Policy and Review: The IRB’s Imperative in Incidental Findings in Research

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Children’s Hospital Affinity Group of the Academic Medical Centers and Teaching Hospitals and In-House Counsel Practice Groups

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The problem of incidental findings in imaging studies is well known: obtain a diagnostic image for one purpose but see a concerning lesion nearby, for instance.\(^1\) With the advent of genomics\(^2\) research, however, we can anticipate increased incidence of incidental or secondary findings in this context.\(^3\) For example, a genomic analysis to determine whether a certain genetic mutation exists and correlates with a specific pediatric cancer diagnosis could reveal sex-linked chromosomal aberrations or a predisposition to conditions that may manifest in childhood, or may not manifest (if at all) until adulthood, such as Huntington’s disease or cardiac problems. Under what circumstances should such incidental findings in research results, seemingly unrelated to the reasons the testing was performed, be returned to a research participant? Both the Presidential Commission for the Study of Bioethical Issues and the American Society for Human Genetics advise investigators to have a plan for disclosing and managing incidental and secondary findings (collectively, incidental findings)\(^4\) and to include that plan as part of the protocol submitted to the Institutional Review Board (IRB) for review.\(^5\) In turn, IRBs are expected to evaluate the investigator’s plan and assess its adequacy.\(^6\) This raises the question of what an IRB should require by way of policy and in its reviews of research protocols. This Member Briefing identifies subjects

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2. Genomic testing in both the research and clinical contexts can determine the person’s complete DNA sequence using laboratory testing and extensive analysis. “Genome-scale sequencing” may refer to either whole-genome or whole-exome sequencing. \(\text{Id. at 8.}\)

3. Presidential Commission for the Study of Bioethical Issues, Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts, at 2, available at http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf (Anticipate and Communicate). But see Sebastian Schuol, Christoph Schickhardt, Stefan Wiemann, Claus R. Bartram, Klaus Tanner, Roland Eils, Benjamin Meder, Daniela Richter, Hanno Glimm, Christof von Kalle, and Eva C. Winkler, Opinion: So rare we need to hunt for them: reframing the ethical debate on incidental findings, GENOME MEDICINE 2105 7:83 (Reframing), at 3-4 (arguing that incidental findings are relatively rare). An incidental finding is generally considered a result that arises outside the original purpose for which the test or procedure was conducted. Anticipate and Communicate, at 2. See ASHG Position Statement, supra note 1, at 9.

4. Anticipate and Communicate, supra note 3, at 5; See ASHG Position Statement, supra note 1, at 9. ("When secondary findings are likely to be generated in the conduct of pediatric research, ASHG recommends that investigators develop an IRB-approved plan to manage such findings.")

5. Anticipate and Communicate, supra note 3, at 13, 14.

6. Anticipate and Communicate, supra note 3, at 15.
an IRB should consider addressing in its policies on incidental findings and issues arising in the review of research protocols that are likely to result in incidental findings.

The Common Rule\textsuperscript{7} requires investigators to disclose the risks and benefits of participating in research, including, when appropriate, the possibility of currently unforeseeable risks.\textsuperscript{8} “It could be argued that, at a minimum, this requirement obligates investigators to disclose the fact that significant findings might be discovered during the course of the research and whether or not those will be offered to subjects and/or their physicians.”\textsuperscript{9} Thus, an IRB policy must set forth its standard on disclosure of incidental findings. The policy might require that investigators have a plan for what results they will and will not return to participants. If any results are to be returned, the policy might require that the investigator anticipate all possible incidental findings and disclose up front to participants via the informed consent process which ones will be returned to the participants. “When planning for the disclosure of research results, it is important to distinguish the types of results that will be returned and whether they will include only those related to the indication for research participation or also include incidental findings.”\textsuperscript{10}

\textsuperscript{7} The Federal Policy for the Protection of Human Subjects, also known as the “Common Rule,” was published in 1991 and codified in separate regulations by 15 federal departments and agencies (followed as well by three additional federal agencies). For the U.S. Department of Health and Human Services, these regulations are set forth in subpart A of 45 C.F.R. part 46. The main elements of the Common Rule include requirements for assuring compliance by research institutions, obtaining and documenting informed consent, IRB review of studies, and reporting obligations. Subparts B, C, and D address protections for certain vulnerable research subjects. Subpart D, at 45 C.F.R. 46.401 et seq, addresses pediatric research participants.

\textsuperscript{8} 45 C.F.R. 46.116(a)(2), (a)(3), and (b)(1).

\textsuperscript{9} Amy L. McGuire, Bartha Maria Knoppers, Ma’n H. Zawati, and Ellen Wright Clayton, Can I be sued for that? Liability risk and the disclosure of clinically significant genetic research findings, 24 GENOME RESEARCH 719, 720 (2014) (Can I be sued for that?), available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4009601/.

