D8.04 Incidental Findings: Guidance to HARMONY's Partners

116026 – HARMONY
Healthcare Alliance for Resourceful Medicines Offensive against Neoplasms in Hematology

WP8 Legal, Ethics and Governance

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HARMONY

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Document History

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V1.0	12.07.2018	Initial draft sent to KOLs for input
V1.1	30.10.2018	Draft including KOL's feedback and advice
V1.2	31.10.2018	Draft including suggestions by the Executive Committee
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V1.4	23.11.2018	KOL's feedback completed

List of Acronyms

Acronym	Description
ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
CLL	Chronic Lymphoblastic Leukaemia
DNA	Deoxyribonucleic Acid
IF	Incidental Finding
IMI	Innovative Medicines Initiative
ISS	International Staging System
MRD	Minimal Residual Disease
NGS	Next Generation Sequencing
NHL	Non-Hodgkin Lymphoma
PHM	Paediatric Hematologic Malignancies
RNA	Ribonucleic Acid

D8.04 INCIDENTAL FINDINGS: GUIDANCE TO HARMONY'S PARTNERS

1. PUBLISHABLE SUMMARY:

This document provides a review of the literature available on the topic of incidental findings in genome research, with a particular focus on HARMONY's activities in the context of secondary use of data from clinical research on hematologic malignancies. Drawing from the results of this review guidance is given to researchers and physicians on how to handle potential incidental findings arising from HARMONY's data processing. Although the risk of incidental findings is deemed low by the experts in HARMONY's consortium a concise decision tree is given to assist with deciding whether individual data subjects should be informed of such findings.

2. SCOPE:

This guideline document shall be applicable to all of HARMONY's data processing activities which involve the processing of personal data as defined in the EU General Data Protection Regulation (GDPR), Art. 4 (1):

> "'**personal data**' means any information relating to an identified or identifiable **natural person ('data subject')**; an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the **physical, physiological, genetic,** mental, economic, cultural or social identity of that natural person;"

There will be no possibility to report back incidental findings in cases where anonymous data is being processed as the data subject will no longer be identifiable.

3. PURPOSE AND OBJECTIVES:

This document provides guidance to researchers and physicians on how to handle potential incidental findings arising from HARMONY's data processing activities.

4. INTRODUCTION:

HARMONY is a European big-data research infrastructure project funded by the Innovative Medicines Initiative (IMI) that aims at taking treatment of haematological malignancies to a new level. 53 European partners from the public and private sectors work together in developing a big-data-based solution to developing novel medication for, and treating, an array of different blood cancers by utilising secondary use of data from clinical biomedical research.

This document addresses the issue of incidental findings in genome research and its implications for the HARMONY project. On the one hand, it aims at providing an overview of recent academic discussions within relevant disciplines and to provide guidance to HARMONY partners on how to handle the potential occurrence of incidental findings within datasets utilised for HARMONY. On the other, it strives to present to the project partners a comprehensive compilation of incidental findings anticipatable in the course of HARMONY's data processing.

5. DEFINITIONS:

The definitions table below was originally published in a guideline document issued by the United States' Presidential Commission for the Study of Bioethical Issues, as cited in (Weiner, 2014), which is accessible here: https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf

Tab.1: Definitions of terms in context of incidental findings (Weiner, 2014)

Primary Finding	Practitioner aims to discover A, and result is relevant to A	Example: In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered
Anticipatable Incidental Finding	**Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place**	**Example: Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related**
Unanticipatable Incidental Finding	**Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place**	**Example: When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted**
Unsolicited Finding	Similar to Unanticipatable Incidental Finding (see above)	Included for completeness, according to (Matthijs et al., 2015)

Secondary Finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation	Example: ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits
Discovery Finding	Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results	Example: A "wellness scan," a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body

In this document general guidelines are given on how to address **Unanticipatable** (i.e., not anticipated) **Incidental Findings** within the context of the HARMONY project. However, for immediate practical purposes the category **Anticipatable Incidental Finding** will likely be significant. Thus, medical expertise will be collected from all key opinion leaders (KOLs) within HARMONY to provide a comprehensive overview.

