

Disclosure of Research Results from Cancer Genomic Studies: State of the Science

Lynn G. Dressler

Abstract Although the cancer research community has supported a “nondisclosure” position about the return of individual results to research subjects, new technologies, such as genome wide association studies, will reveal clinically relevant findings, some of which cannot be ignored. What recommendations exist that can guide researchers and Institutional Review Boards (IRBs) about this issue? This article summarizes the relevant public documents about the disclosure of individual research results to inform policy development. Four stakeholder groups were selected to make this comparison: federal, professional, advisory, and advocacy groups. Regardless of a group’s position on disclosure, there was consensus that if research results were to be disclosed under any condition, the results must be analytically and clinically validated and that the researcher should not make this decision alone, but in conjunction with the IRB. There was no consensus, however, on the specific determinants for disclosure or what constitutes clinical validity. Although sufficient agreement exists to begin developing general guidelines about the process for disclosure of individual research results, the actual determinants with which to guide this decision remain challenging. An alternate framework that addresses the threshold of uncertainty a stakeholder is willing to accept, the positive predictive value of the research finding, and the magnitude of harm of returning results may be more effective to guide decision making. These assessments, along with what is considered *useful* information, requires the involvement of the research subject community to inform decision-making and move the policy process forward.

Setting the Stage

The recent NIH Policy for GWAS suggests that the researcher and her/his IRB or designated institutional official are expected to devise a plan to address the possibility of revealing clinically relevant information identified through the course of genomic research.^{1,2} This suggestion has moved the controversial issue of disclosure of individual research results to the forefront of cancer research, not only for GWAS but for the entire spectrum of cancer research studies. Currently, many issues remain unclear, including the conditions that warrant disclosure of individual versus aggregate research results, how to handle findings unrelated to the original research, who should make these decisions, and who should be responsible for

communicating findings to the research subject. Researchers and IRBs need guidance to help address these issues and develop responsible, consistent policies to protect the rights and welfare of research subjects, and to engender the public’s trust in the research enterprise. For more than a decade, many professional, federal, advisory, and advocacy groups have presented guidelines or recommendations to address issues of disclosure of individual research results. What can we learn from these efforts? The purpose of this article is to review and comment on results from a systematic analysis of the existing recommendations, present a set of guidelines on the basis of areas of consensus, and identify next steps to facilitate policy development and translation into practice.

Consider the following scenario: An investigator conducting a GWAS in newly diagnosed breast cancer patients uncovers a polymorphism recently reported to be associated with a lethal toxicity to a certain class of drugs. The polymorphism is observed in 5% of the study patients, and the class of drugs is related to current treatments for neutropenia. What should the investigator do with this information? What if the toxicity were not lethal? Is the researcher responsible for communicating these findings to the research subject or the treating clinician? (Table 1).

Author’s Affiliation: University of North Carolina School of Pharmacy, Division of Pharmaceutical Outcomes and Policy, Institute for Pharmacogenomics and Individualized Therapy, Chapel Hill, North Carolina
Received 12/1/08; revised 3/13/09; accepted 4/19/09; published OnlineFirst 6/23/09.

Grant support: This work was funded by a National Institutes of Health/National Human Genome Research Institute (NIH/NHGRI) Training Grant, 1F32HG004200, conducted under the mentorship of Dr. Eric Juengst, Department of Bioethics, Case Western Reserve University, Center for Genetic Ethics, Research and Law. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Lynn G. Dressler, University of North Carolina Eshelman School of Pharmacy 1091 Genetic Medicine Building, 120 Mason Farm Road, CB 7361 Chapel Hill, NC 27599-7361. Phone: 919-966-9480; Fax: 919-966-5863. E-mail: lynn_dressler@unc.edu.

©2009 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-08-3067

¹ NIH Guidance for Developing Data-Sharing Plans for GWAS (2007). Available from: <http://grants.nih.gov/grants/gwas/gwas.data.sharing.plan.pdf>.

² NIH Points to Consider for IRBs and Institutions in their Review of Data Submission Plans for Institutional Certifications under NIH’s Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome Wide Association Studies (GWAS) (2007). p13. Available from: <http://grants.nih.gov/grants/gwas/gwas.ptc.pdf>.