\textsuperscript{10} Sarah Scollon, Katie Bergstrom, Laurence B. McCullough, Amy L. McGuire, Stephanie Gutierrez, Robin Kerstein, D. Williams Parsons, Sharon E. Plon, Pediatric Cancer Genetics Research and an Evolving Preventative Ethics Approach for Return of Results after Death of the Subject, J. LAW MED. & ETHICS Fall 2015, 529-537, at 536 (Preventative Ethics).
Non-Return of Incidental Findings

If some kinds of incidental findings can be anticipated but will not be shared, these should be identified in the plan and specified in the informed consent. For example, the IRB’s policy should require the investigator’s plan to tell participants if a discovery of adoption, non-paternity, or consanguinity will not be revealed.11 If the investigator does not wish to return incidental findings to participants, the reasons for this decision should be stated in the investigator’s plan after anticipating the kinds of incidental findings that may result. If the investigator plans to return no incidental findings at all (because they are generated from a non-Clinical Laboratory Improvement Amendments of 1988 (CLIA) laboratory, as discussed below, or for other reasons), the IRB policy should facilitate IRB discussion and review, including its rationale for approval or non-approval. The IRB will want to ensure that non-return is ethical and that investigators shirk no ethical duty by returning no results. The policy also should require the informed consent to explain the “no-returns” plan to participants.

Returning Incidental Findings

If the IRB’s policy requires the investigator’s plan to address all possible incidental findings or permits the investigator in the research protocol to decide to return some or all incidental findings, details as to which kinds of incidental findings will be returned, under what circumstances, and to whom, must be set forth in the investigator’s plan. “If specific findings might influence the [participant’s] willingness to continue participation in the research, then there may be a duty to offer those results,”12 and the plan should take this into account.

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11 ASHG Position Statement, supra note 1, at 13-15. Revealing misattributed parentage can have substantial ethical implications. Id.
12 Can I be sued for that?, supra note 9 at 720; see 45 C.F.R. 45.116(b)(5) (requiring the informed consent document to include, if appropriate, a “statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.”).
Further issues that the IRB should require the plan to consider are discussed below. Many of the highlighted legal and ethical issues below arise in research with adults or children, but the challenges are particularly vexing in the pediatric context.\textsuperscript{13}

**Clinical “Actionability”**

Although some have argued that all possible results should be returned to all patients or research participants,\textsuperscript{14} consensus may be emerging that only clinically “actionable” results should be returned—meaning only those incidental findings that an individual or practitioner can make use of or act upon for health, personal, reproductive, or clinical decision making.\textsuperscript{15} If incidental findings are clinically actionable, investigators are much more likely to feel that they have an ethical duty—founded in the ethical principle of beneficence—to disclose the incidental findings.\textsuperscript{16}

Even in the clinical (non-research) setting, this subject is found to be evolving. In 2013, the American College of Medical Genetics and Genomics (ACMG) urged analysis and reporting on potentially damaging but not diagnostically related variations in a set of 56 genes that have been associated with the risk of various medical conditions.\textsuperscript{17} This approach sparked criticism and debate, including about what genes should be on the

\textsuperscript{13} ASHG Position Statement, supra note 1, at 1.

\textsuperscript{14} Anticipate and Communicate, supra note 3, at 23-24; see also Wylie Burke, Barbara J. Evans, and Gail P. Jarvik, Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care, 166 C AM. J. MEDICAL GENETICS, 105, 105 (2014) (Distinctions Between Research and Clinical Care).


\textsuperscript{16} Anticipate and Communicate, supra note 3 at 30.

\textsuperscript{17} See ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing at 15 Genetics in Medicine 565-574 (2013) (ACMG’s Incidental Findings Recommendation) available at www.nature.com/gim/journal/v15/n7/full/gim201373a.html.
list of returnable genes and whether patients should be able to refuse results.\textsuperscript{18} Then, in April 2014, the ACMG reported that it would be revising its guidelines to make it possible for clinical sequencing patients to opt out of receiving information on alterations not related to the diagnosis at hand based on feedback from its members, and it revised its recommendations in September 2014 as promised.\textsuperscript{19} More recently, the American Society of Human Genetics (ASHG) recommended in the clinical context that pediatric genomic incidental findings be offered “only when the information has clear clinical utility for the child and/or his family members” after a robust informed consent process.\textsuperscript{20} However, the ASHG advised that parents must be told, in the clinical context, if an incidental finding would have “urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat.”\textsuperscript{21}

Even had the ACMG not softened its position requiring receipt of certain incidental findings in the clinical context, many posit that these requirements should not be applied in the research context (at least if not substantially integrated with the health care context) given the different goals and duties of research.\textsuperscript{22} Challenging this view of allowing an opt-out or only reporting incidental findings that are “actionable,” however, are those who press for the return of all incidental findings because, even if not

\textsuperscript{18} E.g. Lanie Friedman Ross, Mark A. Rothstein, Ellen Wright Clayton, Mandatory Extended Searches in All Genome Sequencing: Incidental Findings, Patient Autonomy, and Shared Decision Making, 310 J. AM. MEDICAL ASS'N, 367-68 (2013) (arguing that implementing mandatory testing for conditions beyond the scope of the original purpose of testing “is in conflict with key ethical principles of patient autonomy and shared decision making” and is clinically unsound because the mutations likely are not pathogenic in low-risk groups).