6. ETHICAL CONSIDERATIONS:

Since the advent of next-generation genome sequencing both time and cost for sequencing an entire human genome were reduced dramatically. This development not only put genomic testing within reach of clinical application, but also fuelled a discourse on how to handle incidental findings, the occurrence of which was deemed probable.

A considerable body of publications has been issued in the fields of ethical aspects and guidelines to physicians regarding handling incidental findings in clinical genome analysis. Most publications either argue for a general need to thoroughly address the issue of incidental findings, or analyse existing practices of physicians and patients' views when confronted with the concept. Only few documents so far have been issued which give practical guidelines on the handling of incidental findings in the context of genomic analysis. A recent publication (Marron & Joffe, 2017) reviews the literature in the field of ethics in genomic testing for hematologic disorders in particular which will be of high relevance to HARMONY.

In their report on ethical implications of new health technologies and citizen participation (EGE, 2016) the European Group on Ethics in Science And New Technologies (EGE) provides general ethical guidance on handling incidental findings in genome research:

> *"In the case of genetic data, a genomic sequence may reveal probabilistic information or disease traits or other characteristics in biological relatives. In such cases, there is a conflict between the autonomy expressed through consent by the individual (who gives permission for data access) and the privacy interests of others who may be affected by this permission. This situation is difficult to manage in current data protection mechanisms. Consent, in these cases, should include information on the willingness or unwillingness to receive the results of research, the information about the possibility of 'incidental findings' (unexpectedly revealing results that may be difficult to be known, regarding risks or susceptibility to incurable illnesses), in respect of the subject or his/her relatives"*

6.1. General ethics discussion

6.1.1. The American College of Medical Genetics and Genomics (ACMG)

An important attempt at providing comprehensive guidelines to physicians on how to handle incidental findings in genomic research was made in the guidelines of the American College of Medical Genetics and Genomics, ACMG (Green et al., 2013). Although initially ACMG recommended mandatory return of selected incidental findings in genome-wide association studies (GWAS), they subsequently endorsed an opt-out option in response to criticism from geneticists, bioethicists and others.

6.1.2. Genomics England's "100,000 Genomes Project"

In their "100,000 Genomes Project" Genomics England (www.genomicsengland.co.uk/taking-part/results), a big data in healthcare initiative launched by UK's National Health Service (NHS), provides a thorough procedure for study participants into learn about possible "additional" or "secondary" findings ("anticipatable incidental findings" in the terminology of this paper). In analogy to ACMG's guidelines Genomics England provide for study participants' consent to analyse, and be informed about, a set of pre-defined genetic disease predispositions (Ormondroyd et al., 2017). However, at the time of writing they did not have a policy regarding "unanticipatable incidental findings".

6.1.3. Nuffield Council on Bioethics

The Nuffield Council on Bioethics' positions on incidental findings (Meulen, Newson, Kennedy, & Schofield, 2011) comprises in particular:

> *(28) Another aspect of returning results is 'incidental findings.' Given its large scale and open-ended nature, it is almost certain that GWAS studies will identify genetic associations that were not previously anticipated. A study may also disclose information that is tangential to health, such as misattributed biological relationships (for example, paternity). The significance of these results is often uncertain at the time they are identified and further studies are often needed to replicate results in different populations. If returning results to participants does become more common than it is now, researchers may need to consider incidental findings when developing protocols for returning results, including any duty of care that may be owed. This will also have an impact on consent processes.*
>
> *(29) A 'right not to know' one's genetic information, while contested in the literature, does tend to be accepted in practice in both research and clinical contexts. That is, if a participant does not wish to know his or her genetic status following research participation, that wish will be respected. How this right could or should be construed in GWAS remains uncertain. For example, a research participant may express a desire not to know her research results but a finding may come to light (whether anticipated or incidental) that has serious health implications and for which there is a proven intervention. In this kind of scenario researchers may have to determine whether disclosure against a participant's previously expressed with can be justified.*

