Informed Consent for Genetic Research Involving Pleiotropic Genes: An Empirical Study of ApoE Research

by Zachary N. Cooper, Robert M. Nelson, and Lainie F. Ross

In the traditional understanding of the ethical, legal, and social implications of genetic testing is based on the premise that a particular gene generates information about a single trait or condition. Pleiotropy refers to the ability of a single gene to influence multiple traits or conditions. Increasing genetic knowledge suggests that pleiotropy may be more common than previously believed. While some of the ethical issues that are raised by pleiotropy in the clinical setting have been explored, the ethical issues raised by pleiotropy in the research setting have not been investigated. Specifically, how to address pleiotropy in the consent form and informed consent process has not been studied empirically.

There are three distinct ways that pleiotropy may be important to informed consent in the research context. First, the pleiotropic nature of the genes under study may already be known. Second, a gene known to be related to one particular trait subsequently may be found to be pleiotropic. Third, genes may be discovered by researchers studying disparate conditions which are then determined to be the same gene. In all three cases, the pleiotropic potential of the gene under study poses at least theoretical risks to the participants who may not have considered the full implications of the research findings in which they are enrolled.

Apolipoprotein E (ApoE) serves as a paradigm for the situation in which the pleiotropic nature of the gene is known. The ApoE gene has three common alleles: epsilon 2, 3 and 4. The ApoE epsilon 4 allele is associated with a variety of conditions including Alzheimer's disease (AD), coronary artery disease (CAD), hyperlipidemia, and the severity of neurological sequelae following head trauma. Individuals with two copies of the ApoE epsilon 4 alleles are at greater risk for these conditions than are individuals with one or no copies, although having one or two ApoE epsilon 4 alleles is neither necessary nor sufficient to predict disease.

Having one or two copies of the ApoE epsilon 4 allele is not fully predictive of disease and is only associated with an increased susceptibility. The clinical utility of ApoE testing in the neurology and cardiology clinic is therefore widely contested. A variety of professional groups have concluded that ApoE testing is not an advisable clinical
Table 1. Research Topics of the Qualifying Articles*

<table>
<thead>
<tr>
<th>Research Topics</th>
<th># (%) of Articles n=149</th>
<th># (%) of Articles from Respondents n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Disease</td>
<td>93 (62)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>General Neurological Conditions/Diseases (Impact of Head Trauma, Memory &amp;</td>
<td>49 (33)</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Cognition, Stroke, Non AD Dementia, Parkinson's Disease, Palsy and Seizures)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological Cadaver Studies</td>
<td>14 (9)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Cardiovascular Disease and Related Conditions (Cardiovascular Disease,</td>
<td>11 (7)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Hyperlipidemia and Hypertension)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune Diseases (Multiple Sclerosis, Diabetes and Lupus)</td>
<td>5 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Other (Pharmacogenetics, aging/mortality, Down syndrome, transplantation, and</td>
<td>17 (11)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>psychological conditions)</td>
<td></td>
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</table>

* The number of topics adds up to more than 100% because the articles often addressed more than one topic.

Test for predicting AD in asymptomatic individuals, although there is some support for using ApoE testing as a confirmatory tool for AD. ApoE testing is also not recommended as a clinical marker in the cardiology clinic because there are better predictive markers for CAD. Despite its lack of clinical utility for individual patients, genetic studies of ApoE may generate valid population predictions, and determining the number of ApoE epsilon 4 alleles is a common feature of both CAD and AD research. Research on ApoE is valuable to understand 1) genotype-phenotype correlation; 2) how genotype is related to the underlying pathophysiology of disease; and 3) the interrelationship between CAD and AD.

Pediatric researchers are also interested in ApoE. They study ApoE and its relationship to neurocognitive development, cholesterol levels and other cardiovascular risks. Other associations in the pediatric literature relate to ApoE polymorphisms and the clinical course of childhood nephrotic syndrome or head trauma. The diversity of clinical correlations makes it more difficult for participants to provide an informed consent.

In this project, we examined whether researchers investigating ApoE were discussing pleiotropy with potential research participants and their families. We analyzed what was described and discussed in the consent forms as a proxy for what would be included in the consent process. We hypothesized that researchers would not discuss pleiotropy in their consent forms. We discuss the implications that omitting pleiotropy may have on the subject's ability to give an informed and voluntary consent.

Methods

We conducted an Ovid Medline search for articles related to ApoE and published between January 1, 2001 and December 31, 2003. We cross-tabulated ApoE and apolipoprotein E with hyperlipidemia, stroke, cerebrovascular accident, multiple sclerosis, CAD, AD, head trauma, and craniocerebral trauma. We repeated the search for January 1, 1999 through December 31, 2000, but limited the studies to those that might involve children (search cross-tabulated with key words: child, pediatric, infant, newborn or adolescent) to increase the number of ApoE studies that involve children in our study sample.

