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MAGNETIC RESONANCE

How to report incidental findings from population whole-body MRI: view of participants of the German National Cohort

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Abstract

Objectives In the German National Cohort (GNC), 30,000 individuals are examined with whole-body MRI (wbMRI), of which about 3000 participants are expected to receive an incidental finding (IF) disclosure. In order to get feedback from participants and to evaluate the IF-management procedure of the wbMRI substudy, a follow-up questionnaire was developed. This single-center pilot trial was aimed to get a first impression on feasibility reproducibility and validity of such a survey in order to take necessary adjustments before initiating the survey among several thousand participants.

Methods The questionnaires were sent out in test–retest manner to 86 participants who received a wbMRI examination in January–February 2016 at the imaging center in Neubrandenburg. The ratio of participants with and without IF notification was 1:1. Descriptive statistics was performed.

Results A first response of 94% and completion proportion of 99% were achieved. Participants were satisfied with the examination procedure. Ninety-five percent of participants considered it very important to receive notification of IFs. Participants reported minimal stress levels while waiting for a possible IF notification letter, but high stress levels when an IF letter was received. Phrasing of the IF reports was rated in 97% as well understandable and in 55% as beneficial to health status.

Conclusions This questionnaire will serve researchers within the GNC as a fundamental instrument not only for quality management analyses but also for the investigation of still unacknowledged scientific and ethical questions contributing to evidence-based guidelines concerning the complex approach to IFs in future population-based imaging.

Key Points

- *Evidence-based guidelines for reporting incidental findings in population whole-body MRI are lacking.*
- *Pilot-testing of a questionnaire for the evaluation of practical and ethical aspects of the procedure to report incidental findings in the German National Cohort shows a high level of acceptance and high return rate by participants.*
- *Participants reported minimal stress levels while waiting for a possible incidental finding notification letter, which increased significantly, when such a letter was received.*

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Keywords Questionnaire design · Incidental discovery · Epidemiology · Tomography

Abbreviations

FU	Follow-up
GNC	German National Cohort
IF	Incidental findings
KORA	Kooperative Gesundheitsforschung in der Region Augsburg
SHIP	Study of Health in Pomerania
wbMRI	Whole-body magnetic resonance tomography

Introduction

Management of incidental findings (IFs) detected in volunteers, examined in a research context, is challenging. Leading international committees are stressing the importance of careful consideration of the ethical and scientific aspects in this regard [1–3]. However, there are still no fully validated, reliable, and objective measures to date.

The German National Cohort (GNC) is one of the largest population-based cohort studies in Europe, involving approx. 200,000 volunteers. The main goal of this interdisciplinary, multicenter cohort study is the investigation of the development of common chronic diseases including cancer, diabetes, cardiovascular, neurodegenerative/psychiatric, respiratory, and infectious diseases [4]. While all 200,000 volunteers of the GNC undergo an initial 2.5-h exam including interviews, questionnaires, variety of physical exams, and the collection of biological samples such as blood, urine, saliva, nasal swabs, and stool, a subgroup of 40,000 examinees participate in an intensified 4-h exam, of whom a subgroup of about 30,000 examinees undergo whole-body magnetic resonance imaging (wbMRI). MRI examinations are conducted at five imaging centers across Germany and comprise a set of scientific sequences, and reading for IFs is performed at each imaging site by board certified and specially trained radiologists; additionally, quality assurance procedures are in place [5].

For the wbMRI substudy, a comprehensive IF-management strategy was developed by a scientific board [6]. This included the development of a list of pre-defined IFs, each usually representing a certain imaging finding or a clinical entity or group of entities, like Bosniak 3 cysts, lobar pneumonia, or spinal cord compression. IFs were classified into three types: (1) urgent notification required, (2) notification required, and (3) no notification required [7], similar to the classification matrix proposed by Wolf and her colleagues [8]. In case an IF is found that requires notification, the participant receives a standardized letter within 10 workdays after the examination. In case urgent notification is required, the participant is informed immediately via phone call [5]. Participants are not offered the chance to opt out from being informed about IFs. Reporting of IFs according to this strict "positive list" has the advantage of revealing preferably only clinically relevant findings to the participants while trying to avoid overdiagnosis, unnecessary work-up examinations, and anxiety.

