Although issues associated with returning individual research results to study participants have been well explored, these issues have been less thoroughly investigated in vulnerable individuals and populations. Considerations regarding return of research results to these individuals and populations, including how best to ensure truly informed consent, how to minimize the risks and benefits of the return of research results, and how best to ensure justice, may differ from those of the population at large. In this article, we discuss the issues and challenges associated with the return of individual research results (such as genomic, proteomic, or other biomarker data) to potentially vulnerable individuals and populations, including those who may be vulnerable for cognitive, communicative, institutional, social, deferential, medical, economic, or social reasons. We explore factors that should be considered in the design, conduct, and oversight of ethically responsible research involving the return of research results to vulnerable individuals and populations and discuss recommendations for those engaged in this work. (Am J Pathol 2022, 189: 1–12; https://doi.org/10.1016/j.ajpath.2022.06.004)
social factors leading to disease and health disparities, and to ensure that all populations benefit from the research.13

In this article, we discuss issues to consider when returning IRRs to potentially vulnerable study participants, focusing our attention on results that originate from testing human biospecimens. Some of these considerations also may apply to returning aggregate research results. We hope this exposition will assist researchers, Institutional Review Boards (IRBs), sponsors, and regulators in the design, conduct, and oversight of ethically responsible research involving return of IRRs.

Who Is Vulnerable?

The term vulnerable can have multiple context-dependent meanings. For our purposes, a vulnerable individual is a research participant who requires additional protections with respect to research participation,14,15 including receipt of IRRs. Some individuals and populations may be vulnerable in research because they may be unable to provide voluntary informed consent; they may be at risk for incurring additional harms (eg, group harms) or subject to exploitation, coercion, or undue influence.15,16 Traditionally, vulnerable populations include minors, pregnant women, prisoners, military service members, students or employees in hierarchical organizations, terminally ill, comatose, and physically and intellectually challenged individuals, institutionalized individuals, elderly individuals, visual or hearing impaired individuals, ethnic minorities, refugees, and economically and educationally disabled healthy volunteers.15 In this article, we modify the Gordon contextual approach for understanding vulnerability to form a seven-part framework (Table 1) for analyzing issues associated with return of IRRs to vulnerable individuals.

Ethical Issues

The Belmont Report defines general principles for human subject protection, including vulnerable research participants (Respect for Persons, Beneficence, and Justice, https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf; last accessed May 29, 2022). Respect for Persons requires protection of autonomy and underpins the requirement for honest and complete communication with research participants, as well as informed consent. It also requires that individuals who have diminished autonomy be provided with additional protections. Beneficence requires that research be performed in a manner that minimizes risks to research participants while maximizing potential benefits. Justice requires the equitable selection of participants and that research participants share equally in the distribution of the potential benefits and risks of research participation, including in the return of any IRRs.

Ethical issues associated with returning IRRs have been debated for many years (https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-b-return-individual-research-results/index.html, last accessed May 29, 2022),14 and there is emerging consensus that returning IRRs can be appropriate when research results are analytically valid and clinically useful. However, controversy remains because returning IRRs has potentially competing risks and benefits. Considerations regarding return of IRRs to vulnerable research participants have not been widely discussed in the existing literature.

Benefits and Risks from Return of Results

Potential Benefits

There are several potential benefits to returning IRRs to research participants. For example, offering to return results can foster transparency and demonstrate respect for participants. In addition, laboratory findings from a research project may sometimes have a direct clinical benefit to the participant. The American College of Medical Genetics and Genomics has recognized the importance of reporting clinically useful secondary findings from genetic and genomics testing in clinical laboratories, because early intervention can reduce the risk of death from causes, ranging from sudden cardiac death to cancer.18,19

Potential Harms

Advocates for returning IRRs have received pushback from authors who are concerned about potential participant harm from receiving IRRs originating in non-clinical laboratories.5,6 Individual harms may potentially come from returning IRRs to any individual, whether vulnerable or not. Research laboratories do not generally operate under the same stringent quality controls as clinical laboratories, which must adhere to procedures that help to ensure the accuracy of their results. These controls include federally mandated requirements for biospecimen identification, test validation, and reporting, as well as both internal quality assurance activities and external proficiency testing. Laboratories that meet these requirements may become certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), may perform the testing routinely, and may operate within an environment designed to deliver care. CLIA laboratory results may be returned to participants and used to guide further patient care.

