Guide to the detection, management and communication of incidental findings for biobanks in BBMRI-NL

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Introduction

Biomedical and biobank research using bodily material or medical data sometimes uncovers incidental findings that may be relevant to the health of individual research participants or donors. In The Netherlands, incidental findings are handled in varying ways. Hence, it is often unclear to researchers whether they are allowed or obligated to report back findings to participants, and how this should be done.

The purpose of this guide is to provide practical support to researchers, research groups, biobanks, research institutions, and research ethics review committees, with the design or evaluation of policies on the management of incidental findings in biomedical and biobank research. The guide sets out a number of minimum requirements based on a practical ethical framework and describes best practices for the detection, management and communication of incidental findings.

In 2016 BioBanking Medical Research Infrastructure the Netherlands (BBMRI-NL) funded one-year voucher projects with the aim of promoting the research infrastructure for biobanks in the Netherlands, including this project, which was carried out by researchers at the Department of Medical Ethics and Philosophy of Medicine, Erasmus MC. The guide was published in December 2017. The translation of this report was funded by BBMRI-ERIC in line with the activities of its Common Service ELSI.
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Anticipating potential incidental findings

Incidental findings are not incidental findings; it is now known that they can occur in certain study populations, and, also, how often they occur [3]. The frequency of incidental findings detected during MRI of the brain, for instance, is just under 1% in healthy research participants [4]. Similarly, in genetics research, population incidental findings occur in an estimated 1-3% of healthy research participants undergoing genome or whole-genome sequencing [5, 6, 7].

We know that incidental findings may occur, as researchers, we therefore not be passive with regard to incidental findings. We have a strong influence on whether or not incidental findings occur. Decisions we make with regards to the research design will determine the frequency of incidental findings. For example, research groups are more likely to detect abnormalities on T2-weighted scans and FLAIR sequences, which are of diagnostic quality and are also used in clinical practice, than on a functional MRI (fMRI). In genetics, exome sequencing produces large quantities of data, and the likelihood of detecting incidental findings is greater than targeted testing of specific candidate genes. To some extent, filters can be used to rule out incidental findings. Furthermore, abnormalities are more likely to be found when images are examined by radiologists than, for instance, by psychology students. In addition, if researchers or lab assistants are instructed to avoid detection of possible abnormalities, they will be less likely to find them if they are explicitly asked to check research data for findings that could be relevant to the health of research participants. The likelihood of incidental findings also tend to occur less frequently in young, healthy research populations than in older, less healthy populations.

Whether or not incidental findings occur, depends partly on a set of [research/biological/technical] and methodological choices made by researchers or research institutions [5]. This implies that researchers and institutions are responsible for these choices and for their consequences for research participants. Researchers should therefore take actions to ensure proper management of incidental findings in research. This characterises a responsible approach to incidental findings? What do researchers or institutions need to consider and what arrangements do they have to make – at the very least – to ensure responsible management of incidental findings?

Recommendations

1.2 Content related

Decide whether the test modality proposed would produce incidental findings.

- Do incidental findings are anticipated and whether these need to be reported to research participants?
- Consult the literature, best practices and/or a multidisciplinary team.
- Draw up a list of anticipated incidental findings in consultation with a multidisciplinary team, and decide together whether these need to be reported.
- When deciding these criteria, consider the following criteria:
  - There is a real risk of a serious disorder?
  - There is a realistic management option that can be offered?

1.2.2 Procedures

What to be organised in advance?

- Set up a committee or multidisciplinary team in case incidental findings occur.
- Make arrangements with experts and or laboratories for consultation and/or follow-up tests to confirm incidental findings.
- Make arrangements with medical specialists for prompt clinical follow-up.

Note on Recommendation 1.2

Research participants do not need to take incidental findings into account when choosing the test modality that will be used. This is discussed in more detail in Recommendation 4 (Analyzing data). Given the chosen test modality, however, research participants do need to consider incidental findings in their research work, and whether incidental findings can be expected. It is advisable to draw up a list of anticipated incidental findings that require to be reported to research participants, to be distinguished clearly from anticipated incidental findings that do not need to be reported. A multidisciplinary team can ideally be involved in composing the list. This team – or a delegation from it – should also be available for consultation in case of the incidental findings that were not anticipated.