6.2. Criteria for disclosure of incidental findings

A general consensus in the field favours disclosure of incidental findings to patients or study participants only if the results satisfy the criteria of **Validity**, **Utility** and **Actionability** (Souzeau et al., 2016):

> *"[Researchers] … could have an ethical obligation to return genomic variants that are of clinical validity (the variant is known to be associated with a particular disease), have clinical utility (the likelihood of a positive health outcome), and are actionable (medical actions can be taken to decrease the risk)."*

6.3. Patients' views

Most cancer patients and study participants wish to receive their genomic results (Blanchette et al., 2014; Gray et al., 2016). In addition to efforts of installing general rules for the disclosure of incidental findings, studies interviewing patients suggest that research subjects demand being asked individually beforehand about whether any incidental findings may be disclosed to them, demonstrating the importance of a patient-centred approach to returning incidental findings (Clift et al., 2015) and its appropriate reflection in the informed consent given at the outset.

6.4. Researchers' views

Opinions of researchers on whether and how to disclose incidental findings from genomic testing vary broadly. Views range from treating every single patient case individually, providing detailed informed consent options to patients to setting up standardised criteria and guidelines to disclose of incidental findings (Downing, Williams, Daack-Hirsch, Driessnack, & Simon, 2013; Williams et al., 2012). An approach of detailed options for patients to consent to is being criticized for its complexity within the clinical context, referring to the limited medical literacy of most patients (Downing et al., 2013; Marron & Joffe, 2017). There is also concern about giving patients an option to opt out of being informed of incidental findings of known clinically significance(Downing et al., 2013).

A specific account on the risks of false-positive incidental findings is given in (Kohane, Hsing, & Kong, 2012). In their study involving whole genome sequencing the authors find four sources for false-positive incidental findings:

1. Erroneous annotations
2. Sequencing error
3. Incorrect penetrance estimates
4. Multiple hypothesis testing

Whether these error sources will equally apply to the tumour-specific genome analyses conducted by HARMONY needs to be established in practise.

6.5. Genomic testing in minors

Children are a vulnerable group of research subjects and genomic testing in this group raises

particularly complex questions regarding incidental findings (Green et al., 2013). At the core of the discussion lie the arguments of the child's right to an open future and its own choice of undergoing genetic testing once coming of age, versus the benefits of early disclosure to both the patient regarding future decision making and its adult relatives by alerting them of potential risks (Marron & Joffe, 2017).

7. BIOBANKS AND BBMRI: a complementary approach

A number of publications were issued in 2009 which currently form the basis of the European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) in terms of handling incidental and secondary findings (J. Bovenberg, T. Meulenkamp, E. Smets, & S. Gevers, 2009a, 2009b; J. A. Bovenberg, T. Meulenkamp, E. M. Smets, & J. K. M. Gevers, 2009). These publications give empirical evidence on opinions on disclosure of genomic analysis' results of both data subjects and researchers. They also provide a range of guidelines based on stakeholder interviews and reviews of contemporary literature.

It might be necessary to bear in mind that these publications originate from a time (2009) in which the discussion on incidental findings was dominated by an anticipatory approach rather than on a significant body of evidence as, e.g., the cost of sequencing genomes was still relatively high but was to fall significantly in the following years (see Fig.1).