Seven hundred and seventy-nine articles met our search criteria. We then reviewed the abstracts and excluded articles if they did not include original data, did not take place at United States institutions, were animal studies, or were case reports (defined as fewer than seven subjects). Only U.S. research was included in the study to avoid confusion over differing ethical research standards abroad.

Articles that met the eligibility criteria were reviewed to determine the objectives of each study and the

Table 2. Subjects in Qualifying Articles*

<table>
<thead>
<tr>
<th>Research Article Demographics</th>
<th># (%) of Studies n=149</th>
<th># (%) of Studies From Respondents n=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults Only</td>
<td>122 (82)</td>
<td>38 (88)</td>
</tr>
<tr>
<td>Cadaver Studies</td>
<td>19 (13)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Extended families (unclear ages)</td>
<td>8 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Extended families (adults only)</td>
<td>5 (3)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Children and Adults</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* Some articles involved more than one demographic sample; therefore responses add up to more than 100%.
subject demographics. The corresponding authors were asked to complete a 16-question survey (see Appendix 1) via fax, mail, email or telephone and to provide us with a copy of their consent form. Authors were contacted a maximum of three times (email, postal service, fax or telephone). If the corresponding authors were not locatable, we attempted to contact the first authors of the articles. Authors could refuse to participate at any time by telephone, fax or e-mail.

If the researchers sent us their consent form, they were told they could answer the final six survey questions or that we would answer the questions based on the consent form that they provided. If we received a consent form and a survey with the final six questions answered, we corroborated and corrected the survey responses because we were studying what was actually written in the consent form. Both ZNC and LFR extracted the information from the consent forms for the six relevant survey questions and consensus was achieved for all questions.

The University of Chicago Institutional Review Board (IRB) and the Children's Hospital of Philadelphia IRB approved the study. The University of Chicago waived the requirement for documenting written informed consent. We obtained a Certificate of Confidentiality (COC) from the National Institutes of Health (NIH) to protect the researchers who were the subjects of our study. The study posed potential risks to the researcher-subjects because an examination of their consent forms could uncover inadequate human subject protections. We also wanted to assure the researcher-subjects that our study would not place their own research subjects at risk of a privacy breach. Statistical significance was determined by Chi-square tests using $p < 0.05$.

### Results

The hundred and seventeen authors were contacted about 162 published articles. Two articles were excluded because we were unable to contact any of the researchers. Eleven articles by seven authors were excluded after the surveys were returned because the research included foreign subjects. One hundred forty-nine articles by 108 corresponding authors were eligible for data analysis. We received 44 complete or partially complete responses (30%) from 39 individual researchers. We received thirteen refusals from researchers regarding 14 articles (9%).

The articles in our literature review sample examined numerous conditions that are associated with ApoE (Table 1). Three-fifths of the articles involved AD (62%), and one-third addressed general neurological conditions and non-AD dementias (33%). Only 11 articles (7%) were related to CAD and related conditions. The percentages of conditions among the articles for which we received a response (column 2) were not statistically different from the literature review sample (column 1).

Table 2 describes the demographics of subjects who were enrolled in the research articles (column 1), and the demographics of our respondents' studies (column 2). The demographics in the articles by our respondents were not statistically different from the study sample overall. The vast majority of articles enrolled unrelated adult subjects (82% and 88% respectively). Cadaveric studies accounted for 13% and 9% of studies respectively.

We asked participants questions about the reporting back of data and the future use of their study samples (Table 3). Most researchers (81%) do not support reporting back of data and most studies were designed not to report back results (either because the results were anonymized or because the researchers stated that they would not report back results in the informed consent process). All respondents (100%) stated that the blood or tissue samples they collected were stored for future use.

Table 4 is a description of information discussed in the consent forms based on researchers' answers and our review of the consent forms. The pleiotropic nature of the ApoE allele was not discussed in most consent forms (88%). Three of the four articles that discussed pleiotropy in the consent form were related to AD and the fourth was related to dementia other than AD. The familial implications of ApoE testing were also not mentioned in most consent forms (86%). Most consent forms did mention whether results would be reported back to research participants (85%). Most discussed the storage of blood and tissue samples (90%). Ten respondents (23%) had obtained a COC.

