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 in. 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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1) Anticipating potential incidental findings

Incidental findings are not coincidental findings; it is now known that they can occur in certain study populations, and, also, how often they occur [1, 2]. The frequency of incidental findings detected during MRI of the brain, for example, is just under 3% in healthy research participants [3, 4]. Similarly, in genetics research, pathogenic incidental findings occur in an estimated 1-3% of healthy research participants undergoing exome or whole-genome sequencing [5, 6, 7].

We know that incidental findings may occur; as researchers, we should 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 affect the frequency of incidental findings. For example, researchers 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 in 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 than if they are explicitly asked to check research data for findings that could be relevant to the health of research participants. 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)technical and methodological choices made by researchers or research institutions [1]. 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. What 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

- ☐ 1.1 Content-related: Decide whether the test modality proposed could produce incidental findings. If so, decide what incidental findings are anticipated and whether these need to be reported to research participants.
  - o Consult the literature, best practices and/or a multidisciplinary team.
  - o Draw up a list of anticipated incidental findings in consultation with a multidisciplinary team, and decide together whether these need to be reported.
  - o When deciding this, consider the following criteria:
  - o Is there a real risk of a serious disorder?
  - o Is there a realistic management option that can be offered?

- ☐ 1.2 1.2 Procedural: What needs to be organised in advance?
  - o Set up a committee or multidisciplinary team in case incidental findings occur that were not anticipated.
  - o Make arrangements with experts and/or laboratories for consultation and/or follow-up tests to confirm incidental findings.
  - o Make arrangements with medical specialists for prompt clinical follow-up.

Note on Recommendation 1.1

Researchers 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 (Analysing data). Given the chosen test modality, however, researchers do need to consider the likelihood of incidental findings in the proposed study, and what 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 should ideally be involved in composing the list. This team – or a delegation from it – should also be available for consultation in the event of incidental findings that were not anticipated.

When defining these lists, researchers can consult published literature, best practices and experts. Appendix 1, for example, specifices 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 Geneticists (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. There should be no feedback unless "it becomes known that the risk of serious harm to one or more individuals [as a result of intervention by the researcher] could possibly be averted"[8]. In such cases, a duty of rescue may apply, and the researcher should try to prevent harm. The following criteria in the Code Goed Gebruik need to be observed here:

- There must be a real risk of a serious disorder.
- There must be a realistic management option, recognised in professional guidelines, that can be offered to the donor.
- It is uncertain whether the finding is already incorporated in the donor's current treatment. [8]

The criterion that management options must be available is usually interpreted as the principle that research participants may only be notified of incidental findings if they relate to diseases that can be treated or prevented. Participants, on the other hand, often say that they are also interested in incidental findings when there is no – proven effective – treatment or prevention available. Nowadays, research groups tend to use the criteria of 'clinical relevance' or 'relevance to the health of the research participant' to decide whether or not to report a finding. This means that sometimes, incidental findings may be fed back even in the absence of therapeutic or preventive options.

Note on Recommendation 1.2

In addition to drawing up a list of anticipated incidental findings and whether these should or should not be fed back, some procedural arrangements need to be agreed upon in advance to ensure proper handling of incidental findings. For example, findings should always be confirmed before they are communicated to participants. Recommendation 5 'Confirming incidental findings' discusses this requirement in detail. Before embarking on the study, researchers should contact experts (and laboratories if necessary) to make arrangements for consultation or follow-up testing, if required, to enable incidental findings to be confirmed during the study. It is important for researchers to arrange for access to and collaboration with experts and laboratories in advance.

This also applies to the clinical follow-up of donors or participants once information about incidental findings has been shared with them. The time that elapses between feeding back an incidental finding and the start of the clinical follow-up should be as short as possible; ideally, the participant should be offered an appointment with a medical specialist at the hospital e.g. within two or three days. Given the waiting lists for specialist appointments, it is advisable to make arrangements for prompt clinical follow-up before the start of the study. However, it may not be feasible for every research group to make arrangements of this kind; it may be easier for research groups attached to hospitals to make arrangements with specialists than for some independent research institutions.

With regards to the confirmation of incidental findings, making arrangements with laboratories will also be easier for some research groups than others. Repeating a test under Good Laboratory Practice (GLP) conditions, for instance, will entail costs. Nevertheless, this *minimal practice* requires consideration to be given to confirming and following up on incidental findings, and preferably making arrangements for both the confirmation and clinical follow-up of incidental findings.