Analytically or clinically invalid results

Returning invalid laboratory test results may harm participants. About two-thirds of medical decisions are based, at least in part, on the outcome of in vitro laboratory testing.20 Inaccurate testing may lead to overdiagnosis of disease with inappropriate, potentially toxic, treatment, or to underdiagnosis that leads to delayed treatment.21 Much research based on biospecimens is conducted in laboratories not CLIA certified to perform clinical testing, at costs lower than those incurred by CLIA laboratories.22 This testing may suggest associations between laboratory tests and health outcomes, which may be misleading to participants who return for IRRs.
and investigators and research participants are often convinced that there is a potential health benefit to sharing these research results. Research participants often express a desire to know their research results, regardless of whether they originate from a research laboratory or from a clinical laboratory. However, non-CLIA research laboratories may lack the rigorous quality assurance activities necessary to ensure accurate biospecimen identification, analytical accuracy, and clinical validity. A National Academies report suggests that this issue may be addressed outside the framework of CLIA, with IRBs assessing whether the quality assurance framework is sufficient.\(^1\) However, the report does not address how institutions would ensure that IRBs have the necessary expertise to perform this task.

Some investigators suggest a hybrid approach in which positive findings from research testing are confirmed in a CLIA laboratory, either before or after returning IRRs. This approach assumes, without justification, the correctness of negative research laboratory results and may (if IRRs are returned before clinical laboratory confirmation) cause uncertainty and anxiety if conflicting reports are received from multiple laboratories. It also puts research participants who lack the resources to obtain additional confirmatory testing at a disadvantage relative to other participants. In addition, for those participants who can afford additional testing, it may cause some economic harm. The difference between CLIA-certified and noncertified laboratories is often not well understood by clinicians not trained in laboratory medicine. The reasons that additional testing is required may be difficult for some investigators to communicate to research participants, and difficult for research participants to

### Table 1: Types of Vulnerability

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive vulnerability</td>
<td>Individuals with decisional capacity limited by cognitive impairment</td>
<td>Serious mental illness, Age-related dementia, Some infections, Chronic drug abuse</td>
</tr>
<tr>
<td>Communicative vulnerability</td>
<td>Individuals who may have limitations in their ability to communicate effectively with the research team</td>
<td>Deafness (congenital or acquired), Blindness, Auditory processing disorders, Stroke-associated aphasia</td>
</tr>
<tr>
<td>Institutional vulnerability</td>
<td>Individuals who are under the authority of others who may have different values</td>
<td>Imprisonment, Parolee status, Group home residence, Assisted living or nursing home residence</td>
</tr>
<tr>
<td>Medical vulnerability</td>
<td>Individuals with serious health conditions for which there is no standard treatment, and who may conflate research investigation with ordinary medical care</td>
<td>Illness (with respect to health care provider), Intimacy (with respect to partner), Employment (with respect to employer)</td>
</tr>
<tr>
<td>Economic vulnerability</td>
<td>Individuals who are disadvantaged in the distribution of income, housing, or health care</td>
<td>Unemployment, Receiving disability payments, Sole income from social security</td>
</tr>
<tr>
<td>Social vulnerability</td>
<td>Individuals who are members of undervalued or marginalized social groups who may be at increased risk of group harm or stigmatization</td>
<td>Racial or ethnic minority, Lesbian, gay, bisexual, transgender, queer (LGBTQ), Migrant, Non–English speaking, Native American, Religious minority</td>
</tr>
</tbody>
</table>

This should by no means be considered exhaustive. Each of these types of vulnerability may include other examples. For example, in some societies, many women exhibit economic and social vulnerability because of cultural issues.
understand, whether or not they are vulnerable. These participants may not obtain additional testing, believing it to have no personal value.

Other potential harms may accompany returning IRRs, whether or not they originate from a CLIA laboratory. These include confusion about the roles of investigators versus health care providers, contextual challenges in the interpretation of IRRs, the inability to equitably benefit from IRRs, and stigmatization of research participants.

Confusion about the investigator role (therapeutic misconception)
Clinical laboratory testing is, in many jurisdictions, considered to be the practice of medicine, and triggers a duty of care that is not typically associated with biospecimen analysis by research laboratories. It is unclear whether return of IRRs from non-clinical research laboratories generates or implies a duty of care on the part of the laboratory, and whether it places the director of such a laboratory in the role of a health care practitioner, for whom licensure may be required. Returning IRRs to individual participants further blurs the line between investigator and health care provider. This may generate confusion for research participants regarding whether a positive health care outcome is expected because of their research participation, or whether instead, their participation in research is a gift that may enable improved health care for all in the future. Although these issues apply to all participants, whether vulnerable or not, they may be exacerbated in those with medical, cognitive, or communicative vulnerability.

