingness of participants to receive their physical examination report has long been listed in the TWB’s informed consent form. However, the return of IF is not explicitly referred to. Therefore, how should contemporary TWB related documents, policy and/or governance rules be amended and/or modified to adapt to technological advancement without infringing on participants’ autonomy. Developing an approach to these issues in a sustainable way will be one of the biggest issues experienced by the TWB.

In the next section, an international comparative study will be conducted to see how the return of IF protocols are formulated and/or implemented by biobank operations on a more global scale.

### 2.1. Current practices that do not acknowledge the return of IF

First and foremost, it is quite legitimate to ask: “Should biobank-users bear the responsibility to inform participants of medical information that arises from IF?” The aim of biobanks is to promote health and wellbeing at the population-level, at no individual cost or risk. One major argument found within the existing body of literature on this topic is that the return of IF can have a number of beneficial and harmful consequences [13–15]. These debates have ranged from recommending full disclosure [13], limited/restrictive disclosure (no feedback except that considered to be life-saving) [14], intermediate disclosure (providing all requested information if the research results meet certain conditions) [14], to no disclosure [15]. The return of IF procedures are difficult to implement in practice due to their high costs and labor consuming nature. Thus, Forsberg *et. al* even went so far as to argue that IF should not be returned. They stated that although researchers have a duty to respect the act of altruism, biobank resources would be better allocated for the public good [16]. In addition, if 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 [17]. Therefore, it is often difficult for participants to exercise their rights to request relevant information.

### 2.2. Emerging “limited obligation” for the return of IF

However, international ideas about whether IF should be returned is changing [4,18]. In the discussion of bioethics in Europe and North America, a consensus has gradually formed about the “limited obligation” for the return of IF [1,3,18–20]. For instance, the UK Biobank conducted an empirical study concerning the necessity to return IF that reveal potential serious findings under its imaging pilot study [21]. Their 2015 research report suggested that “[h]ow incidental findings should be managed – particularly for large-scale imaging research studies – is a matter of international dialogue and bioethical debate...” [21] In the wake of this study, the UK Biobank developed a protocol to inform participants of potentially serious IF for multimodal scan imaging in limited obligation [22]. The protocol described that “[t]he radiographers mainly look at the images to ensure their quality, rather than look for 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 IF procedures will be arranged within a few weeks. The radiographers will inform participants of the relevant abnormal problems and will contact the participants’ general practitioners (GP) or family physicians.” [21,22] The population-based whole-body Magnetic Resonance Imaging (MRI) as part of the German National Cohort (GNC) serves as an additional example [23]. GNC categorized incidental findings into three groups according to clinical relevance and urgency: “actionable,” “reportable,” and “non-reportable.” The center for incidental findings of the GNC includes a committee of radiologists, GP, epidemiologists, and ethicists who determine whether a finding is actionable, reportable, or non-reportable based on the current clinical and scientific knowledge. For actionable results that require immediate medical treatment, the

radiologist will contact the participant directly and refer them to the closest emergency department. For reportable results that might require further examination or medical treatment, the GNC will send the participant a standardized letter within approximately 10 working days after the examination. Nevertheless, non-reportable results without known clinical relevance or a high false-positive rate will not be disclosed to anyone.

The limited obligation is based on the ethical principles of “beneficence,” “reciprocity,” and “respect for persons.” [3] First, due to the principle of beneficence, researchers and biobanks have a responsibility to maximize benefits while also minimizing harm to participants. They operate under the assumption that it is a privilege for participants to contribute to public health initiatives, although returning findings might indeed personally benefit participants—especially in clinically urgent circumstances [14,16].