Translational Relevance

With the emergence of newer and cheaper technology to scan an individual's genome, the likelihood increases that clinically relevant research results will be revealed. This, coupled with the recent National Institutes of Health (NIH) genome-wide association studies (GWAS) policy suggesting that researchers and Institutional Review Boards (IRBs) have a plan to manage this occurrence, has moved the controversial issue of return of individual research results to the forefront of cancer research. A key factor in the development of determinants for disclosure is consistent criteria for determining clinical validity and the involvement of the research subject community to assess what constitutes *useful* information to be returned. This article presents the arguments for and against disclosure, reviews the existing recommendations from federal, advisory, professional, and advocacy groups related to disclosure of results, and identifies common themes and remaining challenges for policy development.

The above scenario, although currently rare, is likely to increase in frequency as researchers worldwide generate data and gain access to a growing resource of large specimen banks and linked databases containing genotypic and phenotypic profiles in diseased and healthy populations (e.g., dbGAP, caBIG, PharmGkb).³ Access to this information, coupled with the expansion of efficient and reliable tools at lower costs, such as whole genome sequencing, will offer unparalleled potential to integrate vast amounts of information to understand etiology, progression, and treatment of cancer. Some information revealed in these efforts will have substantial health or clinical value.

Arguments for and against Disclosure

Given the nature of these issues and the involvement of multiple stakeholders (research subjects, advocacy groups, IRBs, clinicians, researchers, funding agencies, the public, etc.) with different and sometimes conflicting interests, it is not surprising to find strong arguments on both sides of the disclosure issue (Table 2). Nor is it surprising to find national guidance lacking.

Traditionally, cancer researchers in the United States have favored release of aggregate but not individual results (1–3). This position has been justified for several reasons. First, researchers seek to protect research subjects from potentially harmful consequences of receiving preliminary or unconfirmed research results, including false reassurances or unnecessary scares.^{4,5} Second, clinician-researchers seek to distinguish and

Table 1. Disclosure questions

- What should a researcher do when s/he uncovers a research finding that may have health implications for the subject and their family?
- What if the finding is unrelated to the research to which the research subject consented?
- What are the responsibilities, if any, of the researcher to communicate this information to the research subject or the treating physician?
- What guidance does the IRB, researcher, or research subject follow to help make these decisions or, at least, plan for these situations?

keep separate the professional role of scientist from the fiduciary role of clinician. Third, federal law restricts the use of information, including research results, in treatment decisions unless the test is done in a CLIA-approved laboratory⁶ (Clinical Laboratory Improvement Amendments). Finally, because the intent of research is to provide generalizable knowledge, not necessarily to benefit an individual research subject, the return of individual research results is contrary to this perspective. It should be noted, however, that return of aggregate results is still an uncommon practice in the United States, even though cancer patients have indicated a desire for this information (4, 5).⁷

There is an evolving ethic, however, especially at the international level, that challenges the traditional nondisclosure argument in the United States and promotes the return of individual research results, specifically in the context of genetic and genomic studies (6). The Council for the International Organization of Medical Sciences (CIOMS) guidelines stipulate that after study completion, subjects will be informed of findings related to their particular health status.⁸ Proponents of this position view research participants as equal partners in the research enterprise and recognize that some research results may have value to the research subject, such as empowerment or proactive lifestyle changing behaviors (7, 8).⁹ Communication of research results can also be viewed as preventing harm, especially “when the research information provides evidence of immediate risk to the individual and there is an intervention available to ameliorate the risk.”⁹ At the same time, disclosure is not supported when doing so would predictably compromise

⁶ CLIA: Clinical Laboratory Improvement Amendments of 1988. Pub. L. No. 100-578 102 Stat.2908. CLIA. approved laboratories are approved for general quality control and quality assurance practices; the approval process does not necessarily extend to review and approval of the performance of individual tests, genetic or otherwise. Available from: <http://www.fda.gov/CDRH/clia/plf100-578.pdf>.

⁷ Most aggregate results are returned to research subjects in the form of a technical article or abstract and usually following the request of the individual or family. Results of NIH funded studies are also now available to the public on PubMed Central. There are efforts afoot by advocacy and some clinical trials groups to develop lay summaries of research studies to be available by internet, newsletter, or regular mail.

⁸ Council for International Organization of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. Available from: http://www.cioms.ch/frame_guidelines.nov.2002.htm.

⁹ National Action Plan on Breast Cancer (1997). Model Consent Forms and Related Information on Tissue Banking and Routine Biopsies With comments by the PRIM & ARENA Tissue Banking Working Group. Letter to Directors/Chairpersons and Members, Institutional Review Boards. Public Responsibility in Medicine and Research. Available from: <http://www.primr.org>.