Contextual challenges in the interpretation of IRRs
Most laboratory testing is performed either to screen for disease or to facilitate diagnosis and treatment of an ongoing disease process. When investigators test biospecimens, even using standard methods in a clinical laboratory, they may be testing a population that differs from that in which the test was validated and is ordinarily employed. The interpretation of IRRs may, in some cases at least, be more uncertain than the interpretation of the same test obtained during ordinary clinical care. In addition, as new information is developed, the interpretation of test results may change. This is particularly true for genetic tests, for which the understanding of both sequence variation and base modification (such as methylation) evolves over time and generates for the research team an obligation to convey the resulting uncertainty to research participants who receive IRRs.

Potential inability of vulnerable individuals to benefit from returning results
Returning IRRs to vulnerable individuals carries with it special considerations regarding the potential risks and benefits of the research. Members of vulnerable populations may experience limitations in financial and other resources. In countries (like the United States) in which health care is not universally available, they may not be able to benefit from receipt of IRRs (whether they come from a CLIA laboratory or not). If, for example, a research participant is told that his/her genetic sequence puts him/her at high risk for breast cancer, but he/she lacks resources to obtain the recommended follow-up care, there is significant potential for psychological distress; this is exacerbated for those whose results are provided by non-CLIA laboratories and for whom the expense of confirmatory testing falls to the participant. For studies in which both vulnerable and nonvulnerable individuals are enrolled, potential benefits from return of IRRs may not be distributed equally, in violation of the Belmont Report’s principle of Justice. However, the exclusion of these populations from either research participation or the receipt of results provided to other research participants also violates the principle of Justice. The spectrum of potential negative consequences of returning IRRs must be considered, and efforts must be made to ensure equal benefit for vulnerable participants. Research institutions should consider directing participants to available medical and financial resources to enable them to potentially benefit from return of their IRRs.

Stigmatization and discrimination
When returning IRRs to vulnerable populations, special consideration should be given to potential stigmatization, which may result in individuals being viewed as “undesirable [and] rejected,” and discrimination, which may limit the rights and power of participants from these groups. Furthermore, “…the accuracy and desirability of linking ethnic groups to genetic disease…can exaggerate genetic differences among ethnic groups and lead to unequal access to testing and therapy.” Genetic testing in the Ashkenazi Jewish population provides one example. The notion that this population was genetically unique had both positive and negative public health implications, including increased awareness and testing among the Jewish population and concerns about discrimination regarding insurance and employment.

Similarly, the African American population experienced significant discrimination because of misuse of information from population-based screens for sickle cell anemia.

Focused attention on specific racial or ethnic groups may also further exacerbate health disparities by impacting the likelihood of inclusion or exclusion in genetic screening programs based on group membership. When returning IRRs, the broad social implications of research results should be considered. This is perhaps particularly relevant in the context of genetic results, which have implications for future medical care and on future generations. Potential benefits to individuals from returning IRRs should be weighed against potential group stigmatization and discrimination.
Considerations Related to Capacity in Returning IRRs

There is a broad range of contexts in which vulnerability may manifest, including cognitive, communicative, institutional, deferential, medical, economic, and social vulnerability (Table 1). Decisional capacity must be considered in all types of vulnerabilities as it is integral to the ethical return of IRRs in individuals with these vulnerabilities.

Decisional capacity refers to a person’s ability to make an informed decision. Capacity, therefore, must always be assessed relative to a specific decision, at a particular time, in a particular context (https://plato.stanford.edu/entries/decision-capacity, last accessed May 29, 2022). With respect to returning IRRs, this includes the ability to appreciate higher-probability and long-term consequences of the information being received.

In general, the capacity to make an informed decision requires at least four elements: i) understanding the facts; ii) appreciating the nature and consequences of the decision that one is making; iii) reasoning, often considered as the ability to weigh the benefits and risks associated with a decision; and iv) making and communicating a choice.

Capacity is a continuous quality that may be present to varying degrees over time and is affected by the decision at hand. Therefore, in some cases, procedures or tests that require consent over extended periods of time may need repeated assessments. Research participants may lose capacity during a research project because of disease progression, injury, or death. There has been excellent scholarship on this issue, and a full exploration of the ethical and legal issues relevant to these participants is not feasible herein.