\textsuperscript{20} ASHG Position Statement, supra note 1, at 9.

\textsuperscript{21} ASHG Position Statement, supra note 1, at 9. The ASHG concluded that genome-scale sequencing is not indicated for “screening in healthy children.”

\textsuperscript{22} The Floor, the Ceiling, at 820; Distinctions Between Research and Clinical Care at 106-07, 109. See also ASHG Position Statement, supra note 1, at 9 (“Clinicians have a primary obligation to act in the best interests of their patient; researchers must protect the welfare of subjects but are primarily charged with the production of generalizable knowledge.”); Reframing, at 5; Susan M. Wolf, Rebecca Branum, Barbara A. Koenig, Gloria M. Peterson, Susan A. Berry, Laura M. Beskow, Mary B. Daly, Conrad V. Fernandez, Robert C. Green, Bonnie S. LeRoy, Noralane M. Lindor, P. Pearl O'Rourke, Carmen Radecki Breitkopf, Mark A. Rothstein, Brian Van Ness, Benjamin S. Wilfond, Returning a Research Participant's Genomic Results to Relatives: Analysis and Recommendations, J. LAW. MED. ETHICS, 440-463, at 441, 446 (Fall 2015) (Returning Results to Relatives) (discussing return of research results, generally).
Reproductive Implications for the Participant or Family Members

An example of a finding that may have reproductive implications is a blood sample examined for other purposes that reveals cells exhibiting a sickle shape. Carriers of one copy of the sickle gene can have blood cells that exhibit the sickle shape without suffering symptoms of sickle-cell disease. This finding could have reproductive significance because offspring could inherit the variant from the participant. The investigator’s plan for returning incidental findings should address whether carrier status and other reproductive implications will be given to the participant. If there is any plan to provide such results to the family, such as in the pediatric context, implications of this plan should be addressed directly. Learning that one is a carrier of a serious disease can be concerning to a participant and his/her family members; thus, potential emotional distress is a possible risk of participation in the genomic research that should be included in the plan and disclosed in the informed consent. However, for some families at high risk for genetic diseases “the baseline uncertainty about risk status can cause psychosocial distress in the absence of genetic testing.” This concern may often arise in the genomic context as well.

Disclosure to Relatives

Parents and more distant relatives may ask the investigator for a research participant’s genomic test results (potentially including incidental findings) because of their

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23 See American College of Medical Genetics and Genomics’ Board of Directors’ Policy Statement: Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics (2015) available at www.acmg.net/docs/ACMG_Clinical%20Utility%20of%20Genetic%20and%20Genomic%20Services%20GIM%20June%202015.pdf; see also Returning Results to Relatives, supra note 22, at 444 (acknowledging value of a child’s genomic results to parental health or reproductive decisions).

24 Anticipate and Communicate, supra note 3, at 38.

25 Id. at 39, 40.

26 ASHG Position Statement, supra note 1, at 7.
reproductive or other health implications. An extensive ethical analysis of this issue, including recommendations, asserted that “[g]iven the usual lack of relationship between investigators and third parties who are not themselves research participants, the research (as opposed to clinical) setting, the need for a third-party relative to obtain their own genetic testing upon learning of a participant’s genomic results to ascertain whether they share the result in question, and the consequent uncertainty about whether disclosure of a participant’s results to relatives is highly likely to avert harm, a legal duty falling in researchers to warn relatives of genomic research results seems improbable.”27 Nonetheless, the majority of the authors of this ethical analysis concluded (with a minority dissenting) that it might be ethical for researchers to offer genomic information to a research participant’s relatives “in the exceptional circumstances of discovering highly pathogenic and actionable variants that the relative is likely to carry, and whose disclosure is highly likely to avert imminent harm.”28 In any event, researchers should anticipate that relatives may make these requests, and should determine participant preferences for sharing this information, including after the participant’s death, and should ask participants to indicate a representative to make decisions about these issues if the participant is unable to do so or is deceased.29

Deceased Patients

The investigator’s plan also should grapple with the possible return of incidental findings to family members of a deceased patient because of the potential reproductive or other impacts to them or to their offspring. The ethical basis for returning these results to family members is beneficence, which also mandates that the research put in place, prior to disclosure, the appropriate resources to explain and provide appropriate follow-up, for example, via genetic counseling.30 Some have suggested that this duty depends on the closeness of the relationship between the researcher and the deceased participant, i.e. whether the researcher also acted in the role of physician to the

27 Returning Results to Relatives, supra note 22, at 447.
28 Id. at 448.
29 Id.
30 Id. at 67.
participant/patient. Ideally, the informed consent or Health Insurance Portability and Accountability Act (HIPAA) authorization signed by study participants will give permission for disclosures of incidental findings to family members in these circumstances, but this may not always be possible.