³ dbGAP, NIH NHGRI “Database of Genotype and Phenotype.” Available at: <http://www.ncbi.nlm.nih.gov/gap/>; caBIG, NIH NCI Cancer Bioinformatics Grid. Available at: <https://cabig.nci.nih.gov/>; PharmGkb, NIH NIGMS Pharmacogenetics and Pharmacogenomics Knowledge Base. Available at: <http://www.nigms.nih.gov/Initiatives/PGRN>.

⁴ OPRR: Human Genetic Research: Issues to Consider (1993). Available from: <http://www.genome.gov/10001752>.

⁵ NBAC. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance - Volume 1 Report and Recommendations of the National Bioethics Advisory Commission (1999). Available from: <http://www.bioethics.gov/reports/past.commissions/nbac.biologica1.pdf>.

Table 2. Arguments for and against disclosure of individual research results**A. Arguments Supporting Disclosure****• Respect for persons**

- i. Self-determination, autonomy
- ii. Consideration of value of research result to research subject

• Beneficence/nonmaleficence

- i. Empowerment/proactive lifestyle changing behavior
- ii. Information should not be withheld when it provides evidence of immediate risk to or significant health information for individual participants
- iii. With-holding information is acceptable if:
 - a. disclosure would predictably compromise the safety of a participant or third party, OR
 - b. disclosure would compromise scientific validity

B. Arguments against Disclosure**• Respect for persons**

- Informed consent: participation under conditions of nondisclosure

• Beneficence/nonmaleficence (maximize benefits, minimize harms)

- i. Research findings must be confirmed, validated, and proven clinically useful, otherwise risk false reassurances or unnecessary scares, doing more harm than good
- ii. In the United States, by law, only CLIA approved laboratories can provide information that will be used in treatment decisions (Clinical Laboratory Improvement Act, 1988).

• Contrary to the intent of research

- i. To create generalizable knowledge, not necessarily to benefit individual research subject

the safety of the research subject or third party (7). Mindful of the limitations and unpredictable nature of research results, there remains growing confidence, especially in the international setting, of the utility of research findings, which are increasing at an exponential pace, and the resulting optimism of their rapid translation into clinical practice. These perspectives fuel arguments in favor of release of individual research results.¹⁰

Between 1990 and 2008, various groups have presented numerous recommendations and guidelines about the disclosure of individual research results. A systematic review of relevant public documents formed the basis for the summary in this article. The review is not meant to include all possible articles, but to be thorough enough to reach saturation of the major issues as described below.

Learning from Existing Recommendations

Positions of professional, federal, regulatory, advisory, and advocacy groups

Professional, federal, regulatory, advisory, and advocacy group positions vary greatly on the issue of disclosure of individual research results, ranging from *never disclose* to

¹⁰ World Health Organization. Genetic Databases: Assessing the benefits and impact on human and patient rights (2003). Available from: <http://www.law.edu.ac.uk/ahrc/files/69.lauriewhoreportgeneticdatabases03.pdf>.

always disclose (Table 3). The National Action Plan on Breast Cancer (NAPBC)⁹, a group composed of breast cancer patient advocates, National Cancer Institute (NCI) representatives, scientists, and others, supports the routine disclosure of genetic research results to participants, whereas both the National Bioethics Advisory Commission (NBAC)⁵ and Office of Human Research Protections (OHRP), formerly Office of Protection of Research Risks (OPPR), only support disclosure of genetic research results in rare circumstances.⁴ NAPBC asserts however, that providing research results that do not meet CLIA and other validity requirements (i.e., analytic and clinical validity) increases risks and may cause “erroneous conclusions to be made that could result in physical, psychosocial or economic harms.”⁹ NBAC and OHRP/OPPR indicate that research data require independent confirmation and a statistically valid study design to associate a research finding with clinical significance. Neither the Common Rule nor the HIPAA Privacy Rule offer guidance about the return of individual research results.¹¹ According to Amdur’s IRB member handbook, there is no ethical requirement to disclose individual research results per se, unless the researcher has indicated such in the informed consent process (7). However, a report by the Department of Energy (DOE)¹² indicates that “the disclosure of individual research results represents the greatest risk to research participants involved in genetic research studies,” citing risks of stigmatization and discrimination beyond health insurance and employment to include life insurance, creditors, and educational institutions.¹² The American Society of Human Genetics (ASHG) (9), National Human Genome Research Institute (NHGRI),¹³ and National Heart Lung and Blood Institute (NHLBI) (10) include more detailed guidance for disclosure, supporting such action only in certain contexts or if the case meets specified criteria (see Table 4).