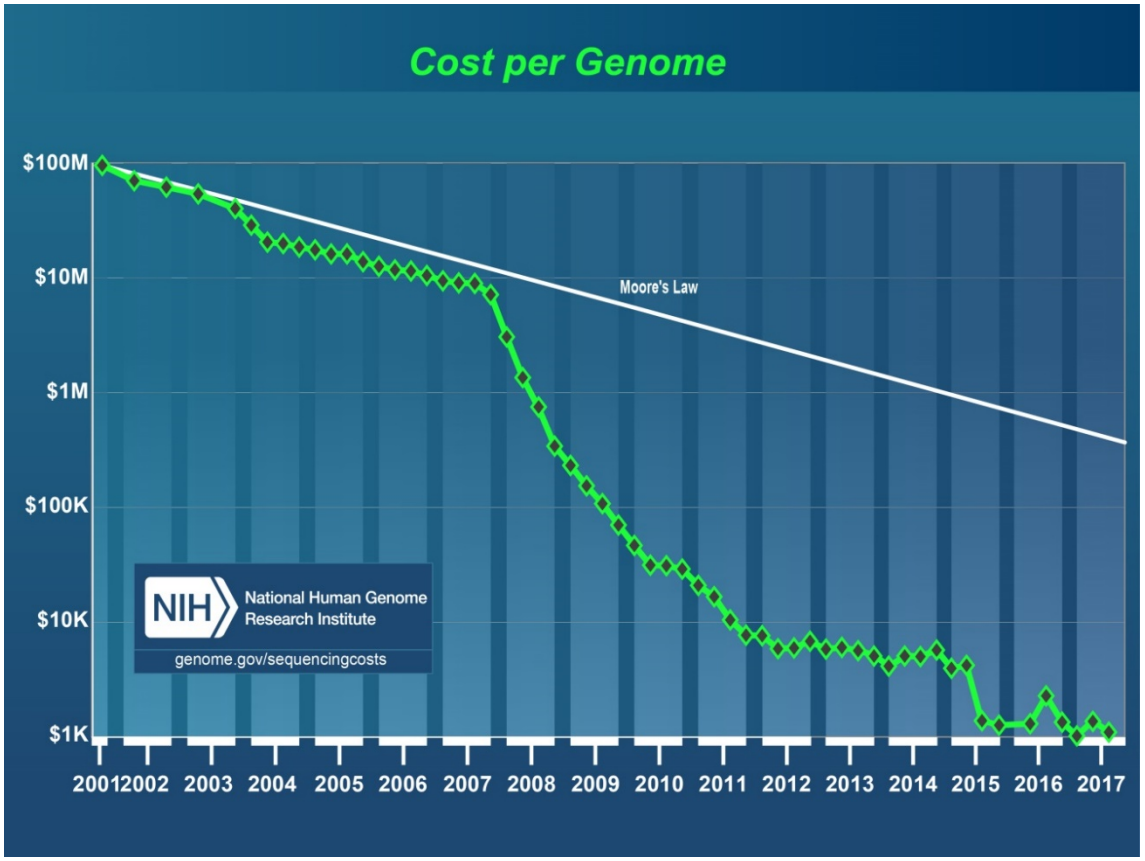

Fig.1: Cost development for sequencing a human genome since 2001 (green line, source: US National Institute of Health, National Human Genome Research Institute, www.genome.gov/sequencingcosts)

7.1. Stakeholder opinions

In their seminal paper (J. Bovenberg et al., 2009a) the authors provide a detailed account on the analysis of interviews they held with members of the society, patients and researchers on key questions of policy regarding disclosure of findings resulting from genomic analysis from tissue samples in biobanks (see Fig.2).