In these circumstances, the plan must address whether HIPAA and the Common Rule permit their release. HIPAA applies even to the medical information of decedents—generally, HIPAA protects the individually identifiable health information of a decedent for 50 years following the date of death of the individual. However, HIPAA allows sharing of decedents’ health information for research purposes in certain situations. And under the Common Rule, a deceased research participant is no longer a “human subject” and thus not under the IRB’s oversight; however, it is recommended that the plan address handling prospective deaths of research participants. In discussing the return of intended results (not specifically incidental findings) in pediatric genomic research, a “preventative ethics approach should … address the risks of non-disclosure, be sensitive to timing [following the death of a child], take study design and the types of results being disclosed into account, and be responsive to ethical concerns.” Thus, it is “essential to anticipate possible research results and have a clear protocol for return of results after the death of pediatric research participants.”

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32 45 C.F.R. 160.103, definition of “protected health information,” paragraph (2)(iv).
33 45 C.F.R. 164.512(i)(1)(iii). In clinical situations, HIPAA allows the sharing of protected health information after death with personal representatives of the decedent, and with the decedent’s family members who were involved in their care, if not inconsistent with the decedent’s wishes. 45 C.F.R. 164.510(b)(5).
34 45 C.F.R. 46.102(f) (f) (“Human subject means a living individual …”).
35 Preventative Ethics, supra note 10, at 534.
36 Id. at 536.
Incidental Findings from Analyzing Previously Stored Tissue Samples

A research study may use samples that are stored from previous clinical or research uses. Under the Common Rule, IRBs have enjoyed the freedom to waive consent requirements for such research, including for using stored samples under 45 C.F.R. 46.116(d) (alteration or waiver of some or all informed consent requirements) and 46.408(c) (waiver of requirement for parental permission for research participation). Additionally, research will not currently fall under the IRB’s purview if the stored samples are de-identified and thus considered not to involve “human subjects” (and thus will be exempt from the Common Rule) consistent with 45 C.F.R. 46.101(b)(4). As a result of these exceptions, participants may not know that their samples, including DNA, are being used in research. Giving participants the choice of whether or how their stored and de-identified samples are used in research was not the norm in the recent past, and it is probably not the norm now under these regulatory standards.

An investigator’s plan for returning incidental findings should take into account whether or not the use of the samples was known to the participants, as returning results will be more complex if the participants will be surprised that their samples were used. The plan also should address any restrictions contained in the existing informed consent documents that the participants signed, which may contain various promises (such as not to contact the participants, not to share information, etc.). If the informed consent under which the samples were obtained does not address these issues up front, the IRB might consider mandating in its policy that such instances be presented to the IRB or a subcommittee of the IRB for case-by-case review of the legal, ethical, and practical issues occasioned by a desire to return incidental findings. Practical issues may include how to locate the participant. If an old tissue sample were used for the research, for example, and the participant is no longer an active participant, what must be done to locate a participant, and how should this be documented? How broad a search must be conducted? Additional practical issues include who should contact the participant, and who should make the disclosure. Whether this is the investigator, the patient’s physician, a geneticist, or a genetic counselor should be determined in advance.

37 Incidental Findings in Genetic Research Using Archived DNA, supra note 3, at 2.
Similarly, the investigator must decide how to make contact. Should the initial approach be made by letter or telephone call or is a face-to-face encounter required? If an in-person appointment is to be required, what arrangements are made for participants who have moved far away? And should the participant be offered the chance to decline to be advised of the incidental findings?

If adopted as written, the Notice of Proposed Rulemaking for updating the Common Rule (issued by the U.S. Department of Health and Human Services on behalf of itself and 15 other governmental departments and agencies) proposes to treat all biospecimens, even if de-identified, as human subjects.\(^3\)\(^8\) This requirement would not apply to existing samples, but would change the rules for specimens collected in the future.\(^3\)\(^9\) The rule also would drastically restrict the waiver of informed consent regarding future use.\(^4\)\(^0\) If these changes are adopted, IRBs will need to address these changes going forward in their policies and in reviewing investigators’ plans.

