Inserm

La science pour la santé
From science to health

Biomedical Research: Incidental and Unexpected Findings. Classification and Management.

Inserm Ethics Committee

June 2014

Working Group: François Eisinger (Coordinator)[1], Marc Brodin, Dominique Daegelen, Anne-Sophie Lapointe, Grégoire Moutel.

This discussion forms part of a wider framework concerning the organization of biomedical researcher and participant relations.

The majority of the currently-applicable ethical guidelines and legal rules aim to govern the research *process*: preliminary information of research participants, consent, protection of privacy and confidentiality, protection of health, and so on. However, our initial objective here is to reflect on the research *results*, although we do not rule out returning to eventual process modifications later on.

Biomedical research can be considered likely to produce three types of information:

1. Expected (aimed at, not incidental) findings; the targets of the research: is drug A superior to drug B? Does risk factor A increase the risk of disease B? Etc. These are findings that generally concern the study population *as a whole*.
2. Expected, incidental findings for some people who agree to participate in research (the information could, if it is available and reliable, be listed by frequency and/or relevance, as is the case of drug side effects). They are expected to occur but are not predictable at the individual level.
3. Unexpected findings.

The key point that we will expand on concerns this type of result, namely the discovery of a *single finding*, whether it refers to biological markers, abnormal imaging examination results or abnormal paraclinical examination results (such as an electrocardiogram).

Our question is, how should the Investigator manage such a situation?

To help put the matter in context, here are a few examples of findings:

- A constitutional mutation of a gene predisposing to a given disease
- A tumor during an imaging examination (*incidentaloma* (1, 2))
- Extrasystole or a conduction disorder during a routine ECG
- Raised plasma calcium during a blood workup

In our opinion, it is the potential plethora of these situations that requires thought to be given ahead of the research.

[1] francois.eisinger@inserm.fr

The option of systematically returning large quantities of unexplained, uncommented on and unqualified findings (“Disclose and sit back”) would,– a even with the consent of the research participants – represent distance without beneficence, sometimes leading to more risks than benefits and, for society as a whole, a considerable burden on time and medical resources.

Our analysis grid is based on the value and relevance of the findings, for which a brief recap on information theory may be useful (3). Information changes our knowledge of the world and so must be interpreted in relation to our pre-existing knowledge and the specific, intrinsic value of the new finding. As such, we do not consider it possible to disconnect our *a priori* knowledge of the world from the information produced by research. From this point of view, the concept of a “positive” or "negative” test is insufficient (and sometimes even unsuitable) and the interpretation must consider both the often-quantitative dimension of the test results (“more or less positive”) and the context (4).

However, for analytical reasons and because it is this element that the researcher will have to manage, a large part of this document concerns the analysis of the finding in itself.

Our basic position is as follows: the discovery of incidental or unexpected biomedical research findings must be managed based on two principal factors: the desire of the research participant to be informed and the medical relevance of the finding.

Evaluating the participant’s desire to be informed

Two scenarios can be distinguished:

1. **Biomedical research participants are asked the question before the incidental or unexpected finding is discovered.**

This question should be asked in a generic manner for unexpected findings. Two sub-scenarios are to be envisaged: 1) asking the question during the enrolment process, or 2) for protocols already implemented, asking the question during study visits or via a mass mailing.

"Should we discover any information about your state of health or about any potential risks during this study, what would you like us to do?"

- Always inform you of anything abnormal. This option is quite simple for researchers, but extremely tricky for people who would seek to give this information meaning). However, this option is in the current context of the primacy of personal decision-making autonomy cannot be refused by the researcher unless society enacts rules to limit this possibility.
- Inform you of any potentially relevant information (relevance deemed by the researchers and clinicians in charge of the study)

- Not inform you unless medical treatment is highly recommended (significant loss of chance)
- Never inform you

Should you wish to be informed, who should we contact?

- Just your healthcare professional (which requires their contact details)
- Just you
- You and your healthcare professional

For incidental findings (i.e. those expected for a more or less large subgroup of people) there are two possibilities: either apply the same rule as for unexpected findings or propose a pre-defined list (in line with the list of potential side effects). The risk with modern technologies such as next-generation sequencing (NGS) is that such a list may be very long and/or not stable.

2. **Biomedical research participants are asked the question after the incidental or unexpected finding is discovered.**

The position of our group would involve sending out a mass mailing (therefore not just to the person concerned) for any "relevant" findings. The message would be structured in this respect (to take into account the right not to know).

