Introduction
UK IRB has determined that investigators obtaining de-identified tissue/specimens are prohibited from making any efforts to re-identify the identity of the individuals who provided the specimens unless return of research results or incidental findings is ethically justified and the process for making the determination and returning the results has been approved by the IRB. The ethical, legal, social, and regulatory issues raised within the context of returning individual research results and incidental findings are challenging.

This Frequently Asked Questions (FAQ) document was prepared to provide guidance to UK investigators who

1) Collect data and/or tissues/specimens/scans from participants in their studies (i.e. Referred to as Principal Investigator (PI) in this document);
2) Access de-identified biological materials/data (e.g. tissue, specimens, and scans) from existing repositories or banks (i.e. referred to as Recipient Investigators); or
3) Establish and operate specimen/tissue banks/repositories (i.e. referred to as bank).

Also, attached is a list of select definitions and a comprehensive bibliography of references which may be of use to banks/repositories, PIs, and Recipient Investigators.

FAQ: PI, Banks & Recipient Investigators
1. To what types of research methodology does this guidance apply?
   This guidance applies to research which may generate results or incidental findings that may significantly affect the health of the participants or their family. This includes but is not limited to research involving:
   • Genetic testing;
   • Imaging - such as MRI scans, CT scans, PET scans and X-rays. Specifically high density images that provide anatomic or physiological data of the type that is used in clinical diagnosis or treatment;
   • Other procedures for which there is probability that the results or procedures could identify results or incidental findings that would meet the criteria outlined in Question 2.

2. What criteria should be used to determine whether individual research results or individual incidental research findings should be returned to a study participant?
   In general, if the research participant can be identified by the bank or the PI, research results/incidental findings that meet all of the criteria listed below should be returned unless the participant states that he/she does not want to know the results or unless the Institutional Review Board (IRB) has approved a written request for not returning results or incidental findings.

   Individual results/incidental findings should be offered to study participants if they meet ALL of the following criteria:
   a) The finding has important health implications for the participant, and the associated risks are established and substantial.
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

b) The finding is actionable, that is, there are established therapeutic or preventive interventions or other available actions that have the potential to change the clinical course of the disease.

c) The test is analytically valid or in case of imaging, qualified professionals interpret the scan and the disclosure plan complies with all applicable laws.

d) The informed consent used to collect the tissue/specimen/data informed the participants that results may be returned or the participant opted to receive his or her individual results.

3. In conducting research involving genetic testing, is there any guidance a bank, PI, or Recipient Investigator may use to determine whether a finding is “actionable”?

For clinical purposes, the American College of Medical Genetics and Genomics Working Group determined a “minimum list” of DNA variants in 57 genes for 37 conditions for which findings in a clinical setting should be reported if the data are readable. This document serves as a useful guideline for determining if a gene is actionable. Other sources of guidance may be available in the future.

4. Is there any guidance available to assist in determining whether an incidental finding from imaging is “clinical quality”?

The research findings or image should be reviewed by a qualified reviewer (e.g., board certified radiologists or qualified physicians). Any images or report of those images that become part of a research participant’s medical record should be considered to be of clinical quality. The American College of Radiology (ACR) Practice Guidelines and Technical Standards describe recommended training, skills, and techniques for specific areas of clinical practice.

5. What standards must be used to determine if the test used was “analytically valid”?

- For laboratory results, Clinical Laboratory Improvement Amendments (CLIA) is the only mechanism available, as there are no other current equivalent validating associations or certifications.
- If tests are performed in a non-CLIA approved laboratory such as a research laboratory and it has been determined that one of the findings needs to be returned to the participant based on the criteria in Question 2, the PI must confirm the specific result in question (e.g., sequencing) in a CLIA approved lab before the finding is returned to the participant.
- For an overview of how CLIA applies to the return of research results, see the Department of Health and Human Services recommendations https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-return-individual-research-results/index.html

6. If the findings could significantly affect a participant’s health or health of a participant’s family but the finding has not been “clinically validated” is the PI/bank/Recipient Investigator required to have the result verified?

Yes. If the result identified has met all criteria, except for “analytical validity”, the IRB expects that results should be returned AFTER the result is clinically verified. Otherwise, justification should be submitted to the IRB why clinical verification is not ethically appropriate or practicably possible, and therefore, the results will not be returned.
7. Can findings be returned if there are no existing accepted standards to “clinically validate” the test?
   If no clinically accepted standard exists for validating the result, the result should not be returned to the participant.