Despite the range of positions of these groups, there was consensus that if research results are to be disclosed under any circumstances, the results must be analytically and clinically validated. Several other common themes have emerged in both *process* and *conditions* for disclosure of individual research results (Tables 3–5).

Responsible party to determine whether to disclose. Most groups include the IRB with or without the input of the research investigator in the decision-making process about the disclosure of individual research results (Table 3). There was no consensus, however, on how this decision-making process would unfold and who else would need to be involved in making this decision. NBAC, OHRP/OPPR, and NHGRI place the burden on the researcher to indicate the intent to disclose

¹¹ Common Rule. Code of Federal Regulations. Title 45, Part 46. Subpart A. Federal Policy for the protection of human subjects. Federal Register, June 18, 1991. Available at: <http://www.hhs.gov/ohrp/policy/index.html#common>. And HIPAA. Health Insurance Portability and Accountability Act. 2002. Available from: <http://www.hhs.gov/ocr/hipaa> and HIPAA Steering Committee/Research Policy, 2003. Available at: <http://www.unc.edu/hipaa>.

¹² DOE. U.S. Department of Energy Office of Science. Human Subjects Protection Resource Book (2006). Available from: <http://humansubjects.energy.gov/doe-resources/files/HumSubjProtect-ResourceBook.pdf>.

¹³ NHGRI. Health Insurance and Employment Discrimination. Genetic Information and Health Insurance enacted legislation. Issue Update (2001). Available from: <http://www.nhgri.nih.gov/Policy.and.public.affairs/Legislation/01UP.INSjan.html>.

Table 3. Comparison of positions on disclosure

Category	NAPBC, 1999	NBAC, 1999	ASHG, 1996	OPRR, 1993	NHLBI, 2006
Position on disclosure of research results	Yes, except in certain circumstances (see Table 4).	No, except in rare circumstances.	Maybe, depends on study. Respect right to know, and right not to know research results.	No, except when a treatment exists to improve the diagnosis.	Yes, if they meet certain criteria (see Table 4).
Responsible party to decide to disclose	IRB	Researchers and IRB. IRB should require researchers to justify disclosure (or not) and a management plan.	Researchers	Researcher and IRB. Researcher to indicate in consent conditions for disclosure.	IRB and Researcher
Individual to give the results	Genetic counselor or geneticist	Appropriate medical advice or referral should be provided.	Only by persons able to provide genetic counseling	Trained genetic counselor	Genetic counselor, or training and experience in genetic counseling
Pre- and post-test counseling required	Yes	Yes	Yes	Yes	Yes. + referrals for medical and psychological care. Subjects responsible for the cost.
Risks defined in informed consent process/document	Yes. Economic, social, psychological harm. No disclosure of misidentified parentage.	Yes, risks along with clear statement whether research results will be disclosed.	Yes, medical risk, carrier status, risk to offspring; family dynamics, stigmatization, discrimination; psychosocial harm	Yes, psychosocial, familial relationships, potential to compromise insurability or employability	Yes. Psychosocial issues, reproductive implications, uncertainty of disease prediction and severity; insurance and employment discrimination
Oversight	Required. Monitor ongoing clinical relevance.	Required. IRB to develop guidelines for disclosure.	Required. Extend IRB review to those not covered by federal regulations	Suggested. IRBs to address implications of research result disclosure and require investigators to think through these issues.	Required. Standard guidelines should be developed. Education for nongenetic members of research team.

or withhold in the informed consent process. NBAC additionally requires the investigator to justify the intent to disclose in the IRB application.⁵ NBAC, NIH GWAS policy, and NHGRI recommend that the investigator, working with the IRB, have a management plan for the potential occurrence when individual research results would be disclosed.^{2,5,13} The NIH GWAS policy suggests that the IRB have a management plan to address not only return of results generated by the primary investigator but also return of results generated by a secondary investigator who would be responsible to contact the primary investigator with a clinically relevant finding.²

Individual to give the results to the research subject. Nearly every group indicated that a medical professional trained in genetic counseling should give the results (e.g., medical geneticist, genetic counselor, medical professional trained in genetic counseling) (Table 3).