Furthermore, it is generally believed that the principle of reciprocity is very important for the establishment of mutual trust. The implementation of reciprocity can create a stable relationship of trust and support among biobank-users and participants [24]. In the “Universal Declaration on Bioethics and Human Rights” published by United Nations Education Scientific and Cultural Organization (UNESCO) in 2005, Article 15 (1) advocates that the benefits resulting from any scientific research and its applications should be shared with the whole of society and the international research community [25]. 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 [25]. In addition, Article 15(2) further advocates that such benefits should not form “improper inducements” for research participants [25]. Still, the return of IF might not constitute an improper inducement to participate in research. For example, Lévesque et al. argued that the principle of reciprocity (or reciprocal justice) under the context of research can benefit a “group”, but it might not always be inferred to benefit an “individual” [26]. In contrast, some individuals have argued that when personally-provided biospecimens are used in research, a participant generally has a strong awareness of the right to know the result [27–29]. Moreover, it is impossible to determine if the return of IF will become an act of exploitation, or infringe on the rights of any vulnerable groups or individuals. Thus, there is no reason to prohibit biobank-users from returning IF to a particular individual, or to argue that it is too categorically ambiguous for ethical standards that apply in a particular situation. Accordingly, we agree that the personal benefit of receiving IF does not violate ethical requirements. This is because not all positive benefits to an individual are defined as “improper”. Even as far as UNESCO’s official document is concerned, there is no further explanation of the term “improper” [30]. Consequently, we conclude that the return of IF should not be considered as one of “improper inducements” to participate in research, and thus an individual participant should not be excluded from the return of IF.

Lastly, based on the principle of respect for persons, Schalowitz et al. argued that even the additional cost and burdens of disclosing IF should not hinder the obligations and responsibilities of researchers or biobanks [13]. In addition, implementing return of IF procedures might help make research more transparent and increase the willingness of participants to join [13]. On May 6, 2018, the United States’ National Institutes of Health (NIH) launched the All of Us Research Program to recruit one million participants over the age of 18 [31]. In this program, participants’ research results are made available through online participant portals or paper-based methods. Information about medical results obtained from physical examinations, including blood pressure and heart rate, are sometimes flagged as an emergency or urgency. After these issues have been flagged, the research staff will either immediately advise participants of their findings, or refer their biological sample to a doctor for further analysis. The genetic/genomic information can also be accessed by participants, depending on their preferences. Obviously, this recent trend in the All of Us Research Program encourages researchers or

biobanks to respect participants and view biomedical encounters as a research “partnership”.

In summary, the “limited obligation” approach is preferable. Abiding by fundamental ethical principles; it makes the return of IF necessary and manageable. To the authors of this paper, this approach is welcome, as it is congruent with the aforementioned WMA Declaration of Taipei. To some extent, the TWB happens to share with the UK Biobank with the same philosophy in its design of policy as well.

### 2.3. Additional issues associated with the return of IF

In addition to the ethical and legal deliberations, the social implication of a pro-return IF policy with various jurisdiction specialties should also be considered. An equitable and manageable protocol for the return of IF becomes essential should the TWB decide to take the “limited obligation” approach and leave the decision for the return of IF in the hands of patients.

Certainly, it is imperative and ethical that there are feasible procedures and arrangements associated with returning IF [4]. To this end, we will further discuss how to establish “a standard guidance for assessing the return of IF” within the TWB. Before we make recommendations, there are three issues worth discussing regarding the feedback process.

First of all, a standard guidance for the return of IF should be pragmatic, scalable, and not too abstract. This is because ambiguous guidance can lead to different standards for the return of IF, which might cause a myriad of communication concerns [1]. Therefore, the context of “a potential and serious risk to participants” should be clearly defined. For example, the research team led by the University of Minnesota, in their 2008 project’s consensus recommendations, suggested that some IF of reproductive importance be communicated to participants, but in their 2012 report, they debated that reproductive importance does not meet all the criteria in the “must return” category [3]. As a result, they suggested that these findings be put in the “should return” category, which is often limited to findings of high health importance to participants [20]. This is an example of where the meanings of “must” and “should” are ambiguous. As we can see, it would be beneficial if these terms were defined clearly in a return of IF guidance.