**Non-CLIA Results**

IRBs at institutions with research laboratories should include in their policy a requirement that investigators consider the handling of results that were obtained from analysis in a non-CLIA laboratory. The CLIA regulations are generally understood to restrict return of individual results obtained in a non-CLIA research laboratory.\(^4\)\(^1\) The restrictions arise from concerns about the validity and accuracy of results obtained in a laboratory that does not meet all of CLIA’s stringent requirements. Thus, IRBs should

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39 Id. at 53993.
40 Id. at 54054.
41 The CLIA regulations state that they do not apply to “Research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.” 42 C.F.R. 493.3(b)(2). This is widely, but by no means universally, taken to mean that results from non-CLIA research laboratories may not be returned to patients or research participants. See *Anticipate and Communicate, supra* note 3, and sources cited therein, at 81-82. See also SACHRP, Attachment C: Return of Individual Results and Special Consideration of Issues Arising from Amendments of HIPAA and CLIA, available at www.hhs.gov/ohrp/sachrp/commsec/attachmentc:letter9/28/15.html. But see *The Floor, the Ceiling, supra* note 15, at 823; *Distinctions Between Research and Clinical Care, supra* note 14, at 107-08.
require investigators analyzing samples in non-CLIA labs to determine how these results will be handled. Will the investigator feel an ethical imperative to return any subset of the incidental findings, such as those suggestive of a serious but treatable illness where time is of the essence? If so, will the institution risk allowing return of such results garnered from the research laboratory? If not, can funding be obtained to repeat the testing in a CLIA laboratory? Regulatory liability is not the only concern, as some have suggested that tort liability also might arise if compensable harm results from return of such incidental findings without appropriate caveats that testing must be repeated in a CLIA laboratory.42

Intersection of CLIA and HIPAA

Amendments to the HIPAA Privacy Rule43 and to CLIA regulations44 have been interpreted to require some research laboratories in HIPAA-covered entities to release the genomic analysis results that include genomic findings (potentially including incidental findings), upon request of the research participant, even though these are not CLIA laboratories and even though CLIA is understood not to allow returning non-CLIA lab results for treatment.45 For prior studies, IRBs may require investigators to seek IRB permission before returning incidental findings from non-CLIA laboratories that would have been returned if gathered from a CLIA laboratory so that case-by-case analysis of the ethical, legal, and institutional risks can be conducted. Even if a study has an IRB-

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42 Can I be sued for that?, supra note 9, at 722.
43 See 79 Fed. Reg. 7290, 7292 (Feb. 6, 2014). (“The Department also proposed to amend the HIPAA Privacy Rule at 45 CFR 164.524(a)(1)(iii)(A) and (B) to remove the exceptions to an individual’s right of access that relate to CLIA and CLIA-exempt laboratories to align the Privacy Rule with CMS’ proposed changes to the CLIA regulations and the Department’s goal of improving individuals’ access to their health information.”)
44 42 C.F.R. 493.1291(l). (“Upon request by a participant (or the participant's personal representative), the laboratory may provide participants, their personal representatives, and those persons specified under 45 CFR 164.524(c)(3)(ii), as applicable, with access to completed test reports that, using the laboratory’s authentication process, can be identified as belonging to that participant.”)
approved plan for the return of incidental findings (such as advocated by this Member Briefing) that limits the incidental findings that will be returned to a certain subset (immediately actionable for a serious health condition, for example, or related only to the purpose of the study, or those recommended in the clinical context by the ACMG), it is nonetheless possible that “a participant could request all of the NGS [next-generation sequencing] data from the laboratory, notwithstanding the decision to limit the return of results”—at least if this information is considered a part of the institution’s “designated record set” under the Privacy Rule. This issue is particularly concerning for research laboratories within HIPAA-covered entities such as academic medical centers. In this context, IRBs may wish to assess their institutional definition of “designated record set” and/or encourage researchers to suspend, via the informed consent process, participants’ access to results of any sort during the research.

FDA LDTs

The U.S. Food and Drug Administration (FDA) announced in 2014 draft guidance that it will expand oversight of laboratory developed tests (LDTs), requiring investigational device exemptions for a broader group of “home brew” tests that are used in human subject research before results can be returned. The draft guidance observed that CLIA does not require evaluation of the ability of a diagnostic device to measure or detect the clinical condition or disease for which the device is intended, also known as the “clinical validity” of a laboratory test.

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46 Barbara J. Evans, Michael O. Dorschner, Wyle Burke, and Gail P. Jarvik, Regulatory changes raise troubling questions for genomic testing, 16 GENETICS IN MEDICINE 799, 800 (Nov. 2014) (Regulatory changes).

47 45 C.F.R. 164.501; see also Id. at 800 (terming the designated record set as applied in genomic testing a “Pandora’s Box”).

