Empirical Analysis of Current Approaches to Incidental Findings

Frances Lawrenz and Suzanne Sobotka

Researchers in the health sciences regularly discover information of potential health importance unrelated to their object of study in the course of their research. However, there appears to be little guidance available on what researchers should do with this information, known in the scientific literature as incidental findings (IFs). The study described here was designed to determine the extent of guidance available to researchers from public sources. This empirical study was part of a larger two-year project funded by the National Human Genome Research Institute (NHGRI) to generate guidance on how incidental findings should be managed in human subjects research, especially genetics, genomics, and imaging research. We generated empirical analysis of publicly available guidance and consent forms to help guide a multidisciplinary Working Group of experts in their formulation of normative recommendations reported in this symposium.[1]

Specifically, we set out to determine what information was publicly available through the Internet, focusing the search on research in genetics and genomics, neuroimaging, and computed tomography (CT) colonography. This paper highlights important findings; a more detailed account will be published elsewhere.[2] Results showed that there is very little public guidance available for researchers as to how to deal with incidental findings, and that the available guidance is not consistent.

Methods

We searched sources on the Internet for documents that might provide guidance on how researchers should deal with IFs. Because the researchers did not collect data from human subjects, the data collection and analysis process for this paper were approved as an exempted study by the University of Minnesota Institutional Review Board (IRB). We searched four different sources using key words designed to help locate any documents related to incidental findings. The four sources were the following: the Web sites of 14 key federal authorities that conduct health research; 22 professional societies germane to the areas of research on which we focused; the 100 top National Institutes of Health (NIH) funded universi-

Frances Lawrenz, Ph.D., *is the Associate Vice President for Research at the University of Minnesota and Wallace Professor of Teaching and Learning in Educational Psychology. Her specialty is research methodology and program evaluation.*
Suzanne Sobotka, M.P.H., *is a candidate for a Master of Arts degree in Health Journalism at the University of Minnesota and has served as a Research Assistant for the University's Consortium on Law and Values in Health, Environment & the Life Sciences.*

ties for guidance documents; and the Internet itself. The federal authorities are listed in Table I. These were the authorities regarded by the project's Working Group as those most involved in health research; these Web sites were searched from October to November 2006. The professional societies we searched, listed in Table II, were determined through consensus of expert opinion on the societies most likely to have information related to the research areas of interest; these were searched in July 2006. We elicited expert opinion by an e-mail survey of relevant experts from the project's Working Group and outside experts in each of the four research domains of interest. The universities searched were the top100 university-affiliated institutions in terms of receipt of NIH grant dollars in fiscal year 2004, as identified on the NIH web site; these were searched in October and November 2006.[3] Finally, the Internet Google search was to locate any English-language consent forms in the U.S. that had been posted for public viewing; that search was conducted in November and December 2005. To locate documents on the Internet, we used the search terms "consent form" and "consent to participate" in combination with "MRI," "magnetic resonance imaging," "fMRI," "genetics," "family genetics," "genomics," and "CT colonography."

All located documents were printed, dated, and categorized by type. The documents collected included a variety of different types: consent form templates (forms that investigators fill in to create a consent form for their study), model consent forms (actual consent forms posted as examples for investigators to follow), guidebooks or manuals, guidelines (portions of Web sites with quick information), assent forms and templates, and adverse event forms. We then performed content analysis on a sample of the university documents and all of the collected documents from the federal authorities, professional societies, and universities, coding the information in each. The coding categories were defined with the help of the Working Group. Inter-rater reliability agreement between the two coders and intra-rater reliability agreement were .95 or above.

The coding captured information about the type of research, information on how the research results would be handled, and information on how the incidental findings would be handled. We noted document type, study type, study population, research team, samples taken, whether the document discussed sharing research results and/or incidental findings, whether the data collected was of diagnostic or research quality, and whether use of the data in future studies was addressed. We specifically coded a number of variables relating to the document's discussion of IFs, including: whether the document defined IFs in a broad or specific reference, whether the document gave research participants the choice to learn of IFs, whether the document provided for researcher consultation with an expert on potential IFs, and whether the document addressed