Ideally, decisional capacity should be carefully considered for every research participant. However, given feasibility and participant burden, it is usually assumed that adults have sufficient capacity in the absence of contrary evidence. Issues of capacity are relevant to many vulnerabilities, and any form of vulnerability may limit a participant’s capacity. We expand on and discuss considerations related to returning IRRs in vulnerable individuals below.

Context-Dependent Vulnerability and Return of Research Results

Return of Research Results to Participants with Cognitive Vulnerability

Research participants with some forms of cognitive vulnerability may have impaired decisional capacity. Capacity is frequently impaired in conditions, including serious mental illness, age-related dementia, some infections (https://www.psychiatry.org/FileLibrary/Psychiatrists/Directories/Library-and-Archive/resource_documents/Resource-Document-2019-Decisional-Capacity-Determinations-in-Consultation-Liaison-Psychiatry.pdf, last accessed May 29, 2022), and chronic drug abuse. Limitations in decisional capacity are not necessarily absolute, and the mere existence of mental or physical illness or disability does not necessarily indicate a lack of decisional capacity.

With respect to returning IRRs, individuals with some forms of cognitive vulnerability may lack sufficient understanding of facts, appreciation of consequences, or reasoning ability to understand the implications of receiving IRRs and, therefore, to consent to receive them. Higher levels of understanding may be required for consent to receive IRRs than to consent to participate because of the complexity of the issues associated with receiving IRRs.

The US Federal Policy for the Protection of Human Subjects says little about returning IRRs to participants. It requires that, when appropriate, the consent documents include a statement regarding whether clinically relevant research results, including IRRs, will be disclosed to subjects, and if so, under what conditions. However, it does not specifically address returning IRRs to vulnerable individuals or populations. The US Federal Policy for the Protection of Human Subjects does require that studies include additional safeguards to protect the rights and welfare of research participants at risk for cognitive impairment. In the context of studies in which IRRs will be returned to participants with cognitive vulnerability, this could include the use of consent or assent forms written in plain language along with additional educational materials related to results to be returned to help ensure understanding.

One federal regulatory protection for those with cognitive impairment is the inclusion of legally authorized representatives in the informed consent process, although no guidance is provided regarding returning IRRs to these individuals. When returning IRRs, we suggest that an investigator explain the implications and limitations of the results to the research participant, as well as to the legally authorized representative. Investigators need to pay special attention to both the capacity to consent to the research (including returning IRRs) and the capacity to understand the results being returned.

Because cognitively impaired individuals often experience societal ostracism or prejudice, special consideration must be given to individual and group harms that may result from dissemination of research findings, or disclosure that an individual is participating in a study. Cognitive impairment and decision-making capacity may vary over time; one cannot assume that an individual who had capacity to consent to return of IRRs at one time is capable of understanding those results at some uncertain point in the future and vice versa. However, when participants express an informed choice regarding results’ disclosure to family members or others but then lose capacity during the conduct of the study, respect for autonomy suggests that their preferences be respected. Indeed, the optimal approach is to...
encourage research participants to consider at the time of consent how they want their results to be handled if they subsequently lose capacity. Evaluating these possibilities will help ensure that potential benefits of IRRs do not outweigh potential harms to the participant.

Return of IRRs to Individuals with Communicative Vulnerability

Research participants with communication challenges may have communicative vulnerability (Table 1). Investigators should not assume that individuals who are affected by these and similar conditions are cognitively impaired but must be aware that neither does cognitive impairment spare these population groups. In some instances, such as with the elderly with hearing loss and those with amyotrophic lateral sclerosis, the likelihood of cognitive vulnerability may be increased. Moreover, individuals with communicative vulnerability are at increased risk of economic vulnerability (https://www.afb.org/research-and-initiatives/employment/reviewing-disability-employment-research-people-blind-visions, last accessed March 14, 2022). Furthermore, stigmatization and other group harms may be particularly relevant to those with communicative vulnerability. For example, much of the public (including the medical community) views deafness as a condition in need of correction, although members of the American Sign Language community view deafness as a cultural identity; this lack of understanding may lead to mistrust and/or exclusion from research. Individuals with communicative vulnerability may not be able to benefit from IRRs if results are not provided in a format the research participant understands.