Dear Sir or Madam,

In context of the … study, a small number of you (participants) may be carriers of … While this abnormality is not an illness, it may, depending on the individual context and on a case-by-case basis, warrant additional investigations that should be discussed with your doctor. Were this case to apply to you, would you like …

In the event of a finding that is considered of great concern, personal contact appears necessary outside of the mass mailing. It would be difficult to do otherwise because the French law on informing relatives requires – should a mutation be discovered – that carriers set up a process of (direct or indirect) notification of their relatives. Researchers cannot exonerate themselves from a legally-imposed task to patients in a different but similar condition.

Analyzing the relevance of research findings

First of all, what is a relevant finding? To answer this question, we propose two sub-questions: who defines a relevant finding and how?

Who determines the relevance of findings?

Several hypotheses can be proposed:

- The person him or herself (moral legitimacy based on autonomy)
- The Principal Investigator/Steering Committee (organizational legitimacy)
- The Committee for the Protection of Research Participants (CPP) (legal structure)
- The Institutional Review Board (IRB) (ethical structure)
- An *ad hoc* structure as yet not formalized. It must be noted in relation to genetics that some teams from English-speaking countries envisage the creation of a list of genes whose pathological variations should be disclosed to participants.
- An *a priori* designated expert: clinician, for example an imager (technical legitimacy)

How are relevant findings determined?

Here it is about giving decision-makers (see above) the tools to help them in their decision. In decreasing order of legitimacy:

Clinical markers (HAS, NICE, etc.) or tests recommended as systematic screening tests (most often for a given subpopulation). For the latter point, which is doubtlessly the most appropriate to our reflection, the research by certain groups could be used (United States Preventive Services Task Force – USPSTF).

Markers recommended by learned societies

ACCE framework: a structured interpretation grid validated by the Center for Disease Control CDC(5), which evaluates four aspects:

- The **analytic validity** of the parameter, based on the following elements:
    - Intrinsic variability (example: blood pressure)
    - Intra-observer reproducibility
    - Inter-observer reproducibility
    - Normal or abnormal nature (independently of the context that contributes to the semiological value of the information). The most emblematic case being for genetic analyses the more or less marked frontier between deleterious variation and variation of unknown significance (6)
    - The existence of a valid, safe, confirmation test…

- The **clinical validity**, based on:
    - The positive and negative predictive values of the parameter on the envisaged pathology
- The **clinical utility**:
    - What impact does early diagnosis have on the ability to modify the natural history of the disease or reduce its negative consequences
- The existence of **ethical, legal or social risks**
- The use of expert appraisals (role of Inserm?)

Three large categories (with unclear boundaries) may emerge, allowing three principal scenarios to be distinguished

- The relevance is known by the scientific community AND by the Investigator (this is the most straightforward scenario)
- The relevance is known by the scientific community BUT NOT by the Investigator
- The relevance is known by neither the scientific community NOR by the Investigator

For the latter two scenarios, it would be desirable to create a database of expertise (replacing or supplementing the informal network of experts that all clinicians possess).

It may also be desirable to verify whether the researchers are aware of the potential utility to people of disclosure.

To avoid needless reanalysis, our Working Group recommends the **creation of an information resource center – a single one, if possible, and "friendly" access. Such a database would contain any findings – particularly sequence variations – considered to be irrelevant/relevant or even critical, together with the reasons used to determine why such judgment had been made.** Inserm could participate in its management. For constitutional genetic data, reflection in partnership with the administrators of Orphanet would no doubt be worth exploring, and maybe even a partnership with HAS.

How are relevant findings managed?

Here it is not about defining how to manage these abnormalities (verification, additional examinations, diagnostic procedures, etc.) but about knowing who, after it has been reported, will interpret this finding by putting it in context and as such inform people of what these results mean, and then to begin an action, if an action is needed ("actionability').

It is evident that access to a clinician is required: this is the preferred option selected by our Working Group. Whether it is a study physician and/or the participant's healthcare professional

who at best should be notified in parallel to the patient (see the section on consent).

Finally, and irrespective of what might be the “right” solution, we must analyze and anticipate any logistical problems that are likely to occur.