To assess the quality of the current IF reporting strategy, a specific follow-up (FU) questionnaire was developed to get feedback from participants within the GNC, in particular from those who received a notification on potentially clinically relevant findings to evaluate the IF-management procedure of the wbMRI substudy. The questions were designed with the objective to provide a feedback channel for ethically and scientifically relevant questions in context of radiology. The questionnaire aims to cover different aspects, e.g., the expectation of participants and their perception of the procedures. With participants who received IF notification, we are interested to learn about their follow-up procedures, correctness of reported IFs, and the level of distress and overall satisfaction. These feedbacks will help us optimize and improve the process. Moreover, the results of this questionnaire could contribute to the development of evidence-based practice guidelines for the management of incidental findings detected in wbMRI examinations involving volunteers. In the GNC, 30,000 individuals are examined with wbMRI, of which about 3000 participants are expected to receive an IF disclosure.

In order to test the feasibility, reproducibility, and validity of the questionnaire, a pilot study was conducted at a single MRI center. In this paper, we report the results and first experiences of this pilot study.

Methods

Participants

The study was approved by the ethic board of the GNC and conforms to the principles of the Declaration of Helsinki. The pilot phase was performed at a single imaging center. The FU questionnaires were sent out in August 2016 to 86 participants who received a wbMRI examination in January–February 2016 at the imaging center in Neubrandenburg. The number of participants in this first questionnaire pilot phase resulted from the number of available participants having finished wbMRI and completed waiting time of 6–7 months between MRI and questionnaire distribution. The 6–7 months after the wbMRI examination was chosen to leave sufficient time for work-up of the disclosed IFs and for final diagnosis. With a ratio of 1:1 with and without IF notification, 86 participants were manually selected in the Imaging Core for Incidental Findings, Heidelberg. In case a FU questionnaire was not returned after 4 weeks, the questionnaire was sent a second

time followed by a reminder phone call. In order to evaluate the test–retest reliability, the exact same questionnaire was sent approximately 8 weeks after the return of the first questionnaire. Test–retest analysis applies only to the pilot phase.

FU questionnaire

The development of the FU questionnaire was based on the questionnaire used in the Study of Health in Pomerania (SHIP) [9, 10] and Kooperative Gesundheitsforschung in der Region Augsburg (KORA) [11]. The FU questionnaire consists of 26 German language questions of which the first 13 questions address both participants, with and without IF notification. The next 13 questions are specifically addressed to participants who received an IF notification. The full questionnaire consists of eight pages and is written in a dedicated questionnaire format (TeleForm, Electric Paper Informationssysteme GmbH, Germany) in order to ease automatic evaluation. The questionnaire includes closed-ended dichotomous, multiple-choice and rating-scale questions, matrix questions and in some cases open-ended question types. In the first part of the questionnaire, participants are questioned for their motivation for participating in the MRI examination, if the information prior the examination was clear enough, how they perceived the duration of the MRI examination itself and if they experienced stress in the time waiting for possible notification of an IF. Furthermore, we asked if they would agree to participate in a FU MRI examination. Participants who received an IF notification were asked if the disclosed finding was previously known, if the language of disclosure was clear enough to understand, and to which degree they were distressed by the notification. Detailed questions were asked about how the disclosed findings were followed up on in terms of if and which specialist was consulted, what kind of work-up was done, about any complications during work-up, time spent until diagnosis and what the exact diagnosis was.

Statistical analyses

Descriptive statistics was provided using means ± standard deviations for continuous variables and frequencies (percentages) for categorical variables. Comparisons between groups were performed with an independent sample *t* test for age and Fisher's exact test for all categorical variables.

To assess the feasibility of the questionnaire, aspects concerning time for completion and compliance were evaluated. The compliance was reflected in the participation and total number of missing values per participant for the first 13 non-filter questions.

In an attempt to assess reliability, test–retest analysis was performed by administering the identical questionnaire to the same participants for a second time 8 weeks later. Following a frequency analysis interrater reliability index (Cohen's kappa) was calculated for every question with respect to the degree of disagreement when necessary. Values are < 0 as indicating no agreement and 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement. By negative simple kappa values due to uneven score answers to estimate the strength of the correlation Spearman correlation coefficient was calculated. A two-sided p value of < 0.05 was considered to indicate statistical significance. All analyses were performed using Stata (SAS 9.4, SAS Institute and Statistica 7.0, StatSoft).

Results

The general characteristics of the participants are shown in Table 1. Briefly, 86 participants (38 male) with a mean age of 58.7 ± 8.0 years were involved in the study, 43 of them with the presence of at least one IF. There has been no significant difference regarding age and gender between responders to the first and second surveys.

Response

Eighty-one out of 86 (94%) participants responded with a completion proportion of > 98% to the first 13 questions with only 11 missing values (1.04%). Compliance is to be considered sufficient, since there has been no incomplete questionnaire (more than 50% missing values). Fifty-eight participants responded to the initial delivery of the questionnaire within 12 ± 6 days. Twenty-four participants responded to the second delivery of the questionnaire and/or telephone reminder within 24 ± 10 days. In the retest round, 55 participants returned the questionnaire (32% less than in the initial batch). Response time was 13 ± 7 days.