Process for disclosure of results. There was consensus that professional (genetic) counseling prior to and after communicating research results should be provided. The cost of this counseling, however, is still an issue. NHLBI indicated that participants should be responsible for the cost (10), whereas other groups (NAPBC) advocate that this cost should be covered in the research budget.⁹

Informed consent requirements. There was unanimous agreement that if disclosure of individual results were intended or possible, the informed consent process must not

only state this, but also include a description of the risks associated with the disclosure. Most groups acknowledged that such risks should include a description of psychosocial risks⁹ (10) including disruption of family dynamics, possible reproductive implications (9, 11), stigmatization, and economic risks, such as potential to compromise insurability in life and health insurance, or employability by misuse of the disclosed findings. In the context of disease susceptibility studies, both ASHG and NHLBI underscore that factors such as uncertainty of disease prediction and magnitude of severity of disease must be part of the risk discussion. NAPBC and OHRP/OPPR suggest that misidentified parentage not be disclosed.

Oversight of the process for determining disclosure and communicating results. Nearly every group indicated the need for an oversight process to ensure that appropriate decisions are being made in an efficient and ethical manner. NAPBC's oversight process includes maintaining up-to-date information on clinically relevant findings revealed through the course of a study and the validation of such findings by other independent investigators. NBAC seeks to ensure that these findings are assessed by the oversight group and communicated to the research participant when warranted. Similar to the NIH GWAS policy, many of the groups put the onus on the IRB to develop a set of guidelines for when disclosure of results was appropriate and a process or management plan for this inevitable scenario.^{5,13}

Table 4. Specific criteria for disclosing individual research results**I. National Action Plan on Breast Cancer (NAPBC, 1999)**

Access to experimental data except when:

- a. Information is obtained under a promise of confidentiality, is about another person, or would cause harm to another;
- b. Access to information may endanger life or physical safety of participant;
- c. Access would break the masking of the study;
- d. Research results are of unproven clinical validity;
- e. IRB has judged there is no benefit to research subjects

II. National Bioethics Advisory Commission (NBAC, 1999)

Access (to research results) in exceptional circumstances, when all the following apply:

- a. Findings are scientifically valid and confirmed;
- b. Findings have significant implications for subject's health concerns;
- c. A course of action to ameliorate/treat concerns is readily available

III. National Heart Lung and Blood Institute Working Group (NHLBI, 2006)

Must meet all of the following criteria:

- a. Established clinical validity (and the test is done in a CLIA certified laboratory); if test is only available in a research laboratory it should be run by two different methods and under the supervision of a CLIA certified laboratory to confirm results.
- b. Associated risk for the disease is replicable and significant (e.g., RR > 2.0); prioritize variants with greater penetrance or associated with younger age of onset;
- c. Disease has important health implications (e.g., premature death; substantial morbidity)
- d. Proven therapeutic or preventive interventions are available
- e. Research results that affect reproductive decisions or carry reproductive risk should be considered for reporting to subjects

IV. Working Group on Incidental Findings (ref. 11): Net Benefit to Subject**A. Strong Net Benefit: Should Disclose**

- i. Condition or risk of condition is life threatening or grave that can be avoided or ameliorated.
- ii. Reproductive decision-making, to avoid a significant risk to offspring of life-threatening/grave condition or ameliorate a condition likely to be life threatening or grave.

B. Possible Net Benefit: May Disclose

- i. Nonfatal condition likely to be grave or serious, but cannot be ameliorated or avoided, when subject deems information important.
- ii. Reproductive decision-making as in A.

C. Unlikely Net Benefit: Do Not disclose

- i. Condition or risk not likely to be of serious health or reproductive importance or in which the importance cannot be ascertained.

Conditions for Disclosure

Requirement for analytic and clinical validity. All groups agreed that research results should be analytically and clinically validated as conditions for returning research results to research subjects. Even the NAPBC, which supports the routine disclosure of experimental data, is clear in its position that "in the absence of clinical validity there should be no requirement for data to be returned to subjects."⁹ NHGRI echoes the criteria developed by NAPBC (Table 4). Both groups (NAPBC and NHGRI) indicate that IRBs need to judge the data worthy of communication to the research subject. If IRBs have determined, at the time of protocol

submission, that research results will not be returned, the informed consent must explicitly state this.¹³

Requirement for medical intervention. In addition to clinical and scientific validity, NBAC requires that "a course of action is available to ameliorate or treat the health concern".⁵ NBAC's position reflects the current perspective of OHRP/OPPR, NHLBI, and much of the clinical cancer research community that, in addition to clinical validation of the result, an intervention needs to be available to warrant disclosure. This position, common among many professional and regulatory groups, is not shared by some advocacy groups, or ASHG (9), especially in noncancer related contexts (e.g., Huntington's Disease, Alzheimer's disease), which support a *right to know* regardless of the availability of an intervention.