Communicative vulnerability is not rare. As many as 5% of children (and presumably adults) experience auditory processing disorders, which may be comorbid with conditions such as attention-deficit and hyperactivity disorders. Similarly, dyslexia affects 3% to 7% of the population.45 There is no direct relationship between either auditory processing disorders or dyslexia and cognitive skill, although both complicate informed consent/assent for IRRs, returning IRRs, and benefiting from IRRs. Although those with auditory processing disorders may benefit from written materials, individuals with dyslexia may benefit from having the elements of informed consent presented orally. Multimodal approaches to both consent and return of IRRs may thus benefit much of the population.51 There is no direct relationship between either auditory processing disorders or dyslexia and cognitive skill, although both complicate informed consent/assent for IRRs, returning IRRs, and benefiting from IRRs. Although those with auditory processing disorders may benefit from written materials, individuals with dyslexia may benefit from having the elements of informed consent presented orally. Multimodal approaches to both consent and return of IRRs may thus benefit much of the population.51

Promote better understanding of how to maximize potential benefit from returning IRRs, while minimizing potential individual and group harms.58

Return of IRRs to Individuals with Institutional Vulnerability

Prisoners are considered a vulnerable population from the perspective of informed consent. They may also be considered vulnerable in the context of return of IRRs because they are under the authority of others who may have different values and priorities. Projects funded by either the Department of Health and Human Services or the Department of Veterans Affairs must undergo a detailed prior review if prisoners are included [Prisoner Research Certification (2020), n.d., https://www.va.gov/Research-and-initiatives/employment/returnof-irrs-to-individuals-with-institutional-vulnerability, last accessed May 29, 2022]. Historically, prisoners have been exploited in research endeavors, although a recent study suggested some do not feel exploited by research participation and are motivated to participate to gain access to treatments. Although it is possible that this desire reflects therapeutic misconception, it may also reflect medical vulnerability associated with a belief, whether well founded or not, that research participation will improve prison medical care because it is being indirectly observed by researchers. As for other vulnerable populations, the risk/benefit ratio for incarcerated research participants must be weighed, particularly as potential for harm increases.51 Moreover, the incarcerated population is significantly more likely to have a history of serious mental illness than are members of the general population.52 Infectious diseases, substance abuse, and other major medical conditions disproportionately affect this group.51 Finally, the privacy rights provided by Health Insurance Portability and Accountability Act of 1996 for returned results are more limited for prisoners than for the general population (https://law.uh.edu/healthlaw/perspectives/Privacy/030128HIPPAAs.pdf, last accessed May 29, 2022). Except for attorney-client interactions, communications are monitored, and materials within the incarcerated person’s possession are subject to inspection. When consenting for the research and for the return of IRRs to prisoners, potential participants should be reminded of these limitations to their privacy.

Although the institutional vulnerability of prisoners is universally recognized, impairments that may occur because of engagement with the criminal justice system as a parolee or as one awaiting trial have not received much attention. Release from incarceration does not restore full autonomy, except perhaps for exonerated and pardoned individuals. Court-ordered supervision, including parole, can potentially affect an individual’s perception of decisional capacity and contribute to coercion or undue influence. Researchers
Returning IRRs to Vulnerable Individuals

Studies contemplating returning results to incarcerated persons or to those with ongoing legal concerns should be designed and executed with advice from attorneys with specialized training and experience in both prison law and practices, as well as health care law. In addition, the consent process should ensure that involvement of the legal system does not impair the capacity of the potential research participant either to consent to return of results or to potentially benefit from any IRRs provided. Finally, the use of Community Advisory Boards may be particularly useful in study populations involving prisoners for addressing some of the issues that arise related to the return of IRRs in this population (eg, input could be provided on what privacy protections are needed).

Return of IRRs to Participants with Deferential and Medical Vulnerability

Deferential vulnerability arises from inequalities among people that may influence behavior, including sex, race, class, or position. Potential for deferential vulnerability is inherent in a medical setting because individuals are usually invited to participate in research because they are ill and have sought medical care. The deference of patients to health care providers may be extended to members of a research team that works in the same environment in which care is provided or in which the treating physician is also the investigator. This may be particularly acute when a potential research participant experiences a serious health condition for which there is no good treatment option (medical vulnerability). A risk associated with returning IRRs to individuals with deferential and medical vulnerability may be further promotion of the therapeutic misconception that the research investigation should benefit the participant directly. The consent process should be carefully designed to make it clear that research participation is a gift to others from which the participant should not expect personal benefit. Researchers need to exercise great care in explaining the limitations of returning IRRs during the informed consent process, particularly with individuals who may have deferential and medical vulnerabilities. For example, to reduce inappropriate deference in the case of medical vulnerability, the process of consenting to returning IRRs should be conducted in the absence of individuals engaged in ordinary medical care who are present. Avoiding the use of traditional medical attire when engaging in the consent process may also reduce deference to study team members.