48 Id.; 45 C.F.R. 164.524(a)(2)(iii).


51 Id. at 9.
analytic specificity, sensitivity, accuracy, and precision in detecting analytes, is not necessarily evaluated under CLIA before the test is used, suggesting that FDA should fill this gap in order to protect patient (and participant) safety.\(^{52}\) Accordingly, IRBs may wish to consider the extent to which test results are based on genomic or genetic LDTs for which clinical or analytic validity are not clearly established, before allowing the results to be shared with participants.

Results from Previously Approved Protocols

Even if incidental findings are addressed in an IRB policy, protocols, and informed consent documents going forward, an institution may have existing protocols (pre-dating the policy) for genomic research that do not address how incidental findings will be handled. In this case, participants are likely unaware of the possibility of such incidental findings and how they are to be handled. These issues are largely similar to those discussed above in “Incidental Findings from Analyzing Previously Stored Tissue Samples.”

Duty to Hunt?

In the clinical context, the ACMG has recommended that 56 genes be affirmatively analyzed.\(^{53}\) Currently, there is considerable debate “regarding the obligation, if any, to search for selected variants with high clinical validity and clinical utility when conducting genome-scale sequencing.”\(^{54}\) The ASHG has recognized that “the ethical responsibilities and risk-benefit considerations differ” in the research context from those in the clinical context for children, and thus, that “actively searching” for incidental

\(^{52}\) Id. at 9-10.

\(^{53}\) ACMG’s Incidental Findings Recommendation, supra note 17, at 15.

\(^{54}\) ASHG Position Statement, supra note 1, at 8. The ASHG advised that, in the clinical context, “targeted testing using genome-scale sequencing, but restricting the analysis to a limited set of genes relevant to clinical indication, is an acceptable alternative to single-gene analysis or targeted gene panel in certain circumstances. Where genome-scale sequencing is performed by the analysis is restricted to a limited set of targeted genes, ASHG finds it ethically acceptable for the laboratory to limit the analysis to the genes of clinical interest.” Id.
findings in genomic research, although ethically acceptable in some circumstances with parental informed consent, “should not be considered ethically required at this time.”\textsuperscript{55} Even less compelling is any claim of a duty to hunt for results that might benefit relatives of the research participant.\textsuperscript{56} Thus, an IRB reviewing research protocols should consider its stance on whether investigators have a “duty to hunt” for certain specific genetic variants that are not related to the purpose of the genomic study. More broadly, the IRB and investigator must recognize that the study design will influence the type of results generated.\textsuperscript{57} Conversely, IRBs and investigators may want to narrowly define the genes or variants they will analyze. The investigators further should be careful about promises made in the informed consent—caution is advised in assuming an unending future duty to hunt or analyze for a large set of variants.

**Identification of Genetic Variants of Unknown Significance**

The clinical significance of most of the genome is yet to be characterized. Thus, genomic test results may include “variants of unknown significance.”\textsuperscript{58} The IRB’s policy should consider requiring the investigator’s plan to address whether or not such findings will be shared with the participants, and why. In addition, if the meaning of one or more of these variants later becomes known, some investigators will feel a duty to disclose at least some of these to participants. However, whether there will be personnel and a budget to support review of former studies, identification of variants, and contact with participants should be considered carefully in the IRB policy and in the investigator’s protocol-specific plan. One suggestion is that the duty to return these results lasts only as long as the period of the funding for the research study.\textsuperscript{59} Another is to have a long-term communication plan, at least in the clinical context.\textsuperscript{60}

\textsuperscript{55} ASHG Position Statement, supra note 1, at 9-10; Returning Results to Relatives, at 450.
\textsuperscript{56} Returning Results to Relatives, supra note 22, at 450.
\textsuperscript{57} Preventative Ethics, supra note 10, at 536; Reframing, supra note 3, at 5.
\textsuperscript{58} ASHG Position Statement, supra note 1, at 7.
\textsuperscript{59} The Floor, the Ceiling, supra note 22, at 820.
\textsuperscript{60} ASHG Position Statement, supra note 1, at 16 (recommending a long-term communication plan “for all results, including consideration of who should be involved in the communication of information and the staging of information sharing on the basis of age, maturity, and capacity to understand” in the pediatric, clinical context).
Ethical Considerations in Returning Results

Many posit that participants should have a voice in whether they receive incidental findings. Under this view, the informed consent communications should address the likely incidental findings, when they might be shared with the subject, or not, and whether the participants will be given a choice of receipt.\(^61\)

The ethical underpinnings of whether to disclose incidental findings are complex and must be balanced against each other. The duty to disclose incidental findings is founded on ethical concepts of respect for persons (autonomy), beneficence (duty to help/assist), and non-maleficence (the duty to avoid harm and/or the duty to rescue). For adult and emancipated minor participants, this ethical stance should be balanced with participants’ right not to know, based on respect for persons (autonomy). A participant may not wish to learn of any genetic risks of developing a future disease. Should this participant’s autonomous desire not to know trump what the investigator may feel is an ethical duty under the principle of beneficence to advise the participant of, for example, a BRCA gene mutation that could influence cancer screening, reproductive planning, or other lifestyle choices?