8. How long do researchers have an obligation to return research results?
   Ideally, the obligation should extend through active use of the specimens for research. At a minimum, the obligation should extend through the availability of study funding.¹

9. Are there any additional participant protections needed in studies involving whole genome sequencing?
   The Presidential Commission for the Study of Bioethical Issues has published recommendations in this area. Because whole genome sequencing can reveal potentially clinically important information that may have implications for the participant and descendants, concerns are heightened. Participants may not anticipate the type of access or variety of uses unless they are adequately informed. Informed consent language or ancillary educational materials should address the issues and potential privacy safeguards.

10. Is there an ethical obligation for researchers to actively look for certain incidental findings?
    Given the current controversy and confusion regarding what researchers should or should not do when faced with incidental findings, coupled with the unique relationship that exists between Investigator and participant (i.e. as opposed to clinician to patient), researchers do not have a duty or ethical obligation to actively look for incidental findings, even if the “raw” sequence data is available.

11. What information should be included in the IRB application concerning return of research results or incidental findings?
    Ideally, a comprehensive disclosure plan would be submitted as part of the initial IRB application. The IRB application should include the following:
    • Description of results that may be returned;
    • Name of the individual who will have the authority to determine whether the research results or incidental findings meet the criteria outlined in Question 2;
    • Qualifications of the individual identified to return the results to the participant;
    • Timing regarding when the results will be returned;
    • Mode of communication to be used;
    • Plans for Pre and post counseling for the participant, if appropriate;
    • If the participant is a minor or an individual of diminished consent capacity, description of to whom the findings will be returned (see Question 14);
    • Description of plans for allowing participants to withdraw (see Question 12);
    • Description of plans for sharing samples with other investigators, if applicable (see Question 17);
    • Requests for Waiver of Informed Consent/Authorization, if applicable;
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

- A description of the consent process and copy of the form, which should include a section on returning of research results and incidental findings (see Question 13); and
- HIPAA Authorization form, if applicable.

12. Must the bank or PI describe procedures for allowing participants to withdraw in the IRB application?
Yes, procedures must be addressed in the informed consent and the IRB application.
Specify in the informed consent that the participant may withdraw their specimen and associated data from inclusion in future analysis and reporting. The withdrawal would not apply to data analyzed prior to the receipt of the participant’s request to withdraw samples from the bank or PI use.

13. What information should be included in the UK IRB approved consent form about return of research results or incidental findings?
For a complete list of IRB expectations and suggested template language, see the following guidance document: Issues to be Addressed in Obtaining Informed Consent Involving Specimen Collection for Tissue/Specimen Repositories.
The sections entitled, Significant New Findings: Participant Access to Individual Research Results or Incidental Findings Including Genetic Data, provide issues to address specific to the return of results, including:
- Inform participants regarding what results or incidental finding will be offered to participants;
- Indicate if findings will be reviewed to determine if appropriate to return;
- Define incidental findings, if applicable;
- Inform participants if results will not be provided and explain why;
- If findings are to be disclosed, describe disclosure procedures (e.g, genetic counseling);
- If findings are to be disclosed, explain implications of making results or incidental findings available;
- Allow participants to opt in or out of receiving results in the future or indicate if participants will be contacted and offered a “result-specific” consent describing implications or ramifications of receiving a result that has been found.

14. If the study banks tissues/specimens collected from minors, must minors be provided with an opportunity to consent when they reach age of majority?
If the study/bank meets these three conditions: a) designed to include minors; b) identifiers will be maintained; and c) it is possible that the minors could reach the age of majority before the study ends or while the bank still has the specimen, the IRB application should describe the procedures for making a reasonable attempt to contact the individual to consent at the age of majority.
If the bank has made the effort but a portion of the participants was not successfully contacted, the bank could request the IRB to approve waiver of informed consent based on criteria in 45 CFR 46.116(d) for the participants that could not be reached.
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)¹

15. What if an unexpected incidental finding is identified and the issue of returning findings had not been addressed during the informed consent process in the form?
Researchers/Banks should submit an Unanticipated Problem report to the IRB which addresses:
• Recommendation regarding whether finding meets IRB criteria outlined in Question 2;
• Also, the disclosure plan which includes elements listed in Question 11.