Table 5 is a breakdown of the information we garnered from reviewing the 15 unique consent forms that we received. Five of our respondents' answers were changed after LFR and ZNC found that the researchers' responses did not match the consent forms they submitted. The word 'Genetic(s)' appeared in every consent form and one-third of the projects had the word 'Genetic(s)' in the title. Six of the consent forms (40%) specifically mentioned ApoE or apolipoprotein E. Thirteen of the consent forms (87%) had a signature line for adult subjects, 11 (73%) allowed a surrogate or legal representative to consent and two (13%) had space for pediatric consent. Reporting back data was discussed in 13 (87%) of the consent forms. Two of the consent forms (13%) documented a COC in the consent forms. Two consent forms included passages telling research subjects that they should tell insurers and other third parties that they had not undergone genetic testing because they would not be
Table 3: Reporting Back of Data and the Future Use of Samples

<table>
<thead>
<tr>
<th>Question</th>
<th>Response (n=43)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you support reporting back ApoE results to participants or their proxy decision makers?</td>
<td>Yes</td>
<td>5 (12)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>35 (81)</td>
</tr>
<tr>
<td></td>
<td>Not Sure</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Were the ApoE results de-identified such that you the researchers could not answer what alleles a particular subject or family member had?</td>
<td>Yes</td>
<td>20 (47)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20 (47)</td>
</tr>
<tr>
<td></td>
<td>Not Sure</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Were ApoE results reported back to participants in your study?</td>
<td>Yes, routinely</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Yes, if asked</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>No, the samples were anonymized</td>
<td>3 (7)</td>
</tr>
<tr>
<td></td>
<td>No, in the protocol we explained that the results would not be reported back</td>
<td>31 (72)</td>
</tr>
<tr>
<td></td>
<td>No, other reasons given or more than one reason given</td>
<td>5 (12)</td>
</tr>
<tr>
<td></td>
<td>Not Sure</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Were ApoE results reported back to family members in your study?*</td>
<td>Yes, if asked</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>No, the samples were anonymized</td>
<td>4 (9)</td>
</tr>
<tr>
<td></td>
<td>No, in the protocol we explained that we would not be reporting back data</td>
<td>29 (67)</td>
</tr>
<tr>
<td></td>
<td>No, other reasons given or more than one reason given</td>
<td>8 (19)</td>
</tr>
<tr>
<td></td>
<td>Not Sure</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Were the blood (or tissue) samples stored for future use? (n=43)</td>
<td>Yes</td>
<td>43 (100)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0 (00)</td>
</tr>
</tbody>
</table>

* Responses do not add up to 100% because of rounding.

informed about their genetic test results.

Discussion

ApoE alleles have been associated with over 20 health conditions, although ApoE research has primarily focused on the relationship of the various ApoE alleles to Alzheimer disease (AD) and coronary artery disease (CAD). Both our sample of the literature and our responses from researchers reflect this focus on AD and CAD (Table 1). While adults are the main population of interest for most ApoE research (Table 2), pediatric researchers explore the relationship of ApoE to neurocognitive development, head trauma, congenital heart disease and other cardiovascular issues.

In the U.S., federal regulations governing research with humans identify what types of information must be included in biomedical research consent forms, but the regulations are open to interpretation. What should be included in consent forms and the consent process for genetic research is particularly challenging because genetic information has familial implications and places subjects and their families at potential risk of social stigma and insurance discrimination. The pleiotropic potential of genes may exacerbate these risks because they may have implications for different conditions at different points in the life cycle.

Our study focused on the ApoE gene in which the pleiotropic nature of the gene is already known. Despite this, only four of 41 researchers (10%) indicated that they discussed the multiple associations of ApoE (pleiotropy) in their consent forms. Only one of the 15 consent forms (7%) that we analyzed mentioned that ApoE had pleiotropic implications. Omitting
Table 4: What Was and Was Not Discussed in the Consent Forms

<table>
<thead>
<tr>
<th>Question</th>
<th># (% of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Were the multiple associations of ApoE discussed in the consent form?</td>
<td>n=41</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (10)</td>
</tr>
<tr>
<td>No</td>
<td>36 (88)</td>
</tr>
<tr>
<td>Not Sure</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Were the familial implications of ApoE testing discussed in the consent form?</td>
<td>n=42</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (12)</td>
</tr>
<tr>
<td>No</td>
<td>36 (86)</td>
</tr>
<tr>
<td>Not Sure</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Was the issue of reporting ApoE results back (to the subject, surrogate or family) discussed in the consent form?</td>
<td>n=40</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (85)</td>
</tr>
<tr>
<td>No</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Not Sure</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was the issue of storage of blood (or tissue) samples for future use stated in the consent form?</td>
<td>n=42</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (90)</td>
</tr>
<tr>
<td>No</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Not Sure</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Was the potential for discrimination discussed in the consent form?</td>
<td>n=42</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (29)</td>
</tr>
<tr>
<td>No</td>
<td>27 (64)</td>
</tr>
<tr>
<td>Not Sure</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

the pleiotropic potential of ApoE may have been an oversight or the researchers may not have considered the other implications of ApoE relevant to their research. However, research subjects need to be aware of the pleiotropic implications of genes being investigated in a research protocol because it could affect their perception of the risks and benefits of participating for themselves, and it could influence the impact their participation has on their families, and their communities. Failure to articulate all of the relevant risks and benefits undermines the informed consent process.