2) Informing and consenting donors/participants

Donors and research participants need to be able to make well-informed, voluntary decisions regarding the use of their bodily material or data for current or future scientific research. A good informed consent procedure also enables donors to make an informed decision regarding the feedback of incidental findings. The information should be presented in such a way that donors and participants know what to expect and have realistic expectations as regards the handling of research findings that may be relevant to their health. The information provided to potential donors or participants should be tailored to the type of research or biobank, and the consent procedure should ideally include an opt-out option, such that participants or donors may choose not to receive information on incidental findings.

Recommendations

- ☐ 2.1 Inform participants of the possibility that incidental findings can be detected.
- ☐ 2.2 Inform participants how incidental findings will be handled.
- ☐ 2.3 Ask participants for informed consent to feed back incidental findings to them and/or a treating physician or GP.
- ☐ 2.4 Only depart from the principle of informed consent in exceptional cases.

Note on Recommendation 2.1

During the informed consent procedure, participants are informed of the likelihood of incidental findings, the types of possible incidental findings and important implications of incidental findings. Information about incidental findings can be confusing for participants, as the message is often ambivalent: 'We are not looking for, but if we do come across something we will tell you.' Nevertheless, researchers need to avoid creating a situation in which participants mistakenly expect to be comprehensively screened for abnormalities or disorders during the study.

Effective expectation management includes offering clear information that is comprehensible to research participants or donors. It is important to state explicitly that participating in the biobank is for the purpose of scientific research and that the researchers will not be searching for specific diseases. The research is not a health check, nor is it intended to improve the participant's health. Researchers need to actively dispel the 'diagnostic misconception', so that participants do not conclude that they are completely healthy if researchers have not said anything about abnormalities or disorders during the study. See Box 1 for examples of informed consent forms and leaflets.

Prospective donors need to be given correct information on all relevant aspects of the study, including incidental findings, through written information and a face-to-face conversation. In the case of genetic research, for example, possible consequences of incidental findings for family members need to be discussed.

I realise that the ERGO study is a scientific study. ERGO is not a preventive screening programme, so there is no specific search for particular diseases. Some tests (e.g. X-rays and certain blood tests) are carried out, but in some cases they will only be assessed years later. Also, the ERGO study does not examine everything throughout the body, so some diseases may go unnoticed. (Rotterdam Study/ERGO)

LifeLines is a population study, but it does not specifically screen for diseases in the way that the breast cancer screening programme does. Participation in the study is not a substitute for normal patient care. If you have any health problems you should go to your GP or specialist. (Lifelines)

Box 1. Examples of clauses from informed consent forms and leaflets.

Other aspects besides information are involved in creating the right expectations among participants. Research managers at UK Biobank, for example, have opted to keep feedback of incidental findings to a minimum. The MRI scanner for the imaging research has deliberately been located on an industrial estate, and the technical assistants do not wear white coats. Participants are explicitly told that it may take years before research scans are examined by a human being. In this way, UK Biobank tries to prevent participants from associating the research with doctors and health care and to justify its no-feedback policy [9]. In this setting, it is easier to make it clear to subjects that the scans will not be checked for abnormalities, and no feedback will be given on any abnormalities. In some neuroscience laboratories where mainly behavioural psychology studies are carried out, associations with health care – and hence the diagnostic misconception – can be avoided relatively easily. As the likelihood of incidental findings in such research settings is small, less effort needs to be put into designing follow-up actions.

This is not the case with a study such as ERGO, where there are doctors walking around the research centre. At the end of each study visit participants will normally have a concluding interview with a doctor about individual research results that are of direct interest to their health (e.g. high blood pressure detected during the day). Participants will – rightly – have different, higher expectations regarding the feedback of incidental findings. Researchers need to take into account such expectations. There should be no mismatch between participants' expectations and actual procedures. Recommendation 6, 'Feeding back incidental findings', goes into more detail on the feedback procedure.

This recommendation is different in the case of a biobank regarding the secondary use of residual bodily material derived from clinical care settings: patients often have no expectations, or minimum expectations, as regards the feedback of any incidental findings. In practice, many patients do not even know that their residual material is being used for research purposes [10]. Although the information provided about secondary use in hospitals has been improved since a 2009 report by the Rathenau Institute, patients' expectations will be low as regards the feedback of incidental findings.