16. If the researcher/bank does not routinely interpret genetic testing, should someone with that expertise be included as study personnel in the IRB application and, if so, what qualifications are recommended?
Yes, the American College of Medical Genetics and Genomics (ACMG) recommends that all clinical molecular genetic test results be reviewed and interpreted by an individual certified in either Clinical Molecular Genetics (ABMG) or Molecular Genetic Pathology (ABPath/ABMG). The professional interpretation of test results should be provided by an individual certified in Clinical Genetics (ABMG), Clinical Cytogenics (ABMG), Clinical Molecular Genetics (ABMG), or Molecular Genetic Pathology (ABPath/ABMG).²

17. If the researchers plan to share the banked specimens/tissues or data with other researchers, what issues must be addressed?
• The IRB application should include a description of the procedures for sharing samples.
• The secondary user is generally prohibited from making efforts to re-identify the individual donor who provided the material.
• The specimen/data may be transferred; however, the responsibility to return results remains with the UK researcher.
• The specimen/data are transferred to the secondary user only after the secondary user agrees in writing to abide by the UK guidance on return of research results.
• A Material Transfer Agreement (MTA) should be used to detail the responsibilities of the recipient investigator including agreement not to re-identify the donor and plans to notify the UK PI regarding research results or incidental findings, as defined in the IRB approved protocol should be used. MTA information is available at https://www.research.uky.edu/office-technology-commercialization/material-transfers-and-confidential-disclosures.
• The participant donor should be informed of the possibility for secondary use of the specimens; ideally, when the specimen is initially collected. Otherwise, the IRB would need to determine if the donor(s) would need to be contacted and re-consented.

18. What if the sharing of the specimens/data was not foreseen in the original protocol?
The UK PI should submit a Modification Request to the IRB describing plan to share specimens/data, plan for handling of incidental findings or research results, re-contact and re-consent. (See Questions 11, 13, and 17)

19. Do the HIPAA requirements apply to the operation of the bank or research conducted by the PI or Recipient Investigator?
If the data obtained from the medical records contain any of the 18 HIPAA identifiers, HIPAA requirements for research do apply.
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

Additional FAQ for Banks/Repositories:

20. Is IRB review and approval required to establish a bank or repository for research purposes or convert existing collections into a research repository?

Yes. The federal Office for Human Research Protections (OHRP) considers activities that exist for the express purpose of research to be in the scope of human research requiring IRB review.

21. To which banks or repositories does this guidance apply?

To banks or repositories that provide human-derived specimens and/or data for research purposes.

22. What information should be included in the IRB application to establish a research bank or repository?

The IRB application for a bank/repository protocol may include, but is not limited to, the following:

- Purpose and scope;
- Description of material (type, leftover, limitations, etc);
- Procedures for collecting, transmitting, storing, sharing of material;
- Safeguards to protect privacy and confidentiality of donors (honest-broker, data-security, firewalls, software programs for separating information from identifiers, coding, encryption, limited access, confidentiality agreements, see the National Cancer Institute (NCI) Best Practices for Biospecimen Resources);
- Process for review of requests to access specimens/data;
- Plan for who will determine if secondary research meets federal definition of human research requiring IRB review;
- Investigator agreements or terms of Material Transfer Agreement (MTA), if required;
- Informed Consent and, if applicable, Authorization Process;
- Policy and procedure for participant’s withdraw of material;
- Policy and procedure for return of research results;
- Existence and purpose of advisory committee, if applicable; and
- Plan for destruction or transfer of material should repository close.

See the University of Kentucky (UK) Office of Research Integrity (ORI) Biospecimen Bank Guidance and Research Registry Guidance for more information.

23. How much detail must be in the consent related to returning results and when should consent be obtained?

The amount of detail to be included in this section of the bank/repository consent depends in part upon the bank/repository proposed consent process (including conditions, timing, expertise of individual obtaining consent, etc.) and the bank’s IRB approved standard operating procedures for returning research results or incidental findings.

If the individuals obtaining informed consent at the time of collection have the expertise needed to explain the complex ramifications of returning the results, then the consent process and form should include detailed information and give the participant the opportunity to indicate whether
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

or not he/she wants to receive results. Sample “opt in” or “opt out” language can be found at [https://www.research.uky.edu/uploads/ori-d580000-issues-be-addressed-and-sample-consent-language-tissuespecimen-repositories-or].