How does pleiotropy influence the benefits and risks of research participation? The subjects of a research study on cardiovascular risks may be interested in knowing how genotype influences their risk for CAD, but they may not know that those same genes may influence their risk for developing AD. Just the association with AD may be enough to provoke anxiety, particularly since there are no known effective treatments to prevent onset although environmental factors may slow down or delay the onset of AD.12

Although all genetic research has familial implications, genetic research with pleiotropic genes has potentially broader ramifications. For example, if you learn that your sibling is at increased genetic risk for CAD because she carries two ApoE epsilon 4 alleles, that means you may be at increased risk for both CAD and AD. And it may make you wary of allowing your 14-year-old child to play soccer because of the hypothetical risk associated with heading the ball.13 Although the prospective participants should be counseled about the difference between association and causality during the consent process, family members may not receive counseling unless they are also research subjects. Thus, family members may be at greater risk of misunderstanding that certain ApoE polymorphisms confer increased susceptibility but are non-predictive.

How clinical information is interpreted within families and the impact of genetic risks on family relationships will vary, and may be further complicated when some relatives are found to be at increased risk and others not. While the family implications of ApoE testing are clinically muted because genotype does

Table 5. Analysis of the Consent Forms We Received

<table>
<thead>
<tr>
<th># (%) of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=15</td>
</tr>
<tr>
<td>Used the word &quot;Genetic(s)&quot;</td>
</tr>
<tr>
<td>Had the word &quot;Genetic(s)&quot; in the title of the protocol</td>
</tr>
<tr>
<td>Used the Word &quot;ApoE&quot;</td>
</tr>
<tr>
<td>Discussed multiple clinical implications of ApoE</td>
</tr>
<tr>
<td>Consent of adult subjects</td>
</tr>
<tr>
<td>Surrogate consent permitted</td>
</tr>
<tr>
<td>Pediatric assent</td>
</tr>
<tr>
<td>Discussed storage of samples</td>
</tr>
<tr>
<td>Discussed whether to report back results</td>
</tr>
<tr>
<td>Documented a certificate of confidentiality</td>
</tr>
</tbody>
</table>
not determine phenotype, different individuals will interpret and respond to genetic information differently. The psychosocial and emotional risks include anxiety, stress, and negative impact on self-esteem.\textsuperscript{14} Those who are at increased risk may be angry with those whose test confirms lower risk and those at lower risk may experience guilt.\textsuperscript{15}

The research subject should also be aware that the genetic information may have community implications. For example, mutations of the BRCA gene are more prevalent in Ashkenazi Jewish women than other Caucasian women.\textsuperscript{16} This observation has the potential to be stigmatizing and to lead to insurance discrimination for all Ashkenazi Jewish women, whether or not they participated in the research, and regardless of whether individual results are reported back. The fact that there are still attempts to correlate race and low intelligence\textsuperscript{17} or race and increased aggression\textsuperscript{18} support the concern that genetic research can have implications for individuals as members of religious, racial or ethnic groups, even when individual results are not reported back.

There are also potential benefits of participating in ApoE research. For example, research subjects may benefit as individuals if specific therapies are developed that are directed to their genotype.\textsuperscript{19} This benefit could accrue to family members and members of the same ethnic group. Another potential benefit is improved family relationships to the extent that family members accept an individual's dementia as a medical condition and not as punishment for bad behavior (e.g., drinking). A third potential benefit comes from the pleiotropic nature of ApoE. Some subjects may view learning about their susceptibility to a variety of conditions as a benefit because the information allows them to be more vigilant about symptoms for disparate problems that may arise in the future.

We found that most ApoE research enrolled living adult subjects (82%). Thirteen percent involved cadaveric samples (13%) and 8% involved extended families. Familial studies raise difficult ethical dilemmas for the researcher both in terms of recruitment,\textsuperscript{10} the privacy of individual subjects,\textsuperscript{11} and ensuring that the consent of the proband and other family members is informed and voluntary.\textsuperscript{12} There is serious controversy about whether secondary subjects, family members who are non-participants but about whom some medical information is collected, should consent to the use of their medical information.\textsuperscript{13} We did not query the researchers about their practice on this matter.