Return of IRRs to Participants with Economic and Social Vulnerability

This category of participants includes individuals who are disadvantaged in the distribution of social goods and services, including income, housing, and/or health care (economic vulnerability), as well as individuals who are part of an undervalued social group that is particularly susceptible to stereotyping and discrimination (social vulnerability). Economic and social vulnerabilities may impair decisional capacity of a cognitively normal individual. Examples include sleep deprivation due to working multiple jobs, exhaustion due to serving as a caregiver, and the impact of physical or mental partner abuse. Economically and socially vulnerable research participants may not be able to benefit from returned results and may be at an increased risk of group harm and stigmatization. Engaging these populations in study decision-making and oversight processes can help mitigate these concerns. For example, when planning for the development of large tissue biorepositories, it is common to use focus groups, surveys, community advisory boards, and other forms of community engagement to develop policies and operating procedures for the project, including for returning any IRR. Ongoing engagement of vulnerable populations may enable a deeper understanding of how return of IRRs may affect members of nonvulnerable and vulnerable groups differently. Membership in economically and/or socially vulnerable groups does not imply that an individual lacks decisional capacity and it is not necessary for investigators to separately evaluate every potential influence on decisional capacity. In many cases, it is sufficient for investigators to illustrate for research participants the ways in which social and societal issues can affect capacity and allow individuals to self-assess in a manner that allows the participant to work within his/her comfort level.

Tribal Consent and Group Harms

The harms associated with returning research results to tribal communities have generated significant discussion, in part because of a legal case involving disputed use of Native American Indian DNA samples, Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow 2004 (discussed by van Assche et al). This case has helped to inform considerations regarding both informed consent and returning research results to tribal communities. In the Havasupai case, the Tribe was consented for studies of diabetes but stored biopspecimens were later used for purposes that the group found objectionable, resulting in dignitary harms to the group.

Research activities within territories under American Indian or Alaska Native Tribal jurisdiction are subject to regulation by Tribal authorities. The US Federal Policy for the Protection of Human Subjects specifically recognizes the rights of Tribes to regulate research by, for example, requiring review by a Tribal IRB as an exception to the single IRB rule in multi-institution (https://www.ncai.org/policy-research-center/research-data/prc-publications/ResearchPolicyUpdate.pdf, last accessed May 29, 2022).
Respect for Persons, as defined by the Belmont Report, may also require recognition of an individual’s membership in an identified ethnic community; this is often the case with indigenous populations, such as American Indians. The American Indian and Alaska Native Genetics Resource Center provides an excellent resource dealing with issues of study design, informed consent, and data sharing [ie, in many ways as applicable to any research involving Native Americans, whether or not a portion of this work, such as biospecimen donation, is conducted on Tribal lands (https://www.ncai.org/policy-research-center/initiatives/projects/genetics-resource-center, last accessed May 29, 2022)]. Additional useful information is found in the Tribal Collaboration Working Group Report to the All of Us Research Program Advisory Panel (https://allofus.nih.gov/sites/default/files/tribal_collab_work_group_rept.pdf, last accessed May 29, 2022).

Many individuals who identify as Native American may belong to groups that are not formally recognized by the US government. However, Respect for Persons requires researchers to be sensitive to concerns of groups that lack such recognition. In addition, nearly 30% of individuals identified as American Indian or Alaska Native are impoverished (https://www.census.gov/newsroom/facts-for-features/2015/cb15-ffj22.html, last accessed May 20, 2022). Both poverty and geographic isolation limit access of these individuals to resources that inform interpretation of IRRs, thus limiting their ability to benefit from IRRs. This imposes responsibility for researchers to ensure that a decision to return results does not disadvantage members of indigenous participants by comparison with others. To the extent that returning IRRs may be expected to influence future medical care, the following language from the Belmont Report is applicable: “...justice demands both that these not provide advantages only to those who can afford them” (https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf, last accessed May 29, 2022). This is a critical consideration in that all research participants should share equally in any benefits from IRRs, with no subpopulations subjected to undue burdens.