Note on Recommendation 2.2

Ideally, future donors or participants should be informed not only about the possibility of incidental findings, but also about the procedures for handling these incidental findings. Will the data be examined for abnormalities, for instance? If so, who will do this, and how? How and when will the donor or participant be notified of any incidental findings? Will the GP or attending physician be notified automatically? Or may a participant or donor opt to be notified by the researchers without the GP or treating physician being notified? The donor or participant may need this information to grant informed consent for participation in the study or the use of their data. See Box 2 for examples of information to participants or donors on the procedures for handling incidental findings.

"'Many diseases and abnormalities could be noticed. Me and my GP will be notified of diseases or abnormalities that are noticed, unless I have opted out from this.

If I state that I do not wish to receive any results from the ERGO study, they will not be given to me. However, if "not knowing" about one or more findings does not outweigh the resulting detriment to myself or others, I will be given them. (ERGO)

Afterwards you and your GP will be informed about the most important results, such as your weight, waist circumference, BMI, blood pressure, blood glucose (blood sugar) level, total cholesterol, HDL and LDL cholesterol, triglycerides, ECG, pulmonary function and the results of the MINI interview. These data and the results of the blood tests will be assessed by doctors. If there are any abnormalities you and your GP will be notified. (Lifelines)

We shall notify you if findings are made from your visits that require medical intervention. (Leiden Long Life Study)

What do we do with findings from scientific research deriving from your ... (blood, DNA, bodily material) that could be of importance to you personally or your relatives?

We cannot rule out issues emerging during future scientific research on your... (blood, DNA, bodily material) that are important to your health and/or that of your family members, for example, findings that point towards a disease or disorder of your... [insert explanation or example of the area in which these findings could occur] or an increased risk of a disease or disorder, e.g. due to a hereditary abnormality that could also occur in your family members. We shall notify you of any such findings if they are indicative of a serious health problem or risk for which treatment is available. We shall always consider carefully whether it is really necessary to notify you of the finding, and ask a committee from the hospital to give advice on the matter. If you do not wish to be notified, you cannot take part in this biobank. (Example from PIF AMC)

Box 2. Examples of clauses from patient information/informed consent forms on the detection and handling of incidental findings.

Note on Recommendation 2.3

Some biobanks ask research participants during the informed consent procedure to decide whether they wish to be given information on individual study findings and/or incidental findings that could be of clinical importance, and whether the treating physician or GP may be notified. By far the majority of donors or research participants wish to receive this information, and also provide consent for notification of the GP or treating physician, but a small minority does not.

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 should be offered an opt-out. Opponents of this practice claim that participants should not be offered the choice of whether or not to be notified of incidental findings; in their view, participants should always be informed about incidental findings. Biobanks should only engage donors who are willing to be given information about incidental findings and who have given informed consent for this [11]. In practice, too, many biobanks operate on a 'no opt-out' policy: every donor or participant must give consent to being given information on incidental findings. Without that consent, participation in the study or biobank is not possible. The reason is that researchers want to avoid being in a situation in which they consider it necessary to notify a participant of a particular finding, without being given the permission to do so. They would face a serious ethical dilemma: on the one hand, they want to respect the participant's autonomous wish, but on the other hand, they want to act in the participant's interests by providing the information nonetheless. This dilemma does not only occur in research settings, it may also occur in clinical settings (see Box 4).

'I agree that results from the ERGO study that are important to a physician will be communicated to my GP.'

☐ *Yes* ☐ *No*

'I would like to be given the results from the ERGO study that are of medical importance to me.'

☐ *Yes* ☐ *No (ERGO)*

"I would like to be given the results from the measurements myself."

☐ *Yes* ☐ *No (Lifelines)*

I know that issues could emerge during future scientific research on my bodily material that are indicative of a serious health problem or risk in myself and/or my family members for which treatment is available, and that I will be notified of these findings by my attending physician. (AMC)

Box 3. Passages from informed consent forms regarding consent for the feedback of findings.