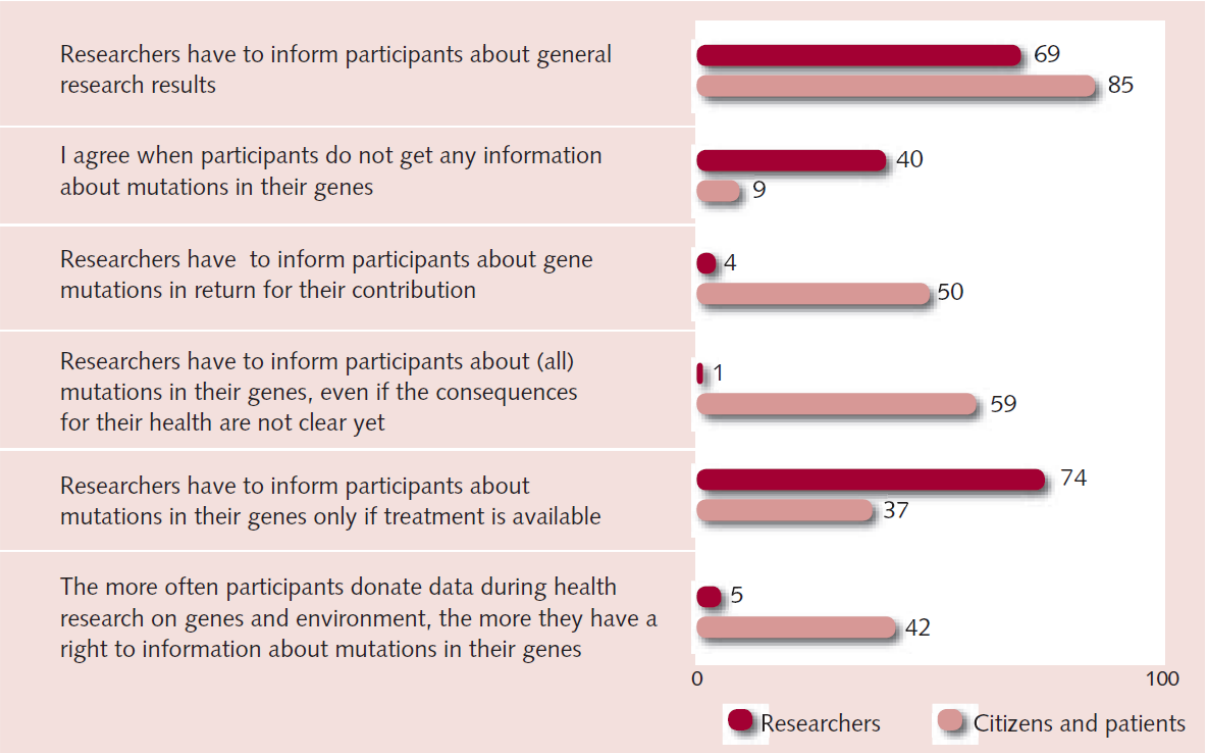

Fig.2: Attitudes towards researchers' duties to communicate research results - percentages agreeing with respective statements (J. Bovenberg et al., 2009a)

7.2. Guidance on disclosure decisions for biobanks

In their papers (J. Bovenberg et al., 2009a; J. A. Bovenberg et al., 2009) the authors give a set of guidelines to the disclosure of biobanking research results which are cited below:

> *14. Decisions to disclose or not to disclose research results should be based on carefully weighing the potential benefits for the participants to receive the information concerned against the possible disadvantages, taking into account the feasibility to implement the decision. Basically, individual feedback should be given where the information relates to a serious health problem and where the possibility of an individual health benefit is realistic.*
>
> *15. In case of a finding with high clinical (or reproductive) significance for an individual participant, any reasonable effort should be made to inform him or her about the risk and the possibilities to prevent or ameliorate the consequences.*

16. In case of findings where the health implications may still be serious but the risks are smaller and/or the potential benefit of being informed is limited or uncertain, participants should be notified of the availability of the relevant information only.

17. In other cases, there should be no individual feedback; validated research results should be made available on a collective basis to interested participants.

18. While acknowledging the interests of next of kin in being advised about some genetic conditions, it is the responsibility of the participant to contact them when needed. The biobank's responsibility is limited to inform the participant about a serious familial risk.

19. If a finding of high clinical significance for some relatives becomes available after the participant has died, reasonable efforts should be made to contact and inform them.