Table I

Web Sites of Federal Authorities Searched for Research Guidance Documents

Centers for Disease Control and Prevention (CDC)*
Food and Drug Administration (FDA)*
National Institutes of Health (NIH)*
Department of Health and Human Services (DHHS)*
Department of Vetrans Affairs (VA)*
Office of Human Research Protection (OHRP)*
Department of Defense (DOD)*
Department of Education (DOE)*
Department of Agriculture (USDA)
Department of Transportation (DOT)*
Department of Energy (DOE)*
Environmental Protection Agency (EPA)
U.S. Agency for International Development (USAID)*
Department of Housing and Urban Development (HUD)
Consumer Product Safety Commission (CPSC)*
Central Intelligence Agency (CIA)
National Aeronautics and Space Administration (NASA)*
National Science Foundation (NSF)*
Social Security Administration (SSA)

**We were able to locate documents from these web sites using our search protocol. Web sites without an asterisk were searched, but we did not obtain any documents using our search terms.*

Results showed that there is very little public guidance available for researchers as to how to deal with incidental findings, and that the available guidance is not consistent.

disclosure of IFs and to whom. We also examined variables related to the document's discussion of returning research results to research participants, including: whether the document defined research results in a broad or specific reference, whether the document gave research participants the choice to learn research results, whether the document provided for disclosure of research results and to whom, and whether the document referenced incidental findings.

In addition to coding the types of information contained on the forms, we performed more inductive analyses on those documents containing references to incidental findings. These analyses allowed more detailed examination of the document's approach to IFs.

Results

The number of documents located from each of the four sources is presented in Table III. Of the 798 documents retrieved from the Websites of the top 100 university-affili-

Table II

Professional Society Web Sites Searched for Research Guidance Documents

General Societies
American College of Physicians and Surgeons
American Medical Association
National Medical Association

Neuroimaging Societies
Cognitive Neuroscience Society
International Brain Research Organization
International Consortium for Brain Mapping
Society for Neuroscience
American Academy of Neurology

CT Colonography Societies
American Roentgen Ray Society
Radiological Society of North America
Society of Gastrointestinal Radiologists
American Gastroenterological Association
American College of Gastroenterology

Genetics and Genomics Societies
American Board of Genetic Counseling
American College of Medical Genetics
American Society of Human Genetics
Association of Professors of Human and Medical Genetics
European Society of Human Genetics
Genetics Society of America
International Federation of Human Genetics Societies
Microarray Gene Expression Data Society

Table III

Number of Documents Located and Coded, and Type of Documents

	Federal Agencies	Professional Societies	Universities*	Consent Forms from Web
# of Documents Collected	154	16	798	55
% of Documents Coded	100%	100%	36.7% (including all templates)	100%
% of Coded Documents Addressing IFs	9%	25%	11%	37%
% of General Guidance Docs	95.4%	50%	91.8%	n/a
% of Genetic / Genomic Docs	4.6%	25%	3.8%	54.5%
% of Neuroimaging Docs	0%	6.3%	1.0%	45.5%
% of CT Colonography Docs	0%	18.8%	0%	0%

**The bottom four rows of the Universities column do not add up to 100% because 3.4% of the university documents were designed as model consent forms, consent form templates, or guidance documents for drug trials that could not be classified specifically as genetic/genomic, neuroimaging, or CT colonography.*

ated institutions in terms of NIH grant dollars received, all of the consent form templates (193 documents) and 100 randomly sampled additional documents were coded for a total of 293 documents. The coding process consisted of separate readings of each document noting the characteristics of each document and whether or not the form addressed research results or incidental findings disclosed, and recording the characteristics in a database for analysis. Table IV presents a list of the terms used to describe incidental findings in those documents and their frequency.

Table V shows the number of federal documents that specified a procedure to deal with incidental findings and the number that provided instructions about disclosure.

Below are two examples of statements from the federal documents, chosen to illustrate statements on IFs that we found in those documents:

> IRBs should ensure that investigators adequately deal with how they will handle incidental findings; that is, what will be done with genetic information that is learned during the course of the study that does not directly relate to the research.... Prospective subjects should be informed during the consent process that the discovery of such information is possible.[4]

> Incidental findings are apparent medical abnormalities that may have clinical implications and are observed in the course of research studies but are unrelated to the topic under study.... At this point, OER [Office of Extramural Research] suggests that investigators who propose studies that may result in incidental findings describe their plans for addressing incidental findings...as follows:
>
> 1. how observed incidental findings will be handled by research staff, and
> 2. how plans for handling incidental findings will be presented to potential participants during the informed consent process.[5]