Best practices are for researchers to engage with native communities early and often and, where IRRs will be returned, to develop plans for returning results with input from both elected representatives of Tribal communities and, when possible, individuals holding no formal office. Issues that concern these communities may not be obvious to those who do not come from them; the only way to effectively identify and address these concerns is community engagement from the point of research design through completion, analysis, and dissemination. We contend that this perspective and approach should be more broadly utilized as it acknowledges not only the importance of research participation from all communities but the unique factors affecting each community.

Vulnerability of Members of Religious or Ethnic Groups

Membership in a religious community may constitute an important part of an individual’s identity and is a potential source of stigmatization. When research targets members of such a community or occurs in areas in which members are heavily overrepresented, community engagement in developing processes used for informed consent and the return of any results may result in improved recruitment, may ensure that those contributing to the research can benefit from the results, and may minimize potential group harms. For example, various Amish communities have contributed greatly to genetic research, which is often conducted in the context of community health clinics to achieve both community benefit and input. Working with existing community health centers enables researchers to serve the community in a sensitive way that is neither stigmatizing nor exploitive. In general, the most important consideration related to returning research results to religious minorities is the need to avoid stigmatization and/or discrimination and minimize group harm. Community engagement may help minimize risks of stigmatization and group harms from returning research results to these populations. It may also help maintain cultural sensitivity and aid in identifying potential sources of bias associated with the study population, such as correlations between religious practices, education, and income (https://www.pewforum.org/religious-landscape-study/educational-distribution, last accessed May 29, 2022).

Return of IRRs to a Child Participant

The vulnerability of children with respect to returning IRRs is often related to the level of cognitive and communicative development. However, children are almost always subject to institutional (parent and the home), deferential (parents), economic, and/or social vulnerability as well. Extensive work regarding returning IRRs to this population has been done by others. Herein, we provide an overview of some of this work along with a brief discussion of some of the most important considerations.

When children are participating in research, returning IRRs should be addressed during an assent process with an older child, and the informed consent process with parents of a younger child (ie, parental permission).32,62 All documents and methods of communication should be adapted to the child’s language, age, and sociocultural context.62 Older children’s preferences regarding whether and what type of results they would be interested in having returned, including a preference to have no knowledge of their research results,32 should be considered alongside the child’s age and development.63 Although the parent or guardian of the child participant retains the right to know health information that is relevant to the maintenance of the child’s health (although this does not imply a right to all the child’s research results), this right disappears when the child...
reaches the age of majority. At majority, it is important to consider again obtaining consent for returning IRRs. In developing protocols, investigators should anticipate whether the child’s IRRs will have relevance to the child’s health or the welfare of other family members. For example, a genetic variant identified in a child is likely to have been inherited from a parent, with potential health implications for both parent and family because the variant may be shared by siblings and other blood relatives. Similarly, the results of testing for environmental toxins might have importance for that child and others that share the exposure. Often in such circumstances, the parents should assist or take primary responsibility for communicating appropriate information to other family members. However, the research team should consider offering support and training for the parents in these situations to confirm understanding and ensure that results can be accurately communicated. In addition, child development professionals and those from related disciplines should be included on the research team to determine the most appropriate methods for relaying information throughout the study process.

With increased availability of genetic testing, the ethical considerations regarding returning secondary or incidental research results concerning adult-onset—only conditions to newborn and young children has been a topic of debate. The rationale offered for returning these results is that genetic testing could provide a personalized medicine strategy for disease management, beginning with preventative measures and including detection, diagnosis, and, ultimately, treatment. However, the types of information and the idea that the child should have rights regarding the kinds of information (commonly referred to as a “child’s right to an open future”) should be considered. The current consensus across multiple disciplines is that children should not be tested for adult-onset—only conditions (reviewed by Ross and Clayton). However, the Genome Sequence-Based Screening for Childhood Risk and Newborn Illness, or The BabySeq Project, suggested the concept of family benefit as a possible justification for returning results related to adult-onset—only conditions.

**Summary and Conclusions**

This article focuses on the considerations when returning IRRs to vulnerable research participants and populations who require additional protections when conducting research. Ethical considerations in returning IRRs, including decisional capacity and contextual vulnerabilities, derive from the ethical principles laid out in the Belmont Report: Respect for Persons, Beneficence, and Justice.