The Medical Treatment Contracts Act (WGBO) lays down that a patient has the right to refuse information and/or treatment: (If the patient has expressed the wish not to be given information, it shall not be supplied, except insofar as the patient's interest therein is outweighed by the harm that could result to the patient or others.). If the patient does not wish to be given information, the treating physician should in principle respect that wish. The physician may make an exception if this could prevent serious detriment to the patient or others. The right to refuse information is based on the ethical principles of respect for patient autonomy and non-maleficence: unwanted information concerning health conditions or risks can be harmful, due to the psychological impact of that information and the possibility of 'overdiagnosis' and overtreatment. The right to refuse information may not be absolute, however; it may be overruled if the patient's life or well-being is at stake.

Box 4. From the Medical Treatment Contracts Act (Wet op de geneeskundige behandelingsovereenkomst, WGBO), Article 449 of the Dutch Civil Code

Although a research participant does not have a medical treatment relationship with the researcher, the same reasoning as in the WGBO could be applied to research participation. If the participant does not wish to be given information about individual research results or incidental findings, the researcher should in principle respect that wish. The researcher may make an exception if a consulted expert argues that this could help to prevent serious detriment to the participant or others. The possibility of making an exception eliminates the main argument for withholding from offering research participants the opportunity of an opt-out: in the event of a conflict of duties, the researcher can decide to report a clinically relevant incidental finding against the wishes of the research participant. If the life of the research participant is in peril, or serious harm could be prevented by notifying the participant, the researcher is permitted to do this, even if the participant has opted out.

The vast majority of research participants or donors do want to receive information about findings. The small group of participants or donors who do not, can be offered an opt-out, i.e. they may be given the opportunity to indicate during the informed consent process that they do not want to receive information about findings. This way, they can participate in research (and therewith, contribute to the public good) without being forced to be informed of individual research results or incidental findings. By offering an opt-out opportunity, the autonomous wishes of research participants can be respected as far as possible, and any harm associated with unwanted information can be avoided.

Note on Recommendation 2.4

Only in exceptional cases may researchers depart from the principle of informed consent for the feedback of incidental findings. Studies currently being organised and biobanks being set up can and must ask donors or participants for consent to feed back incidental findings. Such consent will not always have been obtained for studies and biobanks that have been set up or initiated in the past.

This also applies e.g. to collections of residual material left over after clinical diagnosis or treatment. In hospitals across The Netherlands, residual material is stored on the basis of an opt-out system and is (not anonymised but) coded and (re-)used for scientific research: this is referred to as 'secondary use' of bodily material. An enhanced or 'thick' opt-out system is regarded as acceptable for the secondary use of body material. This means that patients are informed about secondary use and are given the opportunity to opt out. Consent is in effect presumed: in order to refuse consent, patients must take action and have their refusal recorded. Under the opt-out systems in hospitals, then, patients are not asked for consent to feedback of incidental findings.

Ideally, participants should first be asked to consent to feedback also when existing data or bodily material is reused for research and there is a likelihood of incidental findings, but it is not always possible to contact them. Researchers do not always have up-to-date contact details, and some participants may have re-located. Many participants may not even know that they have made data or bodily material available for research, especially if the data or materials were collected years ago. Researchers also fear that if explicit informed consent is required, by mail or through an online platform, many participants will not make the effort to provide it, and as a result, portions of the database or biobank would become unusable. That would be a shame, especially if the proposed research could achieve important scientific or social objectives.

In some cases, therefore, it is possible to make an exception to the consent principle.
The researcher must then argue:

- why incidental findings from the study cannot be ruled out;
- why informed consent for the feedback of incidental findings cannot be obtained or cannot be required, and;
- why the importance of the research warrants the exception.

3) Collecting data

For researchers it is important that data are generated and collected in valid, reliable ways, but also inexpensively and efficiently. Researchers should base decisions about the type of data to be collected primarily on the study question(s) and any practical considerations. The likelihood of incidental findings should not play a role in decisions regarding modalities for data collection. At the same time, however, researchers should assess whether – and when – the possible strategies of data collection could give rise to incidental findings.

Incidental findings may be detected during data collection, or later on, when the data, samples or images are analysed. This will depend largely on the type of test used: when testing blood pressure, for example, it will be immediately clear to the researcher whether or not the person has hypertension. This is not the case with certain blood values or genetic test results, which will only be determined later on in the laboratory. In the case of imaging research, an incidental finding may be detected either during data collection when the participant is present, or later on, when the scan is 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.