Study evaluation

More than 95% of all participants perceived the duration of the wbMRI-exam, which takes approx. 1 h, as not too long and therefore as tolerable. Ninety-two percent were satisfied with the information given prior to the wbMRI examination. Moreover, about 95% would consider participating in an MRI FU examination. Almost all participants (95%) considered it very important to receive notification of IFs, 46% of them would not have even taken part, if the prospect of receiving IF notification had not been given. The emotional stress experienced while waiting for a result letter was estimated severe by 7% of the responders and mild by 34%. Almost half of them would like to be informed about all kind of findings, regardless of their clinical relevance. Only 15% of all responders would prefer to be informed only about medical conditions, which are treatable. During the informed consent discussion, all participants were explained that a notification

Table 1 General characteristics of study participants

	All contacted subjects	Subjects responded to S1	Subjects responded to S2	*p* (S1-responders vs S1-non-responders)	*p* (S2-responders vs S2-non-responders)
N	86	81	55		
Age	58.7 ± 8.0	58.5 ± 8.1	59.1 ± 8.0	0.27	0.41
Male/female	38/48 (44/56%)	35/46 (43/57%)	25/30 (45/55%)	0.65	0.81
Subjects with/without presence of any IF	43/43 (50/50%)	38/43 (47/53%)	20/35 (36/64%)	0.18	0.02
With more than 1 IF	6 (7%)	4 (5%)	1 (2%)	0.05	0.09
With acute IF	4 (5%)	3 (4%)	1 (2%)	0.25	0.23

of an IF is to be expected only if a finding is considered to be clinically relevant or life-threatening. However, 70% of all responders seemed not to be aware of this IF communication principle in the wbMRI study.

IF reporting and follow-up

Out of 86 participants 38 had a prior disclosure of 46 IFs in total, including four IFs that required urgent notification. Standard notification letters were delivered to the participants in 3.6 ± 2.1 weeks. The phrasing of the reports was rated as well or very well to understand by most participants (97%). In a single yes/no question on the subjective estimation of potential benefits from IF disclosure, more than half of the responders (55%) answered with yes, that IF disclosure had a positive influence on their health status; 81% of all disclosed IFs were not previously known to the participant, in 7 cases were IFs previously known to the participant.

Concerning the disclosed IFs, most participants consulted a general physician (68%) or another specialist (58%). Interestingly, 26% consulted their family members or found the World Wide Web useful as well. For further examination, physicians were consulted in 86% of cases. An adverse event during further work-up was reported in one case, an allergic reaction to CT contrast medium. Only one participant reported not to have taken any effort for further work-up the disclosed IF.

Reliability

Perfect agreement was achieved between the IF reporting as documented by the study coordinator and the participants' reply in the survey (100%). As for the reliability, Table 2 (supplementary data) shows the calculated agreement scores for each question along with the strength of the correlation.

Discussion

We considered it important to run a pilot single-center trial in order to get a first impression on feasibility and response rate of such a survey and take necessary adjustments before we initiate the survey among several thousand participants. It must be emphasized though, that the nature of some questions does not exclusively aim at statistical or numerical values but rather takes other aspects into account, e.g., open questions regarding the responders' free opinions or multiple-choice questions regarding the processes of clinical verification of disclosed IFs.

Almost all participants of our pilot trial were satisfied with the informed consent process, perceived the duration of the exam as tolerable and would participate in an FU examination.

The emotional stress experienced while waiting for a result letter was mild; however, a high stress level was reported at receipt of a letter. Nevertheless, almost all participants considered it very important to receive notification of IFs. A large number of participants seemed not to have completely understood IF communication principle despite the informed consent discussion.

There was a very high response and a low proportion of missing answers in the first phase (S1). In the retest round (S2) 55 participants (32% less than in the initial batch) returned the questionnaire. A high agreement was observed between the S1 and S2 phases regarding questions about duration time of the MRI, the information provided prior to the exam, about taking part in a FU exam, receiving notification of IFs, etc. (Table 2, supplementary data). Our questionnaire was developed by experts, based on the questionnaire developed by Erdmann et al used in SHIP [9]. Therefore, a strong external validity can be appraised as the result of an extensive contribution of experts in further improvement of Erdmann's questionnaire. However, it contains questions which are not fully validated with regard to ethical aspects of IF reporting. In line with this, we must emphasize the close relation to the only measure that is in a quality state exceeding preliminary stages of work from Erdmann within SHIP. This close relation accounts for a good internal validity of the current instrument.