For children, the ethical analysis can be even more challenging.\(^62\) Genome-scale sequencing in children is now being considered for “diagnostic testing, predictive testing for childhood-onset conditions, pharmacogenetic testing, and testing in children with cancer to inform diagnosis or therapy” in both the research and clinical contexts.\(^63\) Should beneficence and non-maleficence and the “best interests” of the child outweigh the autonomy of parents who desire not to know of incidental findings that are actionable and could impact the child’s health or well-being? Many would say that, in this case, the principles of beneficence and non-maleficence would trump parental

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62 In July 2015, the ASHG set forth its current opinion on the ethical, legal, and social issues concerning genetic testing in children. See also ASHG Position Statement, supra note 1.
63 ASHG Position Statement, supra note 1, at 8.
autonomy if the findings were of grave significance and actionable during childhood. That is, the parents should not be allowed to refuse (in the research or clinical contexts) incidental findings that could impact their child’s health during childhood. The IRB should require that the investigator consider this issue in the incidental-findings plan and informed consent. It may be that an investigator’s plan for some studies would preclude participation of children whose parents refuse receipt of actionable incidental findings. However, opting in to receipt of genomic results should not be a requirement for participating in studies with therapeutic benefit, for example tumor sequencing in order to select the appropriate chemotherapy.

If genomic incidental findings reveal in a child a condition that is not actionable now but that could affect the child’s future lifestyle choices or reproductive decisions, which principles should control? In this instance, many would say that the beneficence and non-maleficence would counsel that the results not be returned in order to preserve the child’s right to an “open future”—a future not clouded by knowledge of the incidental findings and a future in which the child as an adult may decide if he or she wants to learn of the incidental findings. If the investigator plans not to return such incidental findings, parents should not be offered these results because their decision to receive them will not be respected. Yet they need to be advised of this plan at the outset in order to assess the risks and benefits of taking part in the research. Although hotly debated, many take the position that these incidental findings should be available to parents because they could affect family planning or life choices of other family members.

64 The Floor, the Ceiling, supra note 15, at 822. (“Parents too should be able to refuse the return of results and incidental findings when their children participate in genomic research. This latitude to refuse may be limited, however, when the results hold high and actionable health significance for the minor during childhood. This is in keeping with the broad discretion generally accorded to parents to make health decisions in their child’s best interests, except regarding conditions that threaten life or significant impairment.”)
65 Id. at 822.
66 Id. at 821.
67 Preventative Ethics, supra note 10, at 535.
68 ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing, available at www.nature.com/gim/journal/v15/n7/full/gim201373a.html; Mapping the Ethics of Translational Genomics, supra note 15, at 496.
A further issue in the pediatric context is the role older children and adolescents may play in this decision-making. Unless waived, their assent must be obtained for research. Issues that the investigator’s plan may need to address include assent from adolescents before testing as to what kinds of incidental findings will and will not be provided, subsequent adolescent refusal to receive actionable incidental findings, and demands to know those that the parents refuse. The IRB may, for example, require that the parents and adolescent agree in order to have both parental permission and adolescent assent to the research and to the plan for return or non-return of incidental findings, perhaps with an exception for findings that are highly actionable during adolescence and with serious risk of harm if not addressed. For pediatric participants, “[t]he informed consent process and procedures for returning genomic research results to pediatric patients and their families must be a particularly flexible process, involving the parents and adjusting to the increasing capacity of the patient’s ability to assent, and eventually consent upon the age of majority.”

Liability

Institutions and IRBs also must consider whether returning or, more likely, failing to return, incidental or secondary findings in and of itself could lead to legal liability. Courts may begin to find a duty to return research results as ethical consensus is reached, and then impose liability on investigators for failing to meet that duty. For example, failure to return clearly actionable results that would impact treatment decisions when there is a physician/patient relationship between the investigator and the research participant could possibly be viewed as breach of a duty the investigator