Recommendations

- ☐ 3.1 Use tests or scans that are necessary to answer the research questions. It is not necessary to carry out additional tests or scans with the aim of detecting incidental findings.
- ☐ 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.

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, for example, if the scans are of diagnostic quality than if they are of low diagnostic quality. This also applies to genome-wide testing rather than targeted genetic testing. Decisions on the tests or techniques to be used, then, will have a major influence on whether or not incidental findings are detected. These decisions need to form part of the policy on the handling of incidental findings.

In the case of new studies or biobanks being launched, researchers will need to decide in advance what types of data they are going to collect. Most research institutions do not require researchers to collect additional data with the aim of optimising the detection of incidental findings [12]; researchers should opt for the test that is most appropriate to answer the research question [13]. The National Institutes of Health (NIH) in the United States, on the other hand, requires additional diagnostic-quality scans for all research involving MRI [14], even if they are not necessary for the research. The NIH accordingly requires research scans to be systematically clinically assessed by radiologists. The aim is to have all research scans checked for possible abnormalities.

This is not required in the Netherlands, and in many other European countries it is not standard practice to ask researchers to carry out additional scans that are not necessary for the purposes of the research [15]. Indeed, in the Netherlands, that might be regarded as a type of 'opportunistic screening', which is not permitted under the Population Screening Act (Wet op het bevolkingsonderzoek) without a license [16]. In line with this, the Health Council of the Netherlands has stated that in diagnostic settings, testing modalities should be as targeted as possible [17], to reduce the likelihood of incidental findings. Under Recommendation 4, 'Analysis', we discuss a parallel debate in genetics on whether researchers should, or are permitted to, actively 'hunt' for incidental findings.

Note on Recommendation 3.2

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 data 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 also often sets out what researchers should do if they observe anticipated 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 e.g. whether or not to look for any abnormalities, and what to do if they happen to detect a possible abnormality (including whom to telephone, how to store the data, what they can and cannot say to the subject). 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 a protocol for imaging studies:

- Do we expect radiography personnel to look for abnormalities in the images? Current policies vary enormously [18].
- What 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 radiography personnel deal with possible incidental findings [18, 19]?
- What kind of practical steps should radiography personnel take when detecting an abnormality? It is often standard protocol to alert the principal researcher, study doctor, or the medical specialist associated with the study, who will then take appropriate action. The scan in question will be stored and forwarded for further consultation.
- Is the radiography personnel not permitted to notify the participant of the abnormality at that time? No, any incidental findings must always be confirmed by a radiological expert first. The radiography personnel is not allowed yet to give any feedback to the research participant.
- 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.

If:	Then:
The average diastole in the last two tests is higher than 120	- *Ask at the end of the tests whether the participant has any symptoms (e.g. recent headache, poor vision, nausea or vomiting,shortness of breath, chest pain or pain between the shoulder blades).* - *If not: advise the participant to contact his or her GP within a week.* - *If so: advise the participant to contact his or her GP the next day at the latest.* - *Give the patient a referral note stating the last two blood pressures found and heart rate.* - *Report these blood pressures to the team leader and state the advice given to the participant.*
The average diastole in the last two tests was higher than 100 and lower than 120	- *Advise the participant to contact his or her GP within two weeks.* - *Give the patient a referral note stating the last two blood pressures found.* - *Report these blood pressures to the team leader and state the advice given to the participant.*
The average systole in the last two tests was higher than 180	- *Ask at the end of the tests whether the participant has any symptoms (e.g. recent headache, poor vision, nausea or vomiting, shortness of breath, chest pain or pain between the shoulder blades).* - *If not: advise the participant to contact his or her GP within a week.* - *If so: advise the participant to contact his or her GP the next day at the latest.* - *Give the patient a referral note stating the last two blood pressures found.* - *Report these blood pressures to the team leader and state the advice given to the participant.*

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

4) Analysing data

Once the study data has been collected, they are analysed in order to generate research results. It may often be unclear to researchers whether or not they should, or are permitted to, 'look for' possible abnormalities. Should, for instance, the likelihood of incidental findings from exome or whole-genome sequencing be minimised, e.g. by using filters when analysing the data? Or, by contrast, should the DNA be checked for incidental findings? This is one of the topics on which there is as of yet no consensus among geneticists or ethicists, either in the Netherlands or in Europe. In the Netherlands, management of incidental findings during data analysis may vary. This guide does not offer an answer to this controversial question; instead, it presents possible policy options and examples from practice.