Table IV

Terms Used to Describe Incidental Findings in University Documents Coded

Term	Frequency
Misattributed parentage or lineage, non-relation, non-paternity	18
Abnormalities ("medical abnormality," "brain abnormality," "unintended abnormal finding," "defect already in your brain")	13
"Incidental finding(s)"	10
"Information unrelated to the study"	8 (all forms from the same institution)
"Information that is unknown about your health"	7
"Unanticipated problems," "unexpected problems," "unanticipated medical events," "unforeseen medical problems"	5
"Findings with significant implications"	2
Cancer (not variable under study)	2
"Adventitious findings"	1
Positive HIV-test result (not the variable under study)	1
"Important discoveries"	1
"Untoward medical occurrence"	1
"Risks surrounding research"	1

Table V

Number of Federal Documents that Addressed Management of IFs and Their Disclosure

Procedure Specified in Document to Manage IFs	# of Documents Addressing IFs (N=12)*
Instructions to investigators to address IFs	8
IFs should not be disclosed to anyone	4
IFs should be disclosed to: -participant	2

** The numbers in the second column do not add up to 12 because the categories are not mutually exclusive.*

Table VI shows the number of professional society documents that specified a procedure to deal with incidental findings and the number that provided instructions about disclosure.

Below is a statement found in the professional society documents, to illustrate the few statements on IFs found in those documents:

> They [participants] should be informed of what information may reasonably be expected

Table VI

Number of Professional Society Documents that Addressed Management of IFs and Their Disclosure

Procedure Specified in Document to Manage IF	# of Documents Addressing IFs (N=4)
Instructions to investigators to address IFs	3
IFs should not be disclosed to: -participant's guardian	1

Table VII

Number of University Documents Addressing Management of IFs and Their Disclosure

Procedure Specified in Document to Manage IFs	# of Documents Addressing Ifs (N=32)*
General Instructions to investigators to address IFs	9
IFs should not be disclosed to anyone	12
Researchers will consult an expert on potential IFs before disclosing	2
IFs should be disclosed to:	
-participant	8
-primary care physician	1
-specialist physician	2
Patricipants have an option to learn/not learn IFs	2

** Note that the numbers in the Table add to over 32 because some documents had more than one of the characteristics listed.*

Table VIII

Number of Web-Posted Consent Forms Addressing Management of IFs and Their Disclosure

Procedure Specified in Document to Manage IFs	# of Documents Addressing IFs (N=20)*
Researchers will consult an expert on potential IFs before disclosing	3
IFs should be disclosed to:	
-participant	12
-participant's guardian	2
-primary care physician	6
-specialist physician	3
Patricipants have an option to learn/not learn IFs	3
IFs should not be disclosed to anyone	6

** Note that the numbers in the table add to over 20 because some documents had more than one characteristic listed.*

> to result from the genetic study. Importantly, subjects should also understand that unexpected findings, including identification of medical risk, carrier status, or risk to offspring affected by genetic disease, may arise.[6]

Table VII shows the number of university documents that were reviewed to categorize their characteristics that specified a procedure to deal with incidental findings and the number that provided instructions about disclosure. Thirty-two of the 293 coded documents mentioned incidental findings.

Below are two statements found in the university documents, to illustrate statements on IFs found in those documents:

> Include an adventitious findings clause if an MRI is being performed or if other diagnostics are being used. Notify subjects that proper referral or counseling may be provided as necessary.[7]

> If findings of any kind (e.g., results of genetic studies, clinically relevant information, or incidental findings) are to be disclosed to the participant, describe the disclosure procedures (e.g., who will make the disclosure, and whether genetic counseling is advisable and/or available). Discuss whether subjects will be informed if the experimental results prove to have clinical relevance in the future.[8]

Table VIII shows the number of Web-posted consent forms that specified a procedure to deal with incidental findings and the number that provided instructions about disclosure. Twenty of the 55 coded documents mentioned incidental findings. Of

Table IX

Percentage of Coded Documents from All Four Sources Addressing How to Deal with Future Research and Incidental Findings

	FEDERAL AGENCIES	PROFESSIONAL SOCIETIES	UNIVERSITIES	CONSENT FORMS FROM WEB
% of Documents Addressing Future Data Use	10.4%	25%	19.8%	41.8%
% of Documents Stating Archived Data Will Be Used (to Study Variables Listed in Consent Form) by:				
Investigators	9.1%	25%	19.1%	36.4%
Other Researchers	7.1%	18.8%	9.2%	16.4%
% of Documents Stating Archived Data Will Be Used (to Study Variable Not Listed in the Consent Form) by:				
Investigators	5.8%	18.8%	16.7%	32.7%
Other Researchers	3.9%	18.8%	8.2%	16.4%
% of Forms That Specify the Investigator Will Recontact the Subject If an IF Is Found in Reanalysis	2.6%	0%	1.7%	3.6%

the 30 genetic/genomic forms, 12 (36.4%) addressed incidental findings in some way. Of the 25 neuroimaging forms, 9 (36%) addressed incidental findings. We did not locate any Web-posted CT colonography research consent forms; experts we consulted suggested that this may be because the field of research is growing rapidly and competitively, so that investigators may hesitate to make their consent forms public.