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69 45 C.F.R. 46.408(a); see also 46.404, 46.405(c), 46.406(d), 407(b)(iii).
70 See generally Ellen Wright Clayton How Much Control Do Children and Adolescents Have over Genomic Testing, Parental Access to Their Results, and Parental Communication of those Results to Others?, J. OF LAW, MEDICINE, & ETHICS (2015), 538-544.
71 Preventative Ethics, supra note 10, at 536.
72 Can I be sued for that?, supra note 9, at 721-22; Elizabeth R. Pike, Karen H. Rothenberg, and Benjamin E. Berkman, Finding Fault? Exploring Legal Duties to Return Incidental Findings in Genomic Research, 102 GEORGETOWN L. REV. 795, 814 n. 95 (2014) (Finding Fault?).
73 Id. at 798, 823.
74 Id. at 812-13; Can I be sued for that?, supra note 9.
owes to the participant. Finding a duty becomes less likely when a result is merely an indicator of a possibility or likelihood of developing a certain condition. Conclusions of state courts on the duty to warn the family member or patient in the clinical context differ. Evolving guidance and standards of professional organizations, commitments in informed consent documents, and the extent of the relationship between investigator and participant are among the considerations courts may assess in determining liability for failing to return results. Liability should be limited by taking into account challenges of finding participants to return results, as well as whether information or specimens used in research was de-identified. Laws outside the United States may impact disclosure duties and potential liability for research conducted abroad or with samples from other countries. Liability issues also might arise regarding reporting of child sexual abuse that genomic testing may reveal is likely.

How the Disclosure Is Made

The investigator’s plan must address how disclosure is likely to be made, for example by letter or telephone call to participants or families, or via contact with their physician(s). The risks of the “cold call” to participants to give results or incidental findings from studies that a participant is unaware of are described dramatically by Ellen Clayton Wright. Participants (or patients whose clinical samples have been used in research) may well be shocked to receive a call disclosing incidental finding. Even if a call or letter says there are available results that can be disclosed if desired, participants may be surprised and discomfited. Plans for explanations, counseling, and other advising should be determined in advance. If there is no budget for providing such follow-up plans, the plan should specify that incidental findings will not be returned or should require a clear statement to participants that no assistance in understanding and

75 Finding Fault?, supra note 72, at 810-12, 820-29; Can I be sued for that?, supra note 9, at 720-21.
76 Preventative Ethics, supra note 10, at 530 (comparing cases).
77 Finding Fault?, supra note 72, at 840-843; Can I be sued for that?, supra note 9, at 719.
78 Can I be sued for that?, supra note 9, at 721.
79 Id. at 720.
80 ASHG Position Statement, supra note 1, at 14.
81 Incidental Findings in Genetics Research Using Archived DNA, supra note 15, at 1.
82 Id.
dealing with the incidental findings will be provided, likely increasing the risk of participation in the research.

**Timing of Disclosure**

The timing of disclosure also should be addressed. As one example, parents who may not want results or incidental findings immediately following a child’s death may later desire these results.83

**Informed Consent**

As discussed above, IRBs are charged with ensuring an appropriate, understandable informed consent document.84 Thus, the IRB policy addressing return of incidental findings should require that the consent form be clear about the possibility of incidental findings, what kind of findings will be analyzed (or omitted from the analysis), and any plan to return or not to return those findings. If incidental findings will be given to participants or family members, risks of receiving them must be included.85 These risks might include emotional distress occasioned by learning that one has a genetic predisposition to a disease or that one or one’s family member is a carrier of a disease. Additional risks that should be addressed include the possibility of genetic discrimination against an individual based on genetic incidental findings emerging from a genomic analysis. Certificates of confidentiality do not protect against voluntary disclosure, and the Genetic Information Non-Discrimination Act does not provide protection from all forms of discrimination.86 Recognition that disclosure is among the chief ways to secure and maintain the trust of participants and members of the public who might in the future

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83 *Id.* at 535. See also ASHG Position Statement, *supra* note 1, at 15-16 (recommending, in the pediatric clinical context, a long-term communication plan).
84 45 C.F.R. 46.116.
85 See 45 C.F.R. 46.116(a)(2).
participate in the research enterprise should guide IRBs in setting policies that direct contents of the informed consent documents in the genomics context.87

Finally, a decision not to return incidental findings should be justified to the IRB separately, and should be explained to participants in the informed consent document. Informed consent, of course, is not just a document; it also is discussion and communication of these complex issues between the investigator and the participants or their legal decision makers.

Conclusion

The return of incidental findings has prompted much analysis and debate in part because it is at the intersection of research and clinical care.88 The IRB’s role is essential in formulating policy and reviewing investigator plans regarding incidental findings (including perhaps mitigating the potential for incidental findings, for example by limiting the variants analyzed, if that is possible while achieving the protocol’s goals). Investigators and IRBs, working collaboratively, will better manage these complex issues and their evolution.

87 See Mapping the Ethics of Translational Genomics, supra note 15, at 496.
88 Mapping the Ethics of Translational Genomics, supra note 15, at 494-95 (proposing a “layered” ethics approach of selecting the ethical analytic scheme from different research and clinical options based on which is the most protective of the individual whose genome is being sequenced).