Although challenges faced by many potential research participants are complex and multifaceted, past exploitations of research participants and current health and resource disparities highlight the need for research to be conducted in a manner that is accessible and beneficial to all participants. This may be particularly challenging because most study populations will have participants with a range of vulnerabilities. Returning IRRs may thus require considerable resources beyond those required for performance of the research. This necessitates decisions on how best to allocate available resources between those needed to perform the research and those needed to ensure the ethical return of research results. With this in mind, we offer the following considerations for assessing the decision to return IRRs, for helping to ensure truly informed consent, and for maximizing any benefits from returning research results:

i) Participation of vulnerable individuals in research is critical to ensure the development of effective treatments for these groups and to better understand and mitigate health disparities.

ii) The decision to offer IRRs to participants raises issues of Beneficence and Justice that go beyond those of simple research participation. This should be accounted for when considering return of results to both vulnerable and nonvulnerable research participants. The principle of Justice requires that a decision to return IRRs benefits members of vulnerable and nonvulnerable populations to a similar degree, and that participation not subject members of vulnerable populations to undue burdens or harms.

iii) Some individuals have intrinsic limitations in their ability to understand the implications, risks, and benefits of returning IRRs. Others may have decisional capacity that is limited by group norms or conditions (social vulnerability). These individuals may not be able to benefit from receiving IRRs. These factors should be considered when deciding whether research results should be returned to any study participant, because these vulnerable individuals bear the full risks of research participation, but do not share equally in the potential benefits, thus violating the Belmont Report principle of Justice.

iv) Providing consent to receive research results involves qualitatively different decisions for a research participant than the initial decision to participate in research. The risks associated with receiving IRRs may be more difficult to assess than are risks of the study itself; weighing these risks may be particularly challenging. Several approaches may be used to address these issues:

a. Informed consent should be conducted in plain language, appropriately supplemented with both educational materials and discussions that include research participants and legally authorized representatives (when appropriate). The informed consent process should be performed in a way that accommodates individuals with cognitive and/or communicative vulnerability and should clearly convey an explanation of the research testing and how it differs from routine clinical testing.
additional testing may be needed to enable clinical use of IRRs, investigators should clearly convey the need and likely cost to participants for this testing and follow-up.

b. The informed consent process should be staged in a manner that clearly separates the decision to receive IRRs from the decision to participate in a research investigation.

c. Consideration of decisional capacity is context dependent and is needed not only when obtaining consent but also when returning IRRs. Where appropriate, formal tools may be used to assess the decisional capacity of those who are cognitively impaired.

d. Research participants should be encouraged to consider, at the time of consent, how they would want their IRRs to be handled if they are subsequently unable to make a competent choice.

v) Institutionally vulnerable individuals are at risk because their lives are controlled by others who may have different priorities than they do. Consent procedures for these individuals must effectively insulate research participation from this external control and must ensure that controlling institutions and their personnel cannot obtain and potentially misuse IRRs.

vi) Medically vulnerable individuals, including those who have serious health conditions for which there are no treatment options, may inadvertently come to believe that the research in which they are participating is intended primarily to treat their disease, rather than to find improved treatments for the disease by studying many individuals. Returning IRRs may reinforce this therapeutic misconception and must be conducted in a manner that reduces the likelihood that this will occur. For example:

a. During the informed consent process and when returning research findings, investigators should ensure that participants understand the limitations of any returned IRRs.

b. When discussing return of IRRs with participants, it may reduce the risks of deferential and medical vulnerability as well as therapeutic misconception if the process is conducted with research team members who are not associated with direct patient care, in a location not associated with patient care (when possible), and without the use of traditional medical attire.

vii) Research teams planning to return IRRs should consider obtaining support and training to ensure that IRRs can be effectively communicated to all participants. In addition, relevant professionals and those from related disciplines should be included on the research team to determine the most appropriate methods for relaying information throughout the study process.

viii) Institutions returning IRRs should consider whether additional information or resources might be provided to help individuals whose economic or social circumstances make them unable to benefit from returning any medically actionable research results.

x) When returning IRRs to any individuals (whether vulnerable or not), investigators should:

a. clearly describe how research testing differs from routine clinical testing.

b. tell the participant if the research results may require additional follow-up (such as testing in a clinical laboratory), and

c. provide such assistance as the participants may desire to ensure that they and their health care providers know how to obtain necessary follow-up care, such as genetic counseling.

In summary, return of IRRs to vulnerable individuals may have considerations that are different from those of the population at large. Although general issues of informed consent in vulnerable individuals have been well explored, ethical issues associated with the effects of returning research results in these populations have not been well described. Additional research is needed to better understand the ethical issues and implications of returning research results to vulnerable research participants. Our recommendations must therefore be regarded as tentative until a more robust basis for guidance is developed.

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