Second, although the ethical principles of “beneficence”, “reciprocity” and “respect for persons” constitute a strong ethical responsibility and obligation for biobank-users to return IF, the nature of these ethical principles does not consolidate the autonomy of participants, but rather establishes an obligation of biobank-users to return IF. For example, in the criteria of “must return”, “may return”, and “do not return”, patient autonomy is required to ask whether a participant wants to receive IF in the “may return” category during the informed consent [18]. Furthermore, Hofmann argued that participants also have a right not to know IF of uncertain significance, because negative information may cause psychological harm or social risks for the participants [15]. To protect the best interest of participants, this argument also holds in cases where there are life threatening IF, as participants still retain the right to decide whether or not they want to know the results [15].

Third, determining “what is actionable or reportable” is also a challenge due to uncertainty, which occurs in two ways: (1) researchers may not be able to confidently interpret the meaning of particular research results. For example, even in the case of the well-known BRCA1 and BRCA2 genes, some variants of uncertain significance still exist [13,32]. (2) Most participants do not have a background in medicine, and might not understand some of the complex interpretations of research results; hence, if there is a misinterpretation of IF, it might cause the research participants’ psychological, social, and economic harm, or even unnecessary medical interventions [13,33]. To solve this problem, biobanks must secure the help of health professionals to assist in the return of IF. However, in Taiwan, there are no GP or family physicians in the healthcare system dedicated to integrating research and clinical resources. Thus, it is better for the TWB to cooperate with the

participating medical institutes of the clinically-oriented cohort part of the TWB to form a consulting team; or provide medical information on an on-demand basis directly to participants for further medical diagnosis or treatment.

#### 2.4. Recommendations

We propose the following three conditions for IF assessment established by current cumulative consensus [1,3,14,18–20]. Decisions associated with the return of IF must assess: (1) scientific validity (meaning that a result is accurate and reliable) and clinical utility (meaning that a result is useful to improving health outcomes); (2) life-threatening risk factors (meaning that factors can affect major bodily functions or quality of life); and (3) clinical actionability (meaning that an action can reduce the risk of a disease). Furthermore, based on our previous discussions, we would make three recommendations to update the TWB's ethical governance framework for the return of IF together with the required informed consent process.

##### 2.4.1. Recommendation 1: we recommend that the TWB should return imaging-related IF only for life-threatening situations

In regard to the establishment of policies and practices related to imaging-related IF within the TWB, we note that informing participants of the research results has also not been the standard practice for the UK Biobank. However, in the image pilot study of the UK Biobank, about 2% of participants had an abnormality that a radiologist believed was potentially serious [21]. Therefore, for medical imaging, the UK Biobank decided to inform participants of IF that could have a major impact on the participant's bodily functions or quality of life, or if there was a chance that these abnormalities could potentially be life-threatening. The experience of the UK Biobank image pilot project is a useful reference for researchers and biobanks that need to make decisions for the return of imaging-related IF.

To this end, we suggest that when considering options for the return of IF related to MRI scan imaging, the TWB could combine the advantages of the IF protocol of the UK Biobank's and the GNC's imaging studies. One of the biggest differences between the TWB and these two programs, though, is that GP or family physicians have not yet been identified as a normal community based medical service under the contemporary Taiwanese healthcare system. Rather, it has been recognized as one of the specialty services offered by general hospitals. Therefore, once IF are identified, the TWB must contact the participant directly to provide them with the medical information in a way that does not violate their autonomy, so that they can schedule further reviews or consultations. In general, it may be better to treat the option to receive IF as a separate recommendation, and justify why giving people a choice is justified and feasible (vs. accepting the IF policy as a condition of participation, or instead being offered a wider dynamic menu of choices such as re-consent, return, withdrawal, etc.). For instance, as a supplement to the original health-related consultancy provided by the TWB, we could assign a specific code to participants who are either willing or unwilling to receive IF. For instance, a person who is willing to be informed of IF could receive the code of xxxxx-1, and a person who is unwilling to receive this information could receive the code of xxxxx-0 [19,34]. The code (1 or 0) can indicate “yes” or “no”, respectively, for whether the return of IF process should be continued. In this way, the return or refusal of IF, as decided by participants, could be identified without going through the de-identification process. However, the code can never be taken as a full substitute for participants' autonomy about IF return. Rather, it is a facilitating mechanism to better serve the participant's expression of their will in an efficient and effective way. If necessary, it is also recommended to have participants'

sign a separate consent form to ensure that they understand the potential risks and support associated with the return of IF, which remain available under the original ethical governance framework of the TWB.