20. Research results should be disclosed in ways and by persons designated by the biobank; external researchers should not directly contact research participants.

21. Disclosure of research results should be offered with appropriate supplemental information and with counselling when needed.

22. Biobanks should try to anticipate on disclosure issues that may arise in the future as a result from technological developments, especially in case new information could be derived that is not covered by the participants' informed consent.

23. In case of doubt, decisions to give or to withhold individual feedback on research results should be submitted for prior advice to an independent ethics committee.

8. EVIDENCE FOR INCIDENTAL FINDINGS IN GENOME RESEARCH

In a more recent review paper (Schuol et al., 2015) the authors claim that although there has been a broad discussion on the implications of incidental findings in genome research, in practice so far evidence shows that the frequency of incidental findings, particularly within genomic cancer research, is much lower than expected. The authors argue that the reason for the low level of incidental findings is that the filtering techniques and methods that are being applied during the routine processing of genomic data remove data components which might yield incidental findings.

A similar view is expressed in (Matthijs et al., 2015) who state that "[t]he chance of unsolicited findings in a gene panel is very low and is mainly dependent on the genes involved." In any case, the authors advise that "Laboratories should provide information on the chance of unsolicited findings".

9. KEY OPINION LEADERS' ADVICE

9.1. HARMONY data categories

Regarding entire genomes and exomes, few data on germ line DNA is currently assessed in Multiple Myeloma (MM). Data on RNA are less likely to produce relevant IFs. Regarding molecular data, this is what in MM is recently happening. Researchers have to look only at the differences between tumour and germ line data in order to have a lower risk of incidental findings. In this way you can detect only tumour specific genomic data that usually do not produce relevant IFs.

(Mario Boccadoro on MM)

We do not expect incidental findings ("unsolicited findings" or "secondary findings") as we will not analyze germline DNA from most if not all of our patients.

(Paolo Ghia on CLL)

In the first stage of the HARMONY project, we are incorporating processed NGS data from targeted resequencing studies. In these studies mainly tumor material has been evaluated thus the chance of IFs in germ line DNA is minimal. In accordance, the reanalyzes planned within HARMONY are aiming to better capture the disease heterogeneity, but most likely no additional IFs will be generated for an individual in the HARMONY data base as the individual data sets will not be changed.

(Lars Bullinger on AML and all other HMs)

9.2. Pilot study

No data on targeted treatment are detected in our pilot treatment. The outcome of high risk cytogenetics and high risk ISS patients treated with different novel agents and therapeutic strategies will be assessed. No germ line data will be registered in MM pilot study. The risk of IFs in MM pilot study is very low.

(Mario Boccadoro on MM)

As outlined above, in the AML pilot study targeted resequencing data will be used. However, this data was already analyzed prior to the inclusion into HARMONY and IFs relevant to an individual should have already been dealt with by the respective data contributor. As now raw data files are included in the pilot studies and as now novel analysis will be performed for the data stemming from an individual AML patient, no additional IFs are expected. Furthermore as outline above, data will available on the tumor material only, no germ line data will be entered into the pilot study. This also applies for the other HM pilot studies.

(Lars Bullinger on AML and all other HMs)

9.3. Prospective data collection (post pilot study)

Next Generation Sequencing (NGS) in MM will be used for minimal residual disease (MRD) assessment, whose risk of IFs is very low as it looks at the unique rearrangement sequence of the immunoglobulins, not at the whole genome. Few data on tumour vs. germ line data are currently available in Europe, from a prospective point of view some trials are beginning to collect data on germline and tumour genomes however the risk of IFs could be mitigated as explained above.

(Mario Boccadoro on MM)

For future prospective data sets entering the HARMONY data base, NGS data might comprise whole exome and whole genome sequencing data that includes the analyses of remission blood samples or skin biopsy samples. For these projects, similar to the pilot studies, the individual participating partners will have done the first analysis already and should have encountered IFs if present. By the time evaluated data sets are entered into HARMONY, the risk of additional IFs relevant to an individual are very low (see also comments above). However, as soon as primary raw data are incorporated into HARMONY a respective IC also covering IFs should be present.