- What should we do in the event of irreversible anonymity?
- What about the traceability of information at the individual level (risk of pooling making it impossible to link the data to the right participants)?
- What if the participant changes address or healthcare professional?
- What if the participant changes their mind about wanting to be informed?
- For genetic analyses: what happens in the event of death of a participant and the notification of their relatives?
- What about timelines and developments in knowledge? An irrelevant finding can become relevant. It is about a debate between two risks: one – the storage of large quantities of personal information for a lengthy period of time, and two – the destruction of information that may prove useful at a later date. Indeed, developments in knowledge can affect the interpretation of data, particularly genetic sequences. Variants of unknown significance (VUS) can later be requalified as harmful mutations and as such go from “neutral” to “useful/relevant” information status. A short storage period for raw data may be considered but an end date is needed and, in any case, certainly no later than 10 years (storage period for tumor paraffin blocks)
- Finally, must different procedures be envisaged for cases and controls?

Returning to the initial point regarding the interaction between *a priori* and *a posteriori* knowledge of the health of participants following the chance acquisition of additional findings during research procedures, three major situations can be described.

1. The finding has little relevance because it can only very slightly modify the preventive or therapeutic management of the participant. For example: the detection of a genetic polymorphism that is not considered harmful at present. The list of this situation is, of course, considerable, for example TP53BP1 Glu353Asp(7). In addition, we must be extremely cautious and not consider polymorphisms as harmful based on just one study (8).
2. The finding is relevant in itself, with the context only having a slight effect on its semiological value, for example ventricular extrasystole with severity criterion), fasting glucose > ?, clearly harmful constitutional mutation of the BRCA or MMR genes.
3. Finally, the information warrants clinical contextualization. For example, when an ECG reveals repolarization disorders which would mean very different things to a 30-year-

old woman with no particular risk factors and a 60-year-old man with multiple risk factors.

It would therefore appear that, should the participants agree, the second and third situations require a participant information process. The letters that could be sent to participants must have already been described to them as a possibility. During the initial information process in which the wish of the participant is sought, it must also be explained that such letters do not notify the existence of a known disease but an abnormality which, depending on the cases, may require confirmation, additional tests or no action and that the patient's healthcare professional must be a partner in this process of managing information of a medical nature. While the healthcare professional appears as an important partner, they must not be abandoned but information to help manage these findings must be given to them.

Principal points

1. One key question is that of knowing whether one (society not researchers) have the right to limit participants to have access to each and every information
2. Ask participants about their theoretical position, their wishes, before giving them the information
3. Should they agree, advise the parallel notification of their healthcare professional
4. In such a case, inform the healthcare professional of the known semiological value of the incidental findings and, if designated at the beginning of the study, a specialist who can be contacted. Indeed, in order to avoid this arrangement being a simple transfer of responsibility from the investigators to the participant's healthcare professional, the latter must be informed of the known semiological value (particularly for polymorphisms) and risk management advices
5. Envisage the logistics of the above

1. Kasperlik-Zeluska AA, Roslonowska E, Slowinska-Srzednicka J, Migdalska B, Jeske W, Makowska A, et al. Incidentally discovered adrenal mass (incidentaloma): investigation and management of 208 patients. Clinical endocrinology. 1997;46(1):29-37.
2. Stone JH. Incidentalomas--clinical correlation and translational science required. N Engl J Med. 2006;354(26):2748-9.
3. Benish WA. Relative entropy as a measure of diagnostic information. Med Decis Making. 1999;19(2):202-6.
4. Rifkin RD, Hood WB, Jr. Bayesian analysis of electrocardiographic exercise stress testing. N Engl J Med. 1977;297(13):681-6. Epub 1977/09/29.
5. Valdez R, Yoon PW, Qureshi N, Green RF, Khoury MJ. Family history in public health practice: a genomic tool for disease prevention and health promotion. Annu Rev Public Health. 2010;31:69-87 1 p following Epub 2010/01/15.
6. Eggington JM, Bowles KR, Moyes K, Manley S, Esterling L, Sizemore S, et al. A comprehensive laboratory-based program for classification of variants of uncertain significance in hereditary cancer genes. Clin Genet. 2013. Epub 2013/12/07.
7. Liu L, Jiao J, Wang Y, Zhang D, Wu J, Huang D. Lack of Association of the TP53BP1 Glu353Asp Polymorphism with Risk of Cancer: A Systematic Review and Meta-Analysis. PLoS ONE. 2014;9(3):e90931. Epub 2014/03/08.
8. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG. Replication validity of genetic association studies. Nat Genet. 2001;29(3):306-9.