##### 2.4.2. Recommendation 2: we recommend that the TWB should not return genetic-related IF due to the high uncertainty in the accuracy of interpretation, even if the research participants indicate during consent-taking that they want to be informed in the event of clinically relevant genetically-related IF at this stage

In regard to the establishment of policies and practices related to genetic-related IF, we realize that the next-generation of sequencing techniques increases the sequencing speed, thereby greatly reducing sequencing costs. Thus, the probability of encountering IF for a genetic disease will also increase dramatically. In fact, regardless of whether the result of an IF is positive or negative, a recent Japanese study found that nearly 90% (group 1) and over 80% (group 2) of participants were still willing to receive relevant personal health information, regardless of its outcome [35]. On the other hand, genetic empiricists have expressed a different opinion. They suggest that the penetrance of most mutant genes is still insufficient 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 unknown factors at play. 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.” [36] To further support our recommendation, Janssens et al. reported that “the genome-based predictive value of common diseases would be too small and accuracy is poor for any intervention to be appropriate.” [37] In addition, most research using materials from biobanks is quite different from clinical care. This gap not only makes it easy for researchers to ignore the clinically meaningful information, but also creates the problem of how to “interpret” genetic-related IF.

Therefore, current interpretations of genomic data make it particularly difficult to offer recommendations for the return of genetic-related IF to participants in the context of the TWB. So far there is no consensus on the provision of access for genomic data by participants within the TWB, but it is moving in the direction of positive planning. In the future, it is recommended that the TWB form a clinical advisory committee comprised of experienced researchers, clinicians, ethicists and psychologists to review IF in genomic research.

##### 2.4.3. Recommendation 3: we recommend that National Health Insurance consider covering the costs of returning IF, as a part of health care

One of major barriers to biobanks establishing policies for the return of IF is the additional cost/resources. The substantial increase in the cost has led to researcher apathy regarding the return of IF. In other words, returning IF to participants often results in inflated research budgets—which dissuades many biobanks from partaking in this practice. The return of IF is very costly: from assessing whether or not there is a need to return IF, to re-contacting the original sample provider and hiring consultants; however, most biobank-users do not have a portion of their budgets allocated for this purpose [1]. In addition, IF is associated with a high degree of uncertainty, making it difficult to predict how much of a biobank's budget should be allocated to this goal. This variable makes it difficult to raise the appropriate funds, thus affecting the biobanks research goals. One possible approach to this problem is that the fees can be borne by participants. According to a Canadian study, participants can expect to pay about \$445 US dollars for receiving certain IF from genomic sequencing [38]. This approach allows direct beneficiaries to spend more than other non-beneficiaries, and reduces the idle costs of biobanks. However, it is possible to make this kind of estimate only because the circumstances can be well defined and anticipated, and the beneficiary is intended to receive IF at the outset. If the

circumstances were significantly different, as they can be in many other situations, the costs may be very high and the prospect of treatment can be very low.

Thus, an additional possible approach is for the national healthcare system to cover the cost of returning IF. However, “is it reasonable to expect Taiwan’s NHI to cover the costs?” Indeed, when the return of IF results are conducted on the “limited obligation” basis for “life threatening diseases” only, their return could serve as part of the preventive measures to reduce probable *vis-a-vis* public health expenditures in the future. Thus, it becomes reasonable to cover the cost of returning IF as a part of health care. In Taiwan, the NHI has been “mandatory” and has resulted in “universal coverage”. Almost all the citizen and health institutes are covered under the NHI, which make it possible to link biobank genetic databases with the NHI’s health records. Up until now, the development of precision medicine has been mainly focused on chronic and/or life-threatening diseases, including cancer treatment solutions. The cost of covering the TWB’s IF returns of “limited obligation” would be beneficial for facilitating further policy-making and priority setting in this area. Hence, we suggested that the TWB should promote a horizontal link between biobanks and other health-related institutes through resource pooling in order to jointly accomplish the common goal of returning IF.