Recommendations

☐ 4.1 When analysing data, it is not necessary to generate additional research results with the aim of detecting incidental findings. However, if research results are generated in which incidental findings relevant to the health of research participants are easy to detect or easy to deduce, they may be checked for abnormalities during analysis.

- It is not necessary, for example, to carry out additional analyses to screen DNA for pathogenic mutations, but if the research results include data on such mutations, they may be monitered for them.
- Diagnostic-quality scans, on which incidental findings are easy to detect, may also be checked for clinically relevant findings.

Note on Recommendation 4.1

on images [12]. However, some research institutions in the Netherlands and elsewhere do screen research scans for abnormalities as a standard practice, especially if the acquired scans are of high diagnostic quality [1, 14, 20, 21]. Standard assessment of research scans by a radiologist – referred to as 'routine clinical review' – is also recommended by the UK Medical Devices Agency [20]. This is particularly the case when scans are collected in a clinical setting and participants may expect their scans to be 'checked'. At some institutions the assessment is divided into two stages: the first involves screening of scans for abnormalities performed by trained researchers, the second involves reviewing of the abnormalities by a clinical radiologist and deciding whether they require feedback. The ERGO study, for example, uses such a two-stage assessment process.

Routine clinical review of research scans is not feasible in all studies, however. It can be expensive, unpractical and logistically impossible [22], especially for research groups that are not affiliated to a hospital. In the United Kingdom an estimated 40% of imaging research is carried out by non-medical researchers [22], e.g. at neuroscience research centres that have no connection with hospital-based radiologists. It is not feasible for centres of this kind to organise routine clinical review. In addition, the functional scans carried out at neuroscience research centres are often not of diagnostic quality. Clinical review of scans of lesser quality is generally not feasible nor informative. Nevertheless, a US study shows that reviewing diagnostic-quality scans by a radiologist as standard practice does not need to be costly – 24 dollars per scan (see Box 6) [21].

Given that two-stage review is sufficient, feasible and responsible in certain research settings, we concluded elsewhere that some kind of radiological review should be performed where diagnostic-quality scans are carried out [1, 18], especially in research settings where participants or donors expect this from the researchers. This, however, is a controversial position: some experts consider actively 'looking for' incidental findings to be a form of screening and therefore undesirable or illegitimate. The final word has not yet been uttered on this subject.

> *"Our model began with a mandate from the University of New Mexico Health Sciences Center IRB to have all research MRI scans evaluated for IFs. (...) MRN developed a centralized, standardized approach to IFs that was developed with PIs and implemented over several months. (...) All scans were performed at MRN on 1 of 3 MRI scanners. MRI sequences varied depending on study protocols and included at least one anatomic scan; complete clinical scanning was not part of any study. Using OsiriX (www.osirix-viewer.com/) and an in-house-developed neuroinformatics software system (Medical Imaging Computer Information System [MICIS]), reviews were completed and securely e-mailed to the PI using a code in lieu of participants' names to ensure confidentiality. A copy of the radiology report was mailed to participants with a cover letter thanking them for participating, providing them contact information for questions, and reminding them the scan was for research purposes only. (...) The radiology report used a 5-point Likert rating scale to identify and classify IFs asfollows (modified from Shoemaker et al. [21]): 1) no abnormal findings; 2) no referral necessary; 3) routine referral; 4) urgent referral; or 5) immediate referral. The medical director was immediately notified by the neuroradiologist when a level 4 or 5 finding was discovered. The study PI and the participant (or guardian) were then contacted by the medical director to assist with coordinating clinical care." [21]*

Box 6. Procedure for the routine review of diagnostic scans

In genetics too, opinions are sharply divided on how genetic data should be analysed and to what extent researchers may (or should) look out for abnormalities. If there is a duty to feed back certain clinically relevant incidental findings (when detected incidentally), some have argued, it follows that there is also a duty to *search* for such findings, especially if the data have already been generated and are readily available. Important ethical considerations in support of this position include the participants' best interests, the responsibility of the researcher and the unique opportunity to put genome-wide data to clinical use [23]: now that we have the data – thus runs the argument – it would be a shame not to look at it.