When defining these lists, researchers can consult published literature, best practices and experts. Appendix 1, for example, specifies findings that do or do not require communication to participants or donors from ERGO (Erasmus Rotterdam Health Research) in Rotterdam. These lists are used by Dutch and international research groups.

Appendix 2 contains an overview of incidental findings published by the American College of Medical Genetics (ACMG) in 2013, which many groups use as a guide to the feedback of incidental findings from genetic research. Ideally, biobanks in BBMRI-NL2.0 should use standardised lists based on the international literature or guidelines, but there is at present no consensus on what these lists should contain. Nor are incidental findings pre-defined for every type of data. These lists will need to be developed step by step and revised over time [see Recommendation 7.3].

The ‘Code Goed Gebruik’ (code for the responsible handling of bodily material in research) favours a cautious approach to the feedback of incidental findings. These lists will need to be developed step by step and revised over time. These lists will need to be developed step by step and revised over time. These lists will need to be developed step by step and revised over time. These lists will need to be developed step by step and revised over time.
2.3 Only depart from the principle of informed consent in exceptional cases.

Recommendations

2) Informing and consenting donors/participants

• Donors and participants need to be informed in advance that data or bodily material may be reused in future research. Ideally, participants should first be asked to consent to feedback also when existing data or bodily material is reused.

• Informed consent should be obtained for the re-use of data or bodily material in future research projects. Participants should be informed of the possibility that the research project may generate results that could be harmful or embarrassing to them or their family members, and the right to refuse information. Consent should be in effect presumed: in order to avoid a potential conflict of duties, donors and participants should be offered an opt-out, i.e. they may be given the opportunity to indicate whether they do not wish to receive the information.

• Participants should always be given the opportunity to opt out of feedback if it is identified that the information could be harmful or embarrassing to them or their family members.

• It should be made clear to donors and participants that they may refuse to receive information, including incidental findings, about themselves or their family members, or that they may refuse to receive feedback about their own health or their family’s health. The right to refuse information is an important ethical principle. The right to refuse information is a legal principle in some countries: in the Netherlands, the right to refuse information and/or treatment is laid down in the Medical Treatment Contracts Act (WGBO).

• The researcher may make an exception if a consulted expert argues that this could help to prevent serious health problems or risks. The right to refuse information may not be absolute, however; it may be overruled if withholding from offering research participants the opportunity of an opt-out: in the event of a conflict of duties.

• Participants should be informed that, even in the absence of feedback, they can receive information about their own health and health risks from their own healthcare provider. If participants are given the opportunity to state that they do not wish to receive such information, this is referred to as an ‘opt-out’ (see Box 3 for examples of informed consent). There is no consensus on whether research participants have a right to refuse feedback on incidental findings.

• Researchers need to take into account such expectations. There should be no mismatch between participants’ expectations and what is possible.

• When in doubt, it is better not to be reminded of possible incidental findings. The right to refuse information is a legal principle in some countries: in the Netherlands, the right to refuse information and/or treatment is laid down in the Medical Treatment Contracts Act (WGBO).

• Researchers should not be aware of the possibility of incidental findings. If participants are informed about the possibility of incidental findings, it may be ethical to notify them of these findings. Researchers should be informed of the possibility of incidental findings. They should be given all important information to protect participants from harm.

• Participants should be informed of the possibility that information generated by the research could be harmful or embarrassing to them or their family members, or that it could lead to serious health problems or risks. Participants should be informed of the possibility that the research project may generate results that could be harmful or embarrassing to them or their family members, and the right to refuse information. Consent should be in effect presumed: in order to avoid a potential conflict of duties, donors and participants should be offered an opt-out, i.e. they may be given the opportunity to indicate whether they do not wish to receive the information.