#### 2.4.4. Proposed framework

Finally, the framework of returning IF should be reconsidered in light of the guidance suggested by the WMA Declaration of Taipei (2016). The model framework that we propose to be implemented within the TWB is shown in Fig. 1.

A custom-built (not one-size-fits-all) model to handle IF should be designed based on the Taiwanese research context [29]. The return of IF process normally includes three steps: assessment, re-identification, and communication [19]. The next challenge is: “how to appropriately arrange feedback procedures of the return of IF for precision medicine.” [39] Based on the limited obligations for the return of IF and our recommendations, only a potential image-related IF will move on to the assessment process. It will be up to the assessment committee to review these factors on a case-by-case basis. All research institutes have Institutional Review Boards (IRBs) that determine whether research involving human subjects

meet the current ethical standards. However, members of IRBs might not have enough clinical knowledge or experience to adequately assess IF arising from biomedical research [2,19]. Researchers, on the other hand, are more likely to have the necessary expertise to assess IF. Therefore, we agree with the argument that researchers should be included in the assessment committee to evaluate the risks and benefits of returning individual IF, while IRBs’ role should be limited to examining the feedback policy and process to ensure that they are ethical [19].

According to the proposed framework, if a case refuses to know IF or fails to fulfill the aforementioned three conditions for IF assessment, the return of IF would be rejected at the first stage of assessment [34]. Furthermore, the re-identification of participants can lead to privacy invasions and possible breaches of confidentiality [40]. Thus, it should be managed carefully by authorized personnel that are independent from the research project. This personnel should take all responsible measures to re-identify a participant in a defined circumstance [19]. One potential and practical approach is to use a trusted intermediary, which involves the third party management of a biobank’s database which would protect personal identifiers and at-risk health information. Finally, referring IF handling to the GNC’s standards [23], the TWB will contact a participant directly (actionable results) or via a letter (reportable results) within a few weeks, as determined by the committee on a case by case basis. We believe that this updated framework will provide both the necessary clarity and safeguards to allow the TWB and its users to make better decisions regarding the return of IF.

### 3. Summary

Human biobanks ensure the large-scale and long-term collection of biological data for future research and development. However, in the post-genomic era, personal biological or health information is gradually gaining attention as personal privacy issue. In turn, from a bioethics perspective, how far and in what way a participant’s has autonomy over managing his or her private information is being called into question. This concern has been extended to how IF are being returned within biobanking governance. We believe that refusing to offer IF to participants might not conform to current