On the other hand, if the individual obtaining consent does not have the appropriate expertise to explain the potential implications, the offer to allow the participant to “opt in” or “opt out” of receiving a result or finding could be deferred. The consent form and process would include a brief explanation informing participants that they may be contacted if information becomes available that the researchers believe he/she should know. If a subsequent finding or result is ‘deemed’ returnable, a detailed informed consent would then be obtained allowing the participant to “opt in” or “opt out” of receiving the results or incidental finding. This expanded consent process and form would include the ramifications of returning the results or incidental findings. The results or incidental consent form would need prior IRB review and approval and would be submitted to the IRB as an amendment (Modification Request) to the existing IRB approved protocol. Sample template language can be found at [https://www.research.uky.edu/uploads/ori-d580000-issues-be-addressed-and-sample-consent-language-tissuespecimen-repositories-or].

24. If Recipient Investigators determine that their research results or incidental findings meet the criteria for return to a participant, what should be done?

The Recipient Investigators would follow procedures established in the bank’s IRB approved protocol. The IRB may request that the Recipient Investigator, in cooperation with the bank, submit information to the IRB, including specifics about the result or finding along with plans for returning the result following guidance outlined in Questions 2 to 19.

25. Do research studies that are accessing the material/data from the bank need IRB review?

It depends whether the activities meet the federal definition of “human subjects” and “research”. Ideally, the bank should include in the initial IRB application a description of the proposed procedures for making the determination whether activities meet the federal requirements.

This determination may be handled a number of ways. For instance, an IRB Chair or an advisory committee including an IRB member could be designated to make this determination. Guide for Determining When Protocols Involving Coded Private Information or Biological Specimens Meet the Federal Definition of “Human Research” is available for guidance in making the determination. Considerations pertinent to secondary research involving genetic testing include investigator agreements prohibiting re-identification and potential for stigmatizing or socially harmful outcomes or findings. Or the bank could require the Recipient Investigators to obtain IRB/ORI review for a determination regarding whether the activities meet the federal definitions.

Definitions

**Actionable** - The following description of "actionable results" is taken from the NHLBI working group paper (Circ Cardiovasc Genet 2010), "...finding is actionable, that is, there is established therapeutic or preventative interventions or other available actions that have the potential to change the
Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

clinical course of the disease [or provide important pharmacogenetic information that is likely to impact future care].”

**Biospecimen** - A quantity of tissue, blood, urine, or other human-derived material. Portions or aliquots of a biospecimen are referred to as samples (*NCI Best Practices* working definition).

**Directly identifiable specimen** - is labeled with personal identifiers; for example, name, medical record number, social security number, laboratory accession number, or any elements of dates except dates limited to year alone. Any of the 18 personal identifiers specified under HIPAA constitutes a personal identifier.

**Incidental finding** – a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study (Wolf SM, et al. *Managing Incidental Findings in Human Participants Research: Analysis and Recommendations*. Journal of Law, Medicine & Ethics. 2008;36(2):219–248)

**Indirectly identifiable specimen** - retains a link (or code) to identifiable information about the donor.

**Research Bank or Repository** - an entity involved in procuring, processing, storing and/or distributing material (tissue/specimens/data) expressly for use in research.

**References**

1. “Ethical and Practical Guidelines for Reporting Genetic Research Results to Study Participants: Updated Guidelines from and NHLBI Working Group” *(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3090664/)*

Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)

Select References Reviewed by the Return of Research Results Committee, University of Kentucky
(Grouped by Author)

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Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings

University of Kentucky (UK) Institutional Review Board (IRB)

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NHLBI


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**Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings**

**University of Kentucky (UK) Institutional Review Board (IRB)**

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<td>ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. <em>American College of Medical Genetics and Genomics</em>. March 19, 2013 Web. 21 June 2013. <a href="http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf">http://www.acmg.net/docs/ACMG_Releases_Highly-Anticipated_Recommendations_on_Incidental_Findings_in_Clinical_Exome_and_Genome_Sequencing.pdf</a></td>
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# Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings

**University of Kentucky (UK) Institutional Review Board (IRB)**

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Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)


Caroline Savage Bennette MPH, Susan Brown Trinidad MA, Stephanie M. Fullerton DPhil, Donald Patrick PhD, Laura Amendola MS, Wylie Burke MD, PhD, Fuki M. Hisama MD, Gail P. Jarvik MD, PhD, Dean A. Regier PhD, & David L. Veenstra PharmD, PhD “Return of incidental findings in genomic medicine: measuring what patients value—development of an instrument to measure preferences for information from next-generation testing (IMPRINT)” Genetics in Medicine (30 May 2013). Web 22 October 18. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3823641/


Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings
University of Kentucky (UK) Institutional Review Board (IRB)¹

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Incidental Findings from IMAGING – References


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