Consideration of relative risk and gene penetrance for genetic results. The NHLBI (10), focusing specifically on the release of genetic research results, includes parameters such as relative risk of the research result to predict the condition or outcome (i.e., RR > 2.0) and prioritizing gene associations with high penetrance or early age of onset in the determination for disclosure (Table 4).

Consideration of reproductive factors. Several groups (9, 10, 11) include reproductive decisions as a factor in determining disclosure of results, citing family planning and risk to existing offspring as important issues to consider (Table 4).

Net benefit to research subject. Recently, the Working Group on Incidental Findings¹⁴ developed a classification system for handling incidental findings discovered in the process of research (11). They assign rankings to the findings on the basis of expected net benefit to the research subject: strong, possible, or unlikely net benefit. Each category of benefit considers whether the finding confers a life threatening or grave condition, the degree to which the risk can be ameliorated or avoided, and the implications for reproduction (Table 4).

Table 5. Common themes**A. Process of Disclosure**

- The IRB, the researcher, and other appropriate experts are responsible to make the determination about disclosure.
- Research subjects need to be given an opportunity to decide whether they want to receive the research results.
- Informed consent process and document should indicate if disclosure is planned or likely and describe the risks associated with disclosure.
- Only professionals capable of providing genetic counseling should give genetic or genomic research results.
- Counseling of patients before and after receiving research result is required.
- Oversight of the disclosure process is required.

B. Conditions for Disclosure

- Requirement for analytical and clinical validity.
- Only results from CLIA approved laboratories can be disclosed.
- Existence of proven medical intervention*.
- Consideration of positive predictive value and relative risk.
- Consideration of reproduction factors.
- Consideration of net benefit to research subject.

*This condition was not required by ASHG and some advocacy groups, especially in regards to noncancer diagnosis such as Huntington's Disease, Alzheimer's Disease.

Common Themes, Remaining Challenges, and Next Steps for Policy Development

This analysis revealed several common themes and areas of consensus, most predominantly related to *process* issues (Table 5). These areas of agreement can be used today to move the policy process forward (Table 6). They include having the researcher justify in the IRB protocol his or her rationale for disclosing or withholding results; having not the researcher, but a professional trained in genetics and genetic counseling communicate results to the research subject; giving the research subject the opportunity to accept or refuse the opportunity to have research results returned; and in collaboration with the IRB, researchers, and other experts, having a management plan to address the scenario when a clinically relevant finding is discovered of what to do.

Although attaining agreement to process issues is a good first step, many challenges remain. The first main issue is that these areas of agreement do not yet translate into practical guides for decision making. It may be unrealistic to task an already overburdened IRB to develop decision-making criteria about what constitutes analytically and clinically valid research findings and a management plan to communicate results to research subjects. Kohane and colleagues proposed a model, the Informed Cohort Oversight Board (ICOB), to address this issue (12). The ICOB has an oversight, decision-making, and implementation role, combining features of a clinical Data Safety Monitoring Board (DSMB) with an infrastructure to implement decisions, including tracking and counseling research subjects. The ICOB, composed of a multidisciplinary team of geneticists, genetic counselors, ethicists, statisticians, patients, and communication experts, would identify what information is worthy of being communicated and how best to communicate it to a research subject (12). A research ethics consultation service (RECS) may also take on a similar role (13).¹⁵ The RECS or ICOB could partner with the IRB to ensure that decisions and plans for communication are ethical and comply with applicable regulations.