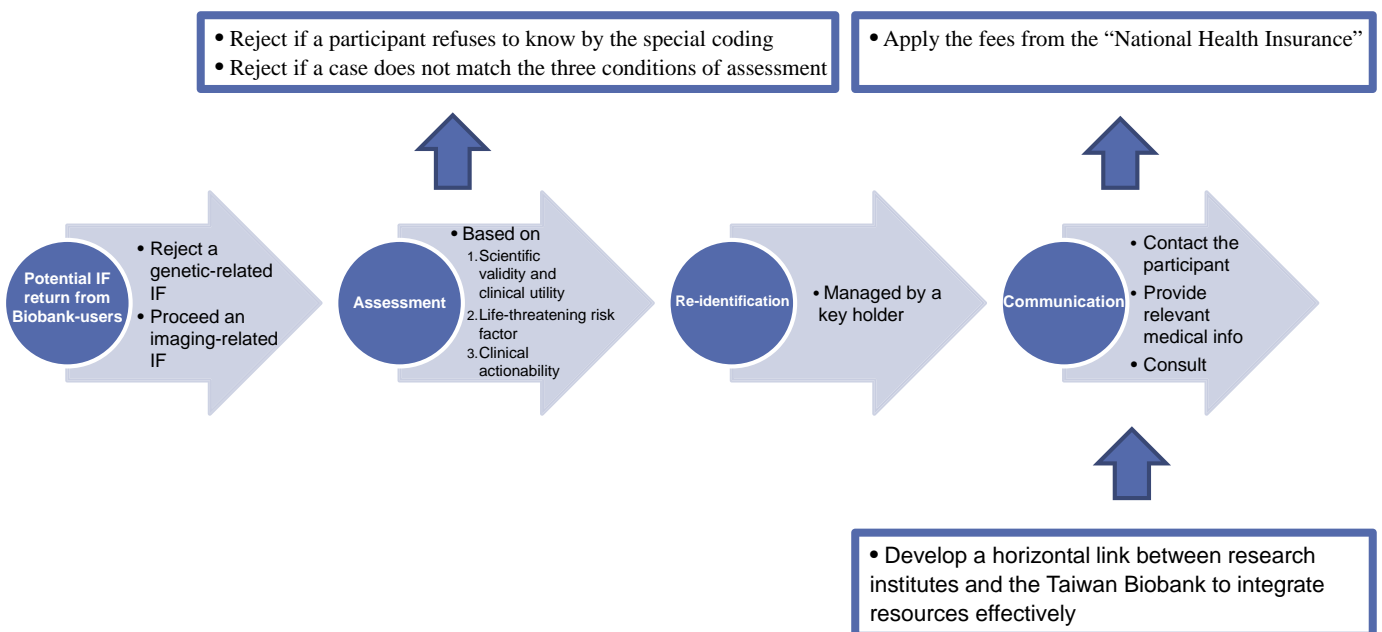


Fig. 1. A Proposed Framework of the Taiwan Biobank in Returning “Incidental Findings”.

international trends for returning IF. A more flexible method of IF return policy shall be undertaken so as to provide participants and the general public with fair, better and more comprehensive health protection.

The “WMA Declaration of Taipei (2016)” recommends implementing procedures for returning IF into the informed consent process, ensuring that the return of IF is gradually integrated into global ethical norms, as is the trend. Although there is no clear instruction for how to carry out this call to action, researchers and biobanks should now consider changing from procedures of informed consent, communication, and research resource allocation in order to grapple with the question of “how to deal with the issue of a return of IF.” Therefore, the return of IF has raised many issues throughout the biobanking research system related to how any such obligations might apply to biobank-users.

From the study of ELSI to the willingness of researchers and biobanks to implement compliance, the active roles of researchers and biobanks in the ethical governance of biomedicine are undoubtedly clarified. In this article, we have identified some practical difficulties and some ambiguities relating to privacy legislation. We also discussed how “large ethical risks” might be a source of harm to human subjects, especially in cases where the possibility of treatment for clinical conditions is not a certainty. However, so far none of the official guidance documents stipulate how to deal with the return of IF in Taiwan. Therefore, as the only national biobank in Taiwan, the TWB is obligated to update and implement a framework and informed consent process associated with the return of IF to promote higher ethical standards to serve as a reference point for other biobanks. This will not only preserve the rights of participants, but also the health benefits of citizens.

#### Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

All authors were heavily involved in drafting the manuscript, and adding substantive input during revisions. JC and CT provided the ethical background and analysis. WWW considered the issues from the research and medical perspective. Recommendations were established through consensus at a number of deliberations between all the authors. All authors read and approved the final manuscript.

#### Declaration of Competing Interest

The authors declare that they have no conflict interests.

