Evaluation of a follow up questionnaire for incidental findings in the German National Cohort: results of the pilot phase

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Aims and objectives

The German National Cohort (GNC) is an interdisciplinary, multicentre, population-based cohort study currently undertaken by a network of over 25 institutions in Germany. Its main goal is the investigation of the development of common chronic diseases (including cancer, diabetes, cardiovascular, neurodegenerative/psychiatric, respiratory and infectious diseases). While all 200,000 volunteers of the GNC undergo an initial extended 2.5 hours exam including interviews, questionnaires and a variety of physical exams, a subgroup of 30,000 examinees will undergo whole-body magnetic resonance imaging (wbMRI) of which about 3,000 participants are expected to receive an incidental finding (IF) disclosure. Image acquisition for the MRI Study is conducted at five imaging centres across Germany. wbMRI is comprised of a set of scientific sequences. Reading for IFs is performed at the imaging sites by board certified and especially trained radiologists and quality assurance procedures are in place. In the GNC IF management policy includes an established list of IFs developed by a scientific board, that classifies IFs as "urgent notification required" (type 1), "notification required" (type 2) and "no notification required" (type 3) [1] similarly to the classification matrix proposed by Wolf and her colleagues [2]. Participants with detected IFs are informed by a standardised letter and in case of a type 1 finding by an additional phone call [3]. As main advantage of this "positive list" it is assumed that the communication of clinically relevant findings is in the best interest and of benefit to the study participants mainly regarding possible treatment options and that adverse effects from reporting of non-relevant findings are reduced to a minimum.

IFs detected in wbMRI research exams are quite challenging due to the lack of sufficient data for the development of a uniform international management strategy. Leading international committees therefore point out the importance of extensive examination of the ethical and scientific aspects regarding IF [4-6], but still, there is no consented (fully validated, reliable and objective) measure of these aspects. In order to get feedback from participants and to evaluate the IF-management procedure of the wbMRI substudy, a follow-up questionnaire was developed.

With the primary objective of internal quality management (optimization of processes, analysis of participants' contentment) and with the scientific and ethical interest to contribute to the development of evidence-based practice guidelines concerning the complex approach to IFs, a follow-up (FU) questionnaire was developed. This instrument will be sent to all participants who received a report of an IF (along with a control group) 6-7 months following a wbMRI in any of the GNC study centres in order to channel their feed-back regarding attitude, experiences and cooping with disclosed IFs. This single centre pilot trial was aimed to get a first impression on feasibility and response rate of such a survey and take necessary adjustments before initiating the survey among several thousand participants.
Methods and materials

Participants:

The FU questionnaire pilot phase was monocentric and was conducted among volunteers who received a wbMRI between 01/2016-02/2016 in the study centre of Neubrandenburg. With a ratio of 1:1 with and without disclosed IF 86 participants were manually selected in the Imaging Core for Incidental Findings, Heidelberg. The questionnaires were sent out 6-7 months after the wbMRI examination, leaving sufficient time for work-up of the disclosed IFs and final diagnosis. In case a questionnaire was not returned after four weeks, the questionnaire was sent a second time followed by a reminder phone call. The exact same questionnaire was sent approximately 8 weeks after the return of the first questionnaire in order to evaluate the test-retest reliability.

FU Questionnaire:

The FU questionnaire was developed on the bases of the surveys applied in the Study of Health in Pomerania (SHIP) and Kooperative Gesundheitsforschung in der Region Augsburg (KORA) [7-8]. The FU questionnaire consists of 26 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 of 8 pages (TeleForm, Electric Paper Informationssysteme GmbH, Germany) 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, how they perceived the duration of the MRI examination itself, if they experienced stress in the time waiting for possible notification of an IF and whether 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±SD for continuous variables and percentages for categorical variables. Comparisons between groups were performed with the use of an independent sample t-test for age, 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, a 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.
Results

Response Rates and Reliability

The general characteristics of the participants are shown in Figure 1.