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Box 5. Standard Operating Procedure (SOP) for testing blood pressure and handling abnormal values.

was higher than 180
The average systole in the last two tests
The average diastole in the last two tests is higher than 120
If:  
- Whom can the radiography personnel contact if incidental findings are detected? It must be clear whom to contact, also if there are any questions. The experts’ names, e-mail addresses and telephone numbers should be listed in the protocol.
- What kind of practical steps should radiography personnel take when detecting an abnormality? It is often possible to eliminate the possibility that the findings are abnormal, for example, if the scans are of diagnostic quality and the data are collected expeditiously (e.g. real-time transfer of the data from the Lifelines biobank).

It is important for research assistants, technicians, laboratory personnel, and researchers to know how to deal with incidental findings that are detected during data collection. These steps should ideally be described in a SOP or protocol for handling incidental findings. Such protocols may make it clear to researchers what they are expected to do while testing, and who can help them if they have any questions. Some important considerations in an SOP or protocol for imaging studies:

1)  Collecting data
2)  Analysis
3)  Reporting

Note on Recommendation 3.1
The decision to use a particular test or scan will determine the likelihood of detecting incidental findings. More incidental findings will be detected if, for example, the scan is of diagnostic quality than if the scans are of low diagnostic quality. This has to be weighed against other aspects such as the time needed to target the data, and the cost of the test. More targeted testing modalities will detect more incidental findings than less targeted testing.

3.2  Ensure that researchers, research assistants and/or laboratory personnel are instructed how to deal with incidental findings that are detected during data collection.

Recommendations
- Do we expect radiography personnel to look for abnormalities in the images? Current policy varies enormously.
- Which kind of background and training does the person carrying out the scans have? This can be a factor in the likelihood of detecting incidental findings.
- How should incidental findings deal with possible incidental findings (e.g. age, sex)?
- What kind of practical steps should radiography personnel take when detecting an abnormality? It is often possible to eliminate the possibility that the findings are abnormal, for example, if the scans are of diagnostic quality and the data are collected expeditiously (e.g. real-time transfer of the data from the Lifelines biobank).

It is important for research assistants, technicians, laboratory personnel, and researchers to know how to deal with incidental findings that are detected during data collection. In the case of MRI research, an incidental finding may be detected either during data collection when the participant is present, or later on, when the scans are analysed. It is important for research assistants, technicians, laboratory personnel or researchers to be instructed how to deal with incidental findings that are detected during data collection.

The process of data collection can give rise to incidental findings, depending on the type of test used. In MRI research, for example, an abnormality may be detected during the time required for scan acquisition, whereas in the case of blood collection, the likelihood of detecting incidental findings during collection is almost nil.

Standard Operating Procedures (SOPs) are used to determine how particular methods or procedures should be carried out by research assistants, technicians, laboratory personnel, or researchers. A SOP often sets out what researchers should do if they observe unexpected abnormalities during data collection. For instance, the SOP may detail what actions to take when the researcher measures a highly elevated blood pressure (see Box 5 for an example from the Lifelines biobank).

It is important for research assistants, technicians, laboratory personnel, and researchers to know how to deal with incidental findings that are detected during data collection. In the case of MRI research, researchers and technicians should be instructed on how to deal with any abnormalities, so that they happen to detect a possible abnormality (including when to telephone, how to store the data, what they can and cannot say to the participant). These steps should ideally be described in a SOP or protocol for handling incidental findings. Such protocols may make it clear to researchers what they are expected to do while testing, and who can help them if they have any questions. Some important considerations in an SOP or protocol for imaging studies:

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4) Analysing data

One of the study data has been collected, they are analysed in order to generate research results. It may often be necessary to carry out additional analyses in order to find the answer to the research question or to generate a more detailed description of the phenomenon. The results of the analyses should be described in such a way as to enable others to reproduce them. The researcher should then proceed to interpret the research results. This is the starting point for discussions in the scientific community.

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5) Confiming incidental findings

Before an incidental finding can be communicated to the research participant, it must first be confirmed by an expert and - if necessary - repeated under Good Laboratory Practice (GLP) conditions. The decision to feed back the finding should be taken in consultation with a relevant expert or clinician. Together, the researcher and the expert decide whether feedback is warranted, ideally based on a predetermined protocol.