Incidental findings are detected in 1-3% of research participants undergoing exome or whole-genome sequencing [5, 6, 7]. These estimates relate to clinically useful (that is, medically actionable) findings, i.e. conditions that are treatable or that could be prevented. These findings are the types of findings that were included in a list of secondary findings that, according to the American College of Medical Geneticists (ACMG), need to be reported to patients undergoing clinical exome or whole-genome sequencing for diagnostic purposes [24, 25] . The list of 57 genes associated with 24 medical conditions was published by the ACMG in 2013. These 57 genes must actively be examined, in addition to the genes which are initially selected to study the problem with which the patient presented him- or herself (i.e. the primary findings). Consequently, these are strictly speaking not incidental findings, but secondary findings (that are actively sought). Although the ACMG-list was intended for use in the clinical setting, some research institutions have adopted the list and use it as a basis for feedback policies in research: incidental findings that have been included in the ACMG-list should be fed back to research participants or donors [26].

In Europe, this kind of opportunistic screening is not accepted within scientific research (or in diagnostics). The European Society of Human Genetics (ESHG) published a recommendation in 2013 that strongly contrasts with the American recommendation: in the opinion of the ESHG, genetic research should be conducted in such a way as to minimise the likelihood of incidental findings [28]. Researchers should decide either to analyse a small, specific part of the genome or to use filters to avoid the generation of additional findings beyond the scope of the research question [28]. This is in line with the Dutch National Health Council's recommendations on handling incidental findings in diagnostics [17]. An example of an approach based on this policy is that of Radboud University Medical Center, which involves using filters and asking donors for explicit consent to use their bodily material for genome-wide analyses. Note, however, that filters cannot prevent the occurrence of all incidental findings: even after a filter has been applied, clinically relevant pathogenic mutations may be detected in the research results.

Many Dutch researchers endorse the aim of preventing incidental findings as much as possible. Also, some research institutions opt for additional anonymisation of data in research involving genome-wide analyses (see Box 7), e.g. by destroying a key or storing it at a location that is unknown or inaccessible to the researcher (e.g. via a Trusted Third Party (TTP)). These institutions wish to prevent researchers from finding themselves in a situation where they have clinically relevant information on a research participant without knowing what to do with it. In particular, it is considered problematic when no agreement with the research participant has been made in advance concerning the communcation of incidental findings. In a fully anonymised study, the researcher will not be able to trace the individual who was the source of the data or bodily material. When researchers find an actionable pathogenic mutation, providing feedback will not be possible, as they do not know from whom the data was derived. Opinions differ as to whether complete anonymisation is possible and desirable in genomic research, as, in principle (and with a disproportionate effort), a donor's identity can be traced from DNA. There is as of yet no gold standard for analysis and communication of genetic incidental findings in research settings. It is hoped that policies on the subject will develop in the coming years.

> *Taking blood at this session will enable us to study characteristics related to heredity and assess them in relation to lifestyle and other conditions that are factors in the development of health problems. The genetic research into diseases will be carried out in such a way that the results cannot be traced back to you personally.*

Box 7: Quote concerning anonymization derived from the Lifelines information leaflet.

[1] The ACMG lays down that all patients undergoing diagnostic exome or whole-genome sequencing should also be checked for 56 actionable genetic variants [24, 25]. This kind of opportunistic screening is not approved in Europe [27, 28].

5) Confirming 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.
  - o In the event of anticipated incidental findings, make decisions in accordance with the predetermined 'list' or protocol.
  - o 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 Goed Gebruik states that feedback should always be given by the treating physician or GP, not by the researcher. Study data are often not anonymised but pseudonymised or coded, with the result that the researcher does not always know the identity of the research participant or biobank donor. Moreover, the researcher may not posses 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 biobanks staff, who had originally collected the data or samples, and who will be responsible for communication with the research participant.This guidance departs from the Code Goed Gebruik, allowing for alternative procedures in which reseachers take on the responsibility of communicating incidental findings to their 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 or 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 that it should be done promptly.

Recommendations

- ☐ 6.1 Organise the procedure for communication of incidental findings with participants in such a way that they are informed with care and promptly. Have the feedback given by a physician or researcher who understands the incidental finding and its possible clinical significance, and has good communication skills.