(Lars Bullinger on AML and all other HMs)

9.4. Data variables and probabilities for incidental findings

Overall the risk of IFs, especially from a genomic point of view, is very low in MM disease pillar.

(Mario Boccadoro on MM)

In CLL incidental findings can occur when analysing germline DNA. In the contrary to Paediatric HMs, the impact of incidental findings that can arise from genomic/genetic testing of CLL cases would be much lower due to relatively high age of majority of CLL patients at the time of diagnosis (with median age around 70) . Most of the genetic disorders would be already manifested and moreover, prevention of potential transmission of hereditary diseases on consequent generation seems to be pointless.

(Šárka Pospíšilová on CLL)

In accordance, to the comments above, IFs are unlikely to be detected in the HARMONY project, as for the first phase only preprocessed data set are included. In case of an IF, this should have been already detected and discussed with the respective patients prior to the de facto anonymization and inclusion into HARMONY.

As soon as the project enters a prospective phase, that will also include the inclusion of raw data, appropriate IC covering the reporting of IF will be necessary.

(Lars Bullinger on AML and all other HMs)

10. CONCLUSIONS

10.1. General considerations

Due to the thorough multi-staged nature of the data de-identification performed by the HARMONY De-Facto Anonymisation process any incidental finding can only be acted upon at a later stage. In those very infrequent cases of incidental findings HARMONY will only be able to inform all their full partners and associated members providing data on that incidental finding, ask them to check closely in their database whether there are a patients with that specific incidental finding and contact the particular data providing institution with the incidental finding.

10.2. Guidance to HARMONY researchers

a. Address IFs in the Consent Process
b. Address the Potential for IFs in Future Analyses of Archived Data
c. Plan for the Discovery of IFs
d. Plan to Verify and Evaluate a Suspected IF, with an Expert Consultant if Needed
e. Plan to Determine Whether to Report IFs, Based on Likely Health or Reproductive Importance
f. Investigators and IRBs Should Create and Monitor a Pathway for Ifs
g. [Address the issue of] IFs in Paediatric and Adolescent Research Participants
h. [Address the issue of] IFs in Adult Research Participants Without Decisional Capacity
i. [Address the issue of]Handling Social and Behavioural IFs [less relevant for HARMONY]

A general purpose decision tree for how to deal with incidental findings in genome research and medical imaging has been proposed by (Wolf et al., 2008) (Fig.3).