**Recommendations**

- **5.1** Confirm incidental findings by having them assessed by an expert and, if necessary, by repeating the test under GLP conditions.
- **5.2** Consult clinical experts about the clinical significance of the finding and decide together whether feedback is warranted.
  - In the event of anticipated incidental findings, make decisions in accordance with the predetermined 'list' or protocol.
  - In the event of unanticipated findings, a committee should be consulted, or multidisciplinary discussions should be held.

**Note on Recommendation 5.1**

Incidental findings may be detected in a variety of research settings, in which the diagnostic quality of the data collected is not always guaranteed. Abnormal laboratory results should first be confirmed by repeating the test under GLP conditions. This is not always necessary: if the original test was already conducted under GLP conditions, the results may be assumed to be valid.

In the event of incidental genetic findings a clinical geneticist should be consulted who has the requisite expertise and is in a position to determine whether and to what extent the findings are clinically relevant and actionable.

In the case of imaging research an incidental finding should first be confirmed by a clinical radiologist or radiological expert before a decision can be made regarding feedback.[15, 18] This requirement applies to all types of imaging research, including e.g. neuroscience studies using fMRI. However, there is no need to make additional scans.

Prior to the study as part of the first stage of anticipating incidental findings, the researcher should contact a relevant laboratory, clinical geneticist or radiologist to make arrangements for consultation in the event of incidental findings (see Recommendation 1).

**Note on Recommendation 5.2**

Researchers encountering possible incidental findings must not decide on feedback by themselves; they must first consult a relevant expert. If the researcher has a predetermined list of incidental findings that should be fed back, it will be sufficient to have them clinically assessed (and confirmed) by the expert, as the list will have been compiled by a multidisciplinary team (see Recommendation 1). In case of doubt, the researcher should ask a multidisciplinary team for advice.

In the event of unanticipated findings, a multidisciplinary committee should be consulted, or multidisciplinary discussions should be conducted. Together with the researcher, the committee or team will then decide whether or not the incidental finding should be fed back.
6) Providing feedback on incidental findings

The Code Good Gebruik states that feedback should always be given by the treating physician or GP not by the researcher. Study data are often not anonymised or pseudonymised or coded, so the researcher may not always know the identity of the research participant or biobank donor. Moreover, the researcher may not possess up-to-date contact details for the participant. In such cases, the researcher may need to trace the research participant back through treating physicians, study doctors or biobank staff, who originally collected the data or samples, and who will be responsible for communicating with the research participant. This guidance departs from the Code Good Gebruik, allowing for alternative procedures in which researchers take on the responsibility of communicating incidental findings to participants. Departures from professional codes are permitted in practice if they are not to the detriment of the patient. There may be reasons to allow for alternative procedures for feedback if these will benefit the research participant or donor.

In practice, the feedback procedure is implemented in varying ways. The GP or treating physician can do so by telephone, by letter in face-to-face. Sometimes feedback is given not by the GP or treating physician but by the (physician-)researcher him- or herself. The most important requirements for morally responsible feedback of incidental findings are that it should be done with care and promptly, and that it should be done promptly.

Note on Recommendation 6.1.

There is no one right way of communicating incidental findings. The most important requirement is that it should be done with care and promptly. ‘With care’ means that the person responsible for feedback understands the incidental finding and its possible clinical significance to the participant or biobank donor’s health. During the feedback conversation, the researcher may not offer a diagnosis or any medical recommendations. Depending on the information provided by the consultative expert and the participant’s level of clinical expertise, the person responsible for feedback may help the participant to interpret the finding. 

There are a number of reasons for carrying out the procedure as quickly as possible. First, prompt feedback may be in the interest of the participant or donor, as their health may benefit from timely medical intervention. Secondly, a prompt procedure expresses respect for the participant or donor. Participants often find it distressing to be informed of incidental findings months or years after data collection, and they may question why the researchers did not ‘look’ at the study data sooner. However, in the case of biobanks, the period between data collection and any feedback cannot always be avoided.