81 out of 86 participants responded to the survey (94% response rate) with a completion ratio of the first 13 questions of 96%. Compliance is to be considered sufficient, since there has been no incomplete questionnaire (more than 50% missing values). 58 participants responded to the initial delivery of the questionnaire within 12±6 days. 24 participants responded to the second delivery of the questionnaire and/or the 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.

An agreement of 100% was achieved between the participants’ reply in the survey and the GNC database with the filter question whether the responder previously received an IF report. Due to high rate of missing values in the retest phase the calculated agreement-scores show diverse strengths of correlation.

Study Evaluation

More than 95% of all participants perceived the duration of the wbMRI-exam, which takes approx. 1 hour, as not too long and therefore as tolerable. 92 % were satisfied with the information given prior to the wbMRI examination. Moreover, about 95% would consider participating in a follow-up MRI examination. Almost all participants (95%) consider 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 to severe by 9% of the responders and mild grade by 34%, while 54% experienced no or minimal stress (Figure 2). Participants were asked what kind of findings they would like to be informed about in general. 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 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 - without difference regarding the presence of IF - seemed not to be aware of this principle of IF communication of the GNC wbMRI study.

IF Reporting and Follow-Up

Out of 86 participants who got the questionnaire, 38 participants had a prior disclosure of 46 IFs in total, including four IFs that required urgent notification (Figure 3). Calculated from the participants’ responses based on their subjective retrospective estimations,
the average delivery time of the notification letters was 3.6±2 weeks, in case of the 4 urgent notifications 2 weeks was reported. Nevertheless, according to the GNC database notification letters were sent out within 3.5±0.3 days. The phrasing of the reports was rated as well to understand by most participants (97% well or very well). In a single yes/no question on the subjective estimation of potential benefits from IF disclosure, more than half of the responders (55%) reported, that IF disclosure had a positive influence on their health status. 81% of all disclosed IFs were not previously known to the participant. 19% (7 cases) of all disclosed IFs were 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 (Figure 2). 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.
Images for this section:

Figure 2: Distress while waiting for the results

Fig. 3

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Figure 2: Frequency of IFs
**Fig. 2**

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<table>
<thead>
<tr>
<th>Subjects Responded to S1</th>
<th>Subjects Responded to S2</th>
<th>p (S1-Responders vs S1-Non-Responders)</th>
<th>p (S2-Responders vs S2-Non-Responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Contacted Subjects</td>
<td>86</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58.7±8.0</td>
<td>58.5±8.1</td>
<td>0.27</td>
</tr>
<tr>
<td>Male/Female</td>
<td>38/48 (44/56%)</td>
<td>35/46 (43/57%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Subjects with/without presence of any IF</td>
<td>43/43 (50/50%)</td>
<td>38/43 (47/53%)</td>
<td>20/35 (36/64%)</td>
</tr>
<tr>
<td>With more than 1 IF</td>
<td>6 (7%)</td>
<td>4 (5%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>With Acute IF</td>
<td>4 (5%)</td>
<td>3 (4%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

*Figure 1: Descriptive statistics was provided using means±SD for continuous variables and percentages for categorical variables. Comparisons between groups were performed with the use of an independent sample t-test for age, Fisher’s exact test for all categorical variables.*

**Fig. 1**

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Conclusion

In this pilot trial we observed a very high response rate and low rate of missing answers with no difference regarding the presence of IF. This result encourages us to conduct this survey in a larger group of participants. Our questionnaire was developed by experts, based on the questionnaire developed by Erdmann et al. used in the SHIP study along with its modifications for the KORA study. All questions were designed with the primary objective to receive feedback on ethically and scientifically relevant questions. 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. 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 regards 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 [9] within the SHIP study. This close relation accounts for a good internal validity of the current instrument.

The established external and reasonable internal validity, the quality criteria of feasibility and effectivity through a high response ratio make it a promising instrument. With this follow-up 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-bases 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 3,000 participants.
Personal information

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References