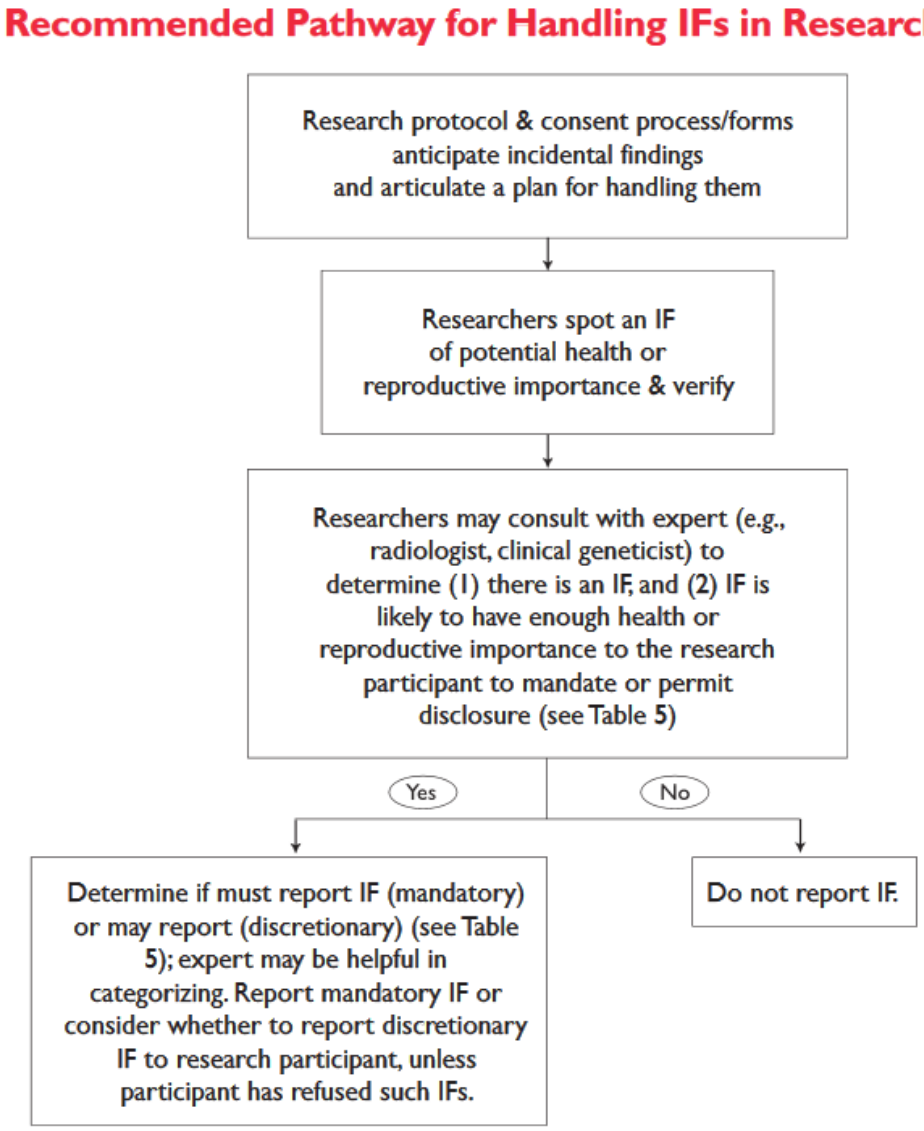

Fig.3 Flow chart representing a decision tree proposed by (Wolf et al., 2008) on how to handle incidental findings (IFs)

In the same paper the authors (Wolf et al., 2008) give more detailed guidelines in a table which lists relevant criteria for decision making (Tab.2).

Tab.2 Classification of Incidental Findings according to (Wolf et al., 2008)

Recommended Classification of Incidental Findings

Category	Relevant IFs	Recommended Action
Strong Net Benefit	• information revealing a **condition likely to be life-threatening** • information revealing a **condition likely to be grave that can be avoided or ameliorated** • genetic information revealing significant risk of a condition likely to be life-threatening • genetic information that can be used to avoid or ameliorate a condition likely to be grave • genetic information that can be used in reproductive decision-making: (1) to avoid significant risk for offspring of a condition likely to be life-threatening or grave or (2) to ameliorate a condition likely to be life-threatening or grave	• **Disclose** to research participant as an incidental finding, unless s/he elected not to know.
Possible Net Benefit	• information revealing a nonfatal **condition that is likely to be grave or serious but that cannot be avoided or ameliorated, when a research participant is likely to deem that information important** • genetic information revealing significant risk of a condition likely to be grave or serious, when that risk cannot be modified but a research participant is likely to deem that information important • genetic information that is likely to be deemed important by a research participant and can be used in reproductive decision-making: (1) to avoid significant risk for offspring of a condition likely to be serious or (2) to ameliorate a condition likely to be serious	• **May disclose** to research participant as an incidental findings, unless s/he elected not to know.
Unlikely Net Benefit	• information revealing a **condition that is not likely to be of serious health or reproductive importance** • information whose **likely health or reproductive importance cannot be ascertained**	• **Do not disclose** to research participant as an incidental finding.

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