Below is a statement from the Web-posted consent forms, to illustrate statements addressing IFs in those forms:

> On occasion, the investigator may notice a finding on a MRI scan that seems abnormal. When this occurs, a neuroradiologist will be consulted as to whether the finding merits further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding.... The investigators, the consulting neuroradiologist, and [name of university] are not responsible for any examination or treatment you undertake based upon these findings.[9]

Table IX shows the percentage of coded documents from each of the four sources that address use of data in future studies. Future studies may include re-analysis by the original investigator or re-analysis by an investigator not affiliated with the original study.

Conclusions

Based on our analysis, we reached the following conclusions.

- Very few documents address IFs (Federal 9%; Professional Societies 25%; Universities 11%; Web-based Consent Forms 37%).
- Terms used to describe IFs are not consistent across documents.
- Although few documents address disclosure, more recommend disclosing individual IFs than recommend disclosing individual research results (Federal 8% IF vs. 6% research results; Professional Societies 19% vs. 12%; Universities 9% vs. 10%; Web-based Consent Forms 25% vs. 13%).

- Very few say to not disclose IFs (Federal 1%; Professional Societies 0%; Universities 4%; Web-based Consent Forms 11%).
- Very few documents recommend checking with a clinical consultant to evaluate whether an IF of concern appears present before disclosing it (Federal 0%; Professional Societies 0%; Universities 1%; Web-based Consent Forms 5%).
- Although some documents address future studies, very few recommend re-contacting the participant if IFs are found in future (Federal: 10% address future studies and 3% recommend recontact; Professional Societies: 25% and 0%; Universities: 20% and 2%; Web-based Consent Forms: 42% and 4%).

In summary, this study showed that there is very little public guidance available for researchers as to how to deal with incidental findings. In addition, the guidance available is not consistent.

Acknowledgement

This publication was made possible by National Human Genome Research Institute (NHGRI) grant # R01 HG003178 (S. M. Wolf, Primary Investigator; J. P. Kahn, F. Lawrenz, C. A. Nelson, Co-Investigators). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NHGRI.

References

1. S. M. Wolf, F. Lawrenz, and C. A. Nelson et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248.
2. S. M. Wolf, S. P. Sobotka, and F. Lawrenz, "Managing Incidental Findings in Human Subjects Research: Empirical Findings," manuscript in progress.
3. National Institutes of Health, *NIH Awards to All Institutions by Rank, FY 2004*, 2005, *available at* <http://grants.nih.gov/grants/award/trends/rnk04all1to500.htm> (last visited February 11, 2008). Note that the list also includes corporations that receive grants from NIH. We excluded those institutions, along with any institution whose web site was not in English.
4. Department of Veterans Affairs, *IRB Guidebook* 2005, *available at* <www1.va.gov/oro/apps/compendium/Files/IRB%20Guidebook%20CH5.htm> (last visited February 11, 2008).
5. National Institutes of Health Office of Extramural Research, *Frequently Asked Questions from Applicants* (May 11, 2006), *available at* <http://grants2.nih.gov/grants/policy/hs/faqs_aps_hsp.htm> (last visited February 11, 2008).
6. American Society for Human Genetics, *ASHG Report: Statement on Informed Consent for Genetic Research*, 1996, *available at* <http://www.ashg.org/genetics/ashg/pubs/policy/pol-25.htm> (last visited February 11, 2008).
7. University of Wisconsin-Madison, *Consent Form Template and Tips*, 2004, *available at* <http://info.gradsch.wisc.edu/research/compliance/humansubjects/hsirbs/forms/consentformdoc> (last visited October 18, 2005; copy on file with author).
8. Oregon Health Sciences University, *IRB Policy/Procedure Manual*, 2002, *available at* <www.ohsu.edu/research/rda/irb/docs/policies/irbpolicy2002.pdf> (last visited October 25, 2005; copy on file with author).
9. Stanford University, *Consent Form for Adult Brain Function Imaging with MR, (1.5T and 3.0T)* 2002, *available at* <rsl.stanford.edu/sawyer/pdf_files/Consent_15T3TAdult_fMRI.pdf> (last visited February 11, 2008).