As a state-of-the-art imaging modality, MRI has an increasing popularity in screening studies [12–16], along with the previous population-based studies of KORA [11] and SHIP [10] wbMRI is performed in UK Biobank [17], the other largest epidemiological study in Europe. Due to comprehensive, high-resolution MRI scans, the prevalence of detected

abnormalities has highly increased; Lo et al reported a 94% incidence of positive findings among asymptomatic volunteers [18]. Both ethical and methodological aspects of IF management in longitudinal, epidemiological studies are more complex than in the clinical context. In a clinical setting, radiologists usually have access to information on patient's symptoms and disease history, and the management of IFs is adjusted to the recommendations of regularly updated international guidelines [3, 19]. In research settings, however, there is still no consensus on what to report and how to report it. The management of IFs mostly depends on the study design and unique ethical considerations for each population-based research project [17, 20–22]. In most research settings, the communication of IFs is intended to be in the best interest of the study participants to facilitate a possible treatment to their benefit. From scientific aspect, this means an intervention with possible impact on the validity of the health-related study outcomes, thus compromising the validity of the study. Each disclosed IF causes deviation of disease course compared to the natural history of disease evolution in the general population. Once an IF has been communicated to a study participant, it is no longer justified to assume, that the study sample represents generalizable knowledge [23]. Moreover, adverse consequences such as psychological distress with a wide range of spectrum and magnitude, disadvantages regarding financial insurance and job matters, costs of subsequent examinations or false positive results along with the burden and complications of a possible treatment form valid arguments for a limited feedback. However, due to the diagnostic misconception, participants tend to conclude that potential advantages outweigh these disadvantages underestimating their negative effects [24, 25]. As the desire to learn more about one's health is the key motivation for participating in epidemiological studies [9, 26, 27], the vast majority of participants are highly interested in receiving reports of relevant IFs [28]. In line with it, almost half of our responders claim not to have taken part in the study if IF disclosure would have been excluded. As long as the recruitment of volunteers for epidemiologic research relies on candidates' hope of health-related benefits, such studies will only be possible when participants expectations are sufficiently met [9]. All participants received comprehensive information on the whole process of wbMRI scan and IF disclosure conditions; though sampled 6 months later, only 25 (31%) of the responders seem to have internalized and remembered the disclosure mechanism. Therefore, special attention must be paid to the informed consent procedure, as it has important impact on participants' expectations, perception, and handling of disclosed IFs.

Only a few studies have so far estimated the actual psychosocial consequences of IF disclosure [8, 10]. It has been shown that the disclosure method itself represents one of the most abundant stress factors [9]. Communication of IFs in a written form may be disadvantageous. In contrast, personalized face-to-face communication might be favorable, since concerned participants have an immediate opportunity to ask questions, mitigating potential fear and anxiety. On the other hand, a written disclosure in the form of standardized reports has better feasibility and the least personal bias in a research setting. Severe emotional stress was experienced by participants with disclosed findings due to the result itself (16%) and through the time-consuming clarification processes. Our pilot trial shows that scientists should keep in mind that participants might need additional support then.

The number of participants included in this pilot trial was not conceptualized to stipulate deeper content-related discussions and would therefore exceed the goal of this manuscript. The established external and reasonable internal validity, the quality criteria of feasibility and effectivity through a high response make it a promising instrument. With this FU instrument, researchers of the GNC will be able to acquire feedback to methodological questions regarding the examination setup and logistics, as well as to ethical questions regarding, e.g., diagnostic misconception or distress through written IF disclosure. The questionnaire will also enable us to assess radiological questions such as the frequency of true and false positive IFs, e.g., the proven incidence of malignant masses among participants with reported suspicious lesions.

In summary, the IF FU questionnaire will serve researchers within the GNC as a fundamental instrument not only for quality management analyses, but also for the investigation of still unacknowledged scientific and ethical questions contributing to evidence-based guidelines concerning the complex approach to IFs in future population-based imaging. The experience gained from the pilot trial was very helpful to improve the questionnaire and overall implementation process. In April 2017, we started to distribute the FU questionnaire to selected participants of the wbMRI substudy. Until the end of 2020, we expect to receive feedback from more than 3000 participants.

Study limitation

Unfortunately, we cannot assume stable properties in the test versus retest phase due to manifold influence that might change the outcome of various items. Such influencing factors could be memory and time effects, the relative large variance of time interval over different subjects, or the high fall-out ratio in the retest phase. Altogether, these factors could be responsible for the poor kappa values observed, especially in multiple-choice questions. On the other hand, to keep the questionnaire short, similar or redundant items were not included in the questionnaire which omits the estimation of consistency.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- prospective
- cross sectional study
- performed at one institution

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