Several procedures for careful feedback are conceivable, depending on the type of study or biobank, and, in practice, procedures are organised in varying ways. In many cases it will be the treating physician who contacts the participant, sometimes by letter or by telephone, e.g. in the case of a biobank making for secondary use of bodily material to be informed of incidental findings. The bodily material will have been collected at some time in the past for diagnostic purposes, and the patient will never have been explicitly asked for consent for secondary use. The ‘donor’ may be in a better position to answer participants’ questions about the psychological impact and the drawbacks of feedback on incidental findings is therefore called for, and attention and sufficient time should be devoted to communicating with participants.

When the study protocol was drawn up, it was agreed with the GPs involved in ERGO that the ERGO physician-researchers who are responsible for providing feedback will be lower if there have been recent, multiple or long-standing contacts with the donor or treatment relationship, by contrast, e.g. in case of treatment of a chronic disease, the barrier may be lower. In the case of an existing, continuing treatment relationship has ended, the barrier to provide feedback may be higher. In the case of an existing, continuing treatment relationship, by contrast, e.g. in case of treatment of a chronic disease, the barrier may be lower. In the situation of secondary use biobanks, the treating physician will be the appropriate person to provide feedback on incidental findings.

Several procedures for careful feedback are conceivable, depending on the type of study or biobank, and, in practice, procedures are organised in varying ways. In many cases it will be the treating physician who contacts the participant, sometimes by letter or by telephone, e.g. in the case of a biobank making for secondary use of bodily material to be informed of incidental findings. The bodily material will have been collected at some time in the past for diagnostic purposes, and the patient will never have been explicitly asked for consent for secondary use. The ‘donor’ may be in a better position to answer participants’ questions about the psychological impact and the drawbacks of feedback on incidental findings is therefore called for, and attention and sufficient time should be devoted to communicating with participants.

Secondly, a prompt procedure expresses respect for the participant or donor. Participants often find it dissatisfying to be informed of incidental findings months or years after data collection, and they may question why the researchers did not ‘look’ at the study data sooner. However, in the case of biobanks, the period between data collection and any feedback cannot always be avoided.

The person responsible for feedback on incidental findings should have good social and communication skills. Initially, participants will be shocked by the fact that the research team has contacted them because of an incidental finding. Also, this contact will often mark the beginning of a longer, sometimes burdensome process of clinical follow-up. Clinical follow-up may lead to health benefits, but it may also be stressful and harmful. Awareness of the psychological impact and the drawbacks of feedback on incidental findings is therefore called for, and attention and sufficient time should be devoted to communicating with participants.

Several procedures for careful feedback are conceivable, depending on the type of study or biobank, and, in practice, procedures are organised in varying ways. In many cases it will be the treating physician who contacts the participant, sometimes by letter or by telephone, e.g. in the case of a biobank making for secondary use of bodily material to be informed of incidental findings. The bodily material will have been collected at some time in the past for diagnostic purposes, and the patient will never have been explicitly asked for consent for secondary use. The ‘donor’ may be in a better position to answer participants’ questions about the psychological impact and the drawbacks of feedback on incidental findings is therefore called for, and attention and sufficient time should be devoted to communicating with participants.

When the study protocol was drawn up, it was agreed with the GPs involved in ERGO that the ERGO physician-researchers who are responsible for feedback on incidental findings does not necessarily need to be performed by the GP or treating physician. In certain research settings, physician-researchers have sufficient clinical expertise to communicate incidental findings themselves. Feedback must always be given carefully and promptly, and in such a way that the participant or biobank donor can understand its significance.
7) Following up incidental findings

Researchers have a certain moral responsibility towards their donors or participants [29]. This responsibility does not go so far as, for instance, the duty of care that physicians owe their patients, with whom they maintain treatment relationship. However, researchers can be expected to assist biobank donors or research participants with any clinical follow-up of incidental findings that is required. They may also be held responsible for regularly evaluating their policies and practices for handling incidental findings and the impact that these have on research participants or donors, and revising them if necessary.