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#### References

- [1] Budin-Ljøsne I, Mascalzoni D, Soini S, Machado H, Kaye J, Bentzen HB, et al. Feedback of individual genetic results to research participants: is it feasible in Europe? *Biopreserv Biobank* 2016;14(3):241–8.
- [2] Abdul-Karim R, Berkman BE, Wendler D, Rid A, Khan J, Badgett T, et al. Disclosure of incidental findings from next-generation sequencing in pediatric genomic research. *Pediatrics* 2013;131(3):564–71. <https://doi.org/10.1542/peds.2012-0084>.
- [3] Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, et al. Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med & Ethics* 2008;36(2):219–48.
- [4] Susan MW. Return of individual research results & incidental findings: facing the challenges of translational science. *Annu Rev Genomics Hum Genet* 2013;14:557–77.
- [5] Thorogood A, Dalpe G, Knoppers B. Return of individual genomic research results: are laws and policies keeping step? *Eur J Hum Genet* 2019;27:535–46. <https://doi.org/10.1038/s41431-018-0311-3>.
- [6] WMA declaration of Taipei on ethical considerations regarding health databases and biobanks. <https://www.wma.net/policies-post/wma-declaration-of-taipei-on-ethical-considerations-regarding-health-databases-and-biobanks/>; 2017, Accessed date: 18 April 2019.
- [7] Lin JC, Chen LK, Hsiao WWW, Fan CT, Ko ML. Next chapter of the Taiwan biobank: sustainability and perspectives. *Biopreserv Biobank* 2019;17(2):189–97. <https://doi.org/10.1089/bio.2018.0119>.
- [8] Mohammad MA, Koul S, Rylance R, Frobert O, Alfredsson JG, Jernberg T, et al. Air temperature as an external trigger of ST-segment elevation myocardial infarction - a SWEDHEART nationwide observational study. *Eur Heart J* 2017;38. [https://doi.org/10.1093/eurheartj/ehx504.2949\\_suppl\\_1](https://doi.org/10.1093/eurheartj/ehx504.2949_suppl_1): ehx504.2949.
- [9] Fan CT, Hung TH, Yeh CK. Taiwan regulation of biobanks. *J Law Med Ethics* 2015;43(4):816–26. <https://doi.org/10.1111/jlme.12322>.
- [10] Personal Information Protection Act. Article 3. <https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=10050021>; 2015, Accessed 18 Apr 2019.
- [11] Bledsoe MJ. Ethical legal and social issues of biobanking: past, present, and future. *Biopreserv Biobank* 2017;15(2):142–7. <https://doi.org/10.1089/bio.2017.0030>.
- [12] Cornel MC. Crossing the boundary between research and health care: P<sup>3</sup>C policy statement on return of results from population studies. *Eur J Hum Genet* 2013;21(3):243–4. <https://doi.org/10.1038/ejhg.2012.160>.
- [13] Scholowitz DI, Miller FG. Disclosing individual results of clinical research, implications of respect for participants. *JAMA* 2005;294:737–40.
- [14] Bredenoord AL, Kroes HY, Cuppen E, Parker M, van Delden JJ. Disclosure of individual genetic data to research participants: the debate reconsidered. *Trends Genet* 2011;27:41–7.
- [15] Hofmann B. Incidental findings of uncertain significance: to know or not to know - that is not the question. *BMC Med Ethics* 2016;17:13.
- [16] Forsberg JS, Hansson MG, Eriksson S. Changing perspectives in biobank research: from individual rights to concerns about public health regarding the return of results. *Eur J Hum Genet* 2009;17:1544–9. <https://doi.org/10.1038/ejhg.2009.87>.
- [17] McGeeveran W, Fatehi L, McGarraugh P. Deidentification and reidentification in returning individual findings from biobank and secondary research: regulatory challenges and models for management. *Minn J L Sci & Tech* 2012;13(2):485–539.
- [18] Wolf SM. The past, present, and future of the debate over return of research results and incidental findings. *Genet Med* 2012;14(4):355–7.
- [19] Thorogood A, Joly Y, Knoppers BM, Nilsson T, Metrakos P, Lazaris A, et al. An implementation framework for the feedback of individual research results and incidental findings in research. *BMC Med Ethics* 2014;15:88. <https://doi.org/10.1186/1472-6939-15-88>.
- [20] Wolf SM, Crock BN, Ness BV, Lawrenz F, Kahn JP, Beskow LM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet Med* 2012;14(4):361–84.
- [21] Attitudes to and impact of the feedback of potentially serious incidental findings from UK Biobank's imaging pilot study. <http://www.ukbiobank.ac.uk/wp-content/uploads/2017/03/TNS-BMRB-qualitative-research-findings-1.pdf>; 2015, Accessed date: 18 April 2019.
- [22] Gibson LM, Sellers J, Sudlow CLM. Management of incidental findings on multimodal imaging in UK biobank. In: Weckbach S, editor. *Incidental Radiological Findings*. Medical Radiology. Cham: Springer; 2016. [https://doi.org/10.1007/174\\_2016\\_91](https://doi.org/10.1007/174_2016_91).
- [23] Bamberg F, Kauczor HU, Weckbach S, et al. Whole-body MR imaging in the German National Cohort: rationale, design, and technical background. *Radiology* 2015;277(1):206–20.
- [24] Kanellopoulou N. In: Kaye J, Stranger M, editors. *Reconsidering altruism, introducing reciprocity and empowerment in the governance in population genomics research, in principles and practice in biobank governance*. Farnham, Surrey; Burlington, VT: Ashgate; 2009. p. 43–5.
- [25] International declaration on human genetic data. UNESCO, Article 15. [https://portal.unesco.org/en/ev.php-URL\\_ID=31058&URL\\_DO=DO\\_TOPIC&URL\\_SECTION=201.html](https://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html); 2003, Accessed date: 18 April 2019.
- [26] Lévesque E, Joly Y, Simard J. Return of research results: general principles and international perspectives. *J L Med & Ethics* 2011;39(4):583–92. <https://doi.org/10.1111/j.1748-720X.2011.00625.x>.
- [27] Kaufman D, Murphy J, Scott J, Hudson K. Subjects matter: a survey of public opinions about a large genetic cohort study. *Genet Med* 2008;10(11):831–9. <https://doi.org/10.1097/GIM.0b013e31818bb3ab>.
- [28] Murphy J, Scott J, Kaufman D, Geller G, LeRoy L, Hudson K. Public expectations for return of results from large-cohort genetic research. *Am J Bioethics* 2008;8(11):36–43.
- [29] Beskow LM, Burke W. Offering individual genetic research results: context matters. *Sci Transl Med* 2010;2(38):38cm20. <https://doi.org/10.1126/scitranslmed.3000952>.
- [30] AMJ Have H, Jean MS, editors. *Universal declaration on bioethics and human rights: Background, principles and application*. Paris: UNESCO Publishing; 2009. p. 233.
- [31] All Of Us Core Protocol v1.7. [https://allofus.nih.gov/sites/default/files/aou\\_core\\_protocol\\_v1.7\\_mar\\_2018.pdf](https://allofus.nih.gov/sites/default/files/aou_core_protocol_v1.7_mar_2018.pdf); 2018, Accessed 18 Apr 2019.