This review illustrates that clinical validity and clinical utility heavily influence the decision to return or withhold individual research results. However, we are faced with a conundrum; no consistent criteria exist for determining when the threshold for clinical validity or utility has been met. According to the Centers for Disease Control and Prevention (CDC), clinical validity refers to the ability of the research assay to predict the associated phenotype, condition, or response to therapy.¹⁶ However, disciplines, groups, and individuals vary in how they determine clinical validity, rendering the possibility of developing consistent criteria questionable. But what if we framed the issue in another way (14) and asked the following question: *Under what conditions would it be acceptable to violate the current nondisclosure practice in the United States?* Answering this

question would require addressing the threshold of uncertainty the different stakeholders (patients, subjects, clinicians, researchers, IRBs, funding agencies) are willing to accept, the degree to which the research findings' predictive value are substantiated, and the magnitude of harm that would result if the prediction is wrong. Addressing these three components may more effectively inform decision making, especially if research subjects are included in the process.

Some may contend that clinical relevance should not be the driving force in decisions about return of individual research results (15) and may not reflect the position of the cancer patient or research subject. This brings us to the second main challenge: the recommendations in this review do not reflect a systematic analysis of the cancer patient's or research subject's perspective. Few studies analyze the concerns, expectations, and positions of cancer patients on the topic of return of individual research results and even fewer relate to cancer genomic data (16). Although the NAPBC involved breast cancer patient advocates, it is important to understand the position of research subjects who may not be patient advocates and who are participating in current cancer genomic studies. In the United States today, neither aggregate nor individual results are returned (1, 17). Do research subjects expect the return of research results that are clinically or health related? Research subjects may want to receive this information regardless of the existence of a medical intervention—for making lifestyle changes or for joining a registry. Research subjects may also consider themselves not just patients, but partners in the research process. As research partners, individuals may consider return of results as a form of benefit-sharing or reciprocity not hinging on relevance to health. Is the clinical perspective reflected in the majority of groups reviewed in this study considered appropriate or overly paternalistic? A need exists for empirical studies to address these and other questions to understand research subjects' perspectives and to consider their positions in the conduct of cancer genomic research and development of research policy.

As more cancer researchers probe the genome with better tools (e.g., DNA sequencing), they will more rapidly identify and validate clinically relevant information, resulting in a protracted timeframe for translating clinically useful research information into clinical practice. Our efforts will uncover unexpected findings, some of which cannot be ignored. As the larger amounts of information we amass about individuals become accessible to clinicians and researchers, the line will further blur between whether that information is considered a research result or clinical information. In this setting, research is likely to benefit not only the public, but also the individual research subject, challenging the current philosophy about the purpose of research.

The return of individual research results would require robust infrastructure, including expert personnel, funding, and informatics to appropriately communicate and counsel research subjects, as well as to track their whereabouts. This type of effort would likely not be feasible for an individual investigator and would instead require a centralized mechanism with appropriate

¹⁴ "An IF is a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This means that IFs may be on variables not directly under study and may not be anticipated in the research protocol" (see ref. 11, p. 219).

¹⁶ CDC. Office of Public Health Genomics. Evaluation of Genetic Testing. ACCE: A CDC-Sponsored Project Carried out by the Foundation of Blood Research. Available at: <http://www.cdc.gov/genomics/gTesting/ACCE.htm>.

¹⁵ A research ethics consultation service, analogous in some ways to a clinical ethics consult, offer researchers and IRBs help in analyzing ethical issues in the context of research. Some services will provide potential solutions or ethically acceptable options for the researcher and IRB to consider to address the issue. The recent development of research ethics consultation services have been supported through NIH funded Centers of Translational Science Awards (CTSA) and NHGRI funded Centers of Excellence in Ethical, Legal, Social Implications of Genetic Research (CEERS).

Table 6. Recommendations for policy development

1. IRBs and/or research ethics consultation services should develop guidelines for researchers to assess the likelihood that the study will reveal clinically relevant information and develop policies to guide how these findings should be managed (i.e., whether they should be communicated to the research participant and/or the treating physician).
2. As part of IRB and grant applications, researchers should assess the likelihood that clinically relevant research results, including incidental findings, would be revealed in the study and develop a plan, in collaboration with the IRB, to determine how the findings should be managed.
3. The researcher should indicate and justify in the informed consent process and document whether or not individual research or incidental findings will be disclosed to the participant and their family.
4. The researcher should plan for the release of aggregate data, in the form of plain language summaries, describing in general terms the findings of the study and not rely on the technical manuscript as the means of communication of aggregate results.
5. If individual research results or incidental findings are to be disclosed to the participant, all of the following should apply:
 - a. The researcher should interact with his/her IRB to determine a management and coordination plan for review, validation, and return of findings.
 - b. The findings must be determined to be analytically and clinically valid and be confirmed in a CLIA approved laboratory or under the supervision of a CLIA approved laboratory.
 - c. The findings must be reviewed by an oversight or DSMB-like committee and deemed appropriate for communication to the research participant.
 - d. The participant be given the opportunity to know or not know the findings.
 - e. The individual communicating the results must be a medical professional with training in genetic counseling.

oversight and measures to ensure sustainability. At the very least, we should be developing ways to communicate aggregate results to patients and research subjects who want this information (1, 17).