Recommendations

☐ 71 Offer participants help with the clinical follow-up of incidental findings, at least by providing information on the findings and by referring them to relevant medical specialists if necessary.

☐ 72 Monitor the effects of the communication of incidental findings, as long as this does not breach participants' privacy.

○ For example, ask participants about the follow-up of incidental findings (and the effects on their lives) at their next study visits.

☐ 73 Regularly evaluate the policy for the management of incidental findings. If necessary, revise lists of anticipated incidental findings that should be reported.

○ For example, have yearly or two-yearly meetings with the multidisciplinary team or committee to evaluate policies and procedures.

Note on Recommendation 7.1

In many cases researchers will not be in a position to conduct clinical follow-up of an incidental finding themselves, but they may take some responsibility for organising it. Researchers can at least help their participants with prompt referral to a relevant medical specialist, e.g. by providing the participant or specialist with study data, lab reports, images and/or reports written by the experts who were consulted. Some research groups contact the appropriate specialist to make an appointment for the participant prior to the feedback conversation to ensure a timely clinical follow-up. Especially in the case of serious incidental findings, prompt and appropriate clinical follow-up is very important, and researchers have a duty to contribute to this. It should be noted that informed consent of the participant or donor is a prerequisite, and that he or she has a right to refuse clinical follow-up of incidental findings.

Certain processes therefore need to be organised prior to the study. Researchers need to determine what medical specialist to refer anticipated incidental findings to, and need to contact that specialist. The specialist needs to be aware of the proposed study and willing to be consulted quickly if incidental findings are detected during the study.

Note on Recommendation 7.2

Researchers have a certain responsibility to monitor the effects of incidental findings on participants. However, in many cases this will not be possible, as it would breach the participants’ privacy. Consequently, researchers have little information regarding the outcomes of notification of incidental findings for research participants. It is thus not clear whether there is an adequate balance between the pros and cons of feedback. In certain research settings, it is possible to monitor the effects of feedback, e.g. in the case of clinical biobanks including long-term treatment relationships between the treating physician (or physician-researcher) and the patient. At the next clinical consultation, the barrier of discussing the incidental finding will be low, and the physician can easily ask about the clinical management of the findings and its impact on the participant’s life since the feedback conversation and referral. Similarly, some population biobanks have long-term relationships between the researchers and the participants. Also, in some longitudinal cohort studies, participants visit the study centre every year, two years, or five years, to undergo testing. The researchers can ask participants about the impact of the incidental findings at subsequent study visits. Case reports of this kind can be collected centrally and provide important input for the ongoing evaluation of policies and practices of handling incidental findings in biobanks (see Note on Recommendation 7.3).

Note on Recommendation 7.3

Research institutions need to evaluate policies for managing incidental findings regularly and revise them if necessary. Lists of anticipated incidental findings that do or do not require feedback should ideally be compiled before the start of the study or biobank, based on the available literature and best practices. There may be reasons to adapt the lists and/or protocols over time, as more and more research is being performed into the frequency and clinical follow-up of incidental findings, as well as the preferences and perceptions of donors or participants. Did notification of the participant or donor about the incidental finding produce any medical benefit? Did the medical benefit outweigh the drawbacks of feedback, e.g. the psychological impact, the risk of overtreatment and any adverse socio-economic consequences?

Policies should be evaluated regularly on the basis of novel literature and experiences from internal case reports at the research study or biobank. A multidisciplinary team, working group or committee should preferably be asked to review policies for the detection, management and communication of incidental findings every year or two years, and to revise, if necessary, the lists of incidental findings about which the research participant or donor should be informed (see Box 9 for a specific example).

When it was found, for example, that none of the thirty or so participants referred to the neurologist needed treatment for small (<2 cm) convexity meningiomas, it was decided to stop communicating findings of this kind, as it turned out that there was no medical benefit to participants.

Box 9. Revising policy on feeding back incidental findings based on evaluation of ERGO policy (see article by Bos D[4]).
References:


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