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's 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 consulted expert and his or her own level of clinical expertise, the researcher may help the participant to interpret the finding ('This doesn't necessarily mean that …' or 'The specialist will decide whether …'). In some cases, (physician-)researchers may have sufficient understanding of the incidental finding and its potential clinical significance such that they may provide the feedback themselves in a responsible way.

'Prompt' means that the procedure for the detection, confirmation and communication of the incidental finding takes place as soon as possible. If abnormalities on images or within test results are detected in the course of the study, they must be confirmed as soon as possible through expert consultation, or, if necessary, by repeating the test under GLP conditions. Decisions on whether or not to report incidental findings must be made as quickly as possible and in the context of a team discussion. Lastly, feedback to the participant or donor must be given as soon as possible. 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 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 in particular, a long interval between data collection and any feedback cannot always be avoided.

The person responsible for feeding back 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 feeding back 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 by letter or by telephone, e.g. in the case of a biobank making for secondary use of residual bolidy material aquired in the clinical setting. 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' was a patient, who was in a treatment relationship with the treating physician but had no relationship at all with the researcher. Also, incidental findings can sometimes be discovered many years later. When the 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.

This is not the case for 'de novo' biobanks, population biobanks or other ongoing research studies. The barrier to provide feedback will be lower if there have been recent, multiple or long-standing contacts with the donor or research participant. Also, the barrier will be lower if information on and informed consent for the use of bodily material and data is explicit and recent. If an incidental finding occurs during a longitudinal cohort study at a population biobank, a researcher him- or herself may take responsibility for giving feedback. An example of a procedure of this kind is the ERGO study (see Box 8). The ERGO physician-researchers who are responsible for feedback are clinical specialists themselves and have sufficient understanding of incidental findings and their potential clinical significance. They are likely to be in a better position to answer participants' questions about the findings than, for instance, the GP or treating physician (of another discipline) in the hospital. The physician-researcher subsequently notifies the GP that the incidental finding has been communicated to the participant, if agreed upon with the participant.

This last example represents a departure from the Code Goed Gebruik, for the benefit of the research participant. This guide argues that communication of 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.

When the study protocol was drawn up, it was agreed with the GPs involved in ERGO that the ERGO physician-researchers would in principle be responsible for feeding back incidental findings from the Scan Study. The neuroradiologist-researcher would inform participants of incidental findings by telephone. Before the telephone call was made to the participant, an urgent outpatient appointment would already have been made with a medical specialist (a neurologist or neurosurgeon) in the hospital for clinical follow-up.

Box 8. Procedure for feeding back incidental findings in ERGO.

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

- ☐ 7.1 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.
- ☐ 7.2 Monitor the effects of the communication of incidental findings, as long as this does not breach participants' privacy.
  - o For example, ask participants about the follow-up of incidental findings (and the effects on their lives) at their next study visits.
- ☐ 7.3 Regularly evaluate the policy for the management of incidental findings. If necessary, revise lists of anticipated incidental findings that should be reported.
  - o 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]).

Sources

Interviews & documentation:

1) Documentation from the Radboud Biobank and the Genetics Department
   Interview with Dr Peggy Manders (21/02/2017), manager of the Radboud Biobank
2) Documentation from the Rotterdam Scan Study
   Interviews with Dr Meike Vernooij (08/03/2017, 26/03/2014), Prof. Aad van der Lugt (08/04/2014) and Dr Jan Heeringa (10/03/2014), all involved in the ERGO study
3) AMC (Academic Medical Centre) documentation on biobank policy
   Interview with Dr Corrette Ploem (20/02/2017) of the Public Health Department, AMC Amsterdam
4) Documentation from the Leiden Long Life Study
   Interview with Dr Marian Beekman (28/02/2017) of the Leiden Long Life Study in Leiden
5) Documentation from Lifelines
   Interview with Dr Marie-José Bonthuis and Dr Aafje Dotinga (21/02/2017), both of the Lifelines biobank, Groningen
6) Documentation from PALGA
   Interview with Dr Lucy Overbeek and Dr Annette Gijsbers (31/01/2017), both (at the time) of PALGA in Houten
7) Documentation from the Erasmus MC Medical Ethics Review Committee
   Interview with Claudia Waardhuizen (20/03/2017), Project Leader, Sophia Biobank, Erasmus MC

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