The next step in developing guidance for decision making in the disclosure of individual cancer genetic and genomic research results requires a deliberative process of consensus-

building that involves all key stakeholders and is informed by appropriate empirical studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Partridge AH, Winer EP. Informing clinical trial participants about study results. *JAMA* 2002;288:363–5. PubMed doi:10.1001/jama.288.3.363.
2. Rigby H, Fernandez CV. Providing research results to study participants: support versus practice of researchers presenting at the American Society of Hematology annual meeting. *Blood* 2005;106:1199–202. PubMed doi:10.1182/blood-2005-02-0556.
3. Partridge AH, Hackett N, Blood E, et al. Oncology physician and nurse practices and attitudes regarding offering clinical trial results to study participants. *J Natl Cancer Inst* 2004;96:629–32. PubMed.
4. Partridge AH, Burstein HJ, Gelman RS, Marcom PK, Winer EP. Do patients participating in clinical trials want to know study results? *J Natl Cancer Inst* 2003;95:491–2. PubMed.
5. Partridge AH, Wong JS, Knudsen K, et al. Offering participants results of a clinical trial: sharing results of a negative study. *Lancet* 2005;365:963–4. PubMed doi:10.1016/S0140-6736(05)71085-0.
6. Knoppers BM, Joly Y, Simard J, Durocher F. The emergence of an ethical duty to disclose genetic research results: international perspectives. *Eur J Hum Genet* 2006;14:1170–8. PubMed doi:10.1038/sj.ejhg.5201690.
7. Amdur RJ. Institutional review board member handbook. Boston: Jones and Bartlett Publishers, Inc.; 2002.
8. Ravitsky V, Wilfond BS. Disclosing individual genetic results to research participants. *Am J Bioeth* 2006;6:8–17. PubMed.
9. American Society of Human Genetics (ASHG). Statement on informed consent for genetic research. The American Society of Human Genetics. *Am J Hum Genet* 1996;59:471–4. PubMed.
10. Bookman EB, Langehorne AA, Eckfeldt JH, et al. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am J Med Genet A* 2006;140:1033–40. PubMed.
11. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med Ethics* 2008;36:219–48, 1.
12. Kohane IS, Mandl KD, Taylor PL, Holm IA, Nigrin DJ, Kunkel LM. Medicine. Reestablishing the researcher-patient compact. *Science* 2007;316:836–7. PubMed doi:10.1126/science.1135489.
13. Cho MK, Tobin SL, Greely HT, McCormick J, Boyce A, Magnus D. Strangers at the bedside: research ethics consultation. *Am J Bioeth* 2008;8:4–13. PubMed.
14. Gert B. Common morality: deciding what to do. New York: Oxford University Press; 2004. p. 74.
15. Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. *N Engl J Med* 2003;348:1383–6. PubMed doi:10.1056/NEJMs030228.
16. Shalowitz DI, Miller FG. Disclosing individual results of clinical research: implications of respect for participants. *JAMA* 2005;294:737–40. PubMed doi:10.1001/jama.294.6.737.
17. Partridge AH, Winer EP. Sharing study results with trial participants: time for action. *J Clin Oncol* 2009;27:838–9. PubMed doi:10.1200/JCO.2008.20.0865.

Clinical Cancer Research

Disclosure of Research Results from Cancer Genomic Studies: State of the Science

Lynn G. Dressler

Clin Cancer Res 2009;15:4270-4276.

Updated version Access the most recent version of this article at:
<http://clincancerres.aacrjournals.org/content/15/13/4270>

Cited articles This article cites 15 articles, 3 of which you can access for free at:
<http://clincancerres.aacrjournals.org/content/15/13/4270.full#ref-list-1>

Citing articles This article has been cited by 7 HighWire-hosted articles. Access the articles at:
<http://clincancerres.aacrjournals.org/content/15/13/4270.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://clincancerres.aacrjournals.org/content/15/13/4270>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.