- [32] Cheon JY, Mozersky J, Cook-Deegan R. Variants of uncertain significance in BRCA: a harbinger of ethical and policy issues to come? *Genome Med* 2014;6(12):121. <https://doi.org/10.1186/s13073-014-0121-3>.
- [33] Wolf SM, Lochmüller H, Riess O, Schaefer F, Orth M, Rubinstein Y, et al. The law of incidental findings in human subjects research: establishing researchers' duties. *J L Med & Ethics* 2008;36(2):361–83.
- [34] Steinsbekk KS, Myskja BK, Solberg B. Broad versus dynamic consent in biobank research. *Eur J Hum Genet* 2013;21:897–902.
- [35] Yamamoto K, Hachiya T, Fukushima A, Nakaya N, Okayama A, Tanno K, et al. Population-based biobank participants' preferences for receiving genetic test results. *J Hum Genet* 2017;62:1037–48.
- [36] Kwon JM, Steiner RD. "I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients. *Neurology* 2011;77:522–3.
- [37] Janssens AC, van Duijn CM. Genome-based prediction of common diseases: advances and prospects. *Hum Mol Genet* 2008;17(R2):R166–73. <https://doi.org/10.1093/hmg/ddn250>.
- [38] Scholtes E. Incorporating cost into the return of incidental findings calculus: defining a responsible default for genetics and genomics researchers. *Minn L Rev* 2016;100(3):1171–208.
- [39] Frizzo-Barker J, Chow-White PA, Charters A, Ha D. Genomic big data and privacy: challenges and opportunities for precision medicine. *CSCW* 2016;25(2–3):115–28. <https://doi.org/10.1007/s10606-016-9248-7>.
- [40] Hansson MG. The risk of re-identification versus the need to identify individuals in rare disease research. *EJHG* 2016;24:1153–558.