Pleiotropy further complicates the ethical dilemmas raised by family studies because it can have implications for different conditions that present throughout the life cycle. Potential subjects need to understand that information learned in a research study may lead to discrimination against themselves or their family members, including those who did not participate. This information may have a profound influence on a subject's willingness to enroll in a research study. For example, a parent may be willing to consent to his child participating in an ApoE study to further knowledge about its correlation with cholesterol and whether cholesterol levels in childhood correlated with cardiovascular disease in adults. A parent may authorize his child's participation despite the possible discrimination against himself or his child in obtaining life insurance based on cardiovascular risks if information were disclosed. However, the same parent may not be willing to allow his child to participate if he understands that the information could be used to suggest that he or his child, or even his siblings (the child's aunts and uncles) have a predisposition to other health problems, particularly those that are not treatable, like AD. Despite this, the vast majority of researchers in our study (86%) did not inform research subjects of the familial implications of their research in the informed consent document.

The overwhelming majority of our respondents (81%) do not support reporting back ApoE test results to their subjects. In fact, over 90% of researchers did not report ApoE results back to subjects and half of the researchers deidentified their data making it impossible to report back results. Their position can be morally and scientifically justified because 1) of the limited correlation between ApoE genotype and phenotype; and 2) ApoE may generate valid population predictions, but it cannot generate useful individual predictions. This is true of the majority of genetic studies that examine weak risk factors. Most conditions and traits will not be explainable by allelic variations in one gene because of secondary modifier genes, gene-gene interactions, and gene-environmental interactions that modulate the impact of genotype on phenotype.

Some may argue that if no results are reported back in practice, then no harm can come to the patient/subjects or their families. This is not the case. As discussed, subjects can be harmed if third parties learn information about them as individuals, and they can be harmed if information is learned about their particular ethnic or racial or religious community. Even if an Ashkenazi Jewish woman does not know whether she has a BRCA mutation, her insurance company knows that she is at statistically increased risk. Subjects can also be harmed from the psychological impact of knowing that they are being studied for these predispositions.

Pleiotropy increases the potential adverse consequences of reporting research results back to subjects. For studies in which subjects can access their results, the researchers should
emphasize that the results may have health implications beyond the focus of the research. While this may be true for much clinical research, in clinical genetic research it is incumbent that the subjects understand that the broad scope of health implications apply to themselves and to their families.

There is much theoretical concern regarding the potential risk of discrimination and stigmatization of genetic information, although empirical supporting data are scant, and some contend that the threat is exaggerated or not real. Even if there is no real threat of genetic discrimination, the public perception of the threat is significant. Under a one gene-one trait paradigm, subjects faced potential discrimination and stigmatization based on risk or susceptibility for a single condition. Although most genes only confer a modest change in risk susceptibility and would therefore not pose a significant risk of discrimination, the public understanding of genotype-phenotype correlations is not this nuanced, and they perceive themselves to be at risk for genetic discrimination. With pleiotropy, subjects can face discrimination stemming from their risk of developing multiple health conditions, some of which may be more stigmatizing, or at least perceived to be more stigmatizing, than the primary focus of the study. Despite this, we found that a substantial number of respondents (64%) did not mention the potential for discrimination in the consent forms. This could be explained, at least in part, because the researchers rarely planned to report back the results. Nevertheless, as discussed, this may not be sufficient protection.

In two of the consent forms we received, there were passages instructing research subjects to tell insurers and third parties that they had not undergone genetic testing because individual data were not reported back to them. These passages are disingenuous because the research subjects did undergo genetic testing, even though they were not given access to their results. The research subjects probably were told not to disclose their genetic testing because the researchers believed that insurers want to know about an individual's genetic status, not whether the individuals had undergone genetic testing. In a privately insured health care system that can and does discriminate against high-risk individuals, this is an attempt to mitigate the risks to the subjects. It involves some deception because insurance companies might be interested in simply knowing that an individual is eligible for such a research study. It would be more appropriate for researchers to tell subjects that it is not clear if third parties should be permitted to ask about an individual's participation in genetic research or if individuals have a moral obligation to reveal their participation to third parties. Researchers should not recommend that subjects lie, even if this means that some individuals will choose not to participate based on their perception of risk. Furthermore, the researchers' suggestion may backfire on the subjects because deception may invalidate their insurance policies, depending on the state in which they live and the policies of their insurers.

At present, it is estimated that there are approximately 307 million stored human samples in the public and private sector. The storage of human tissue samples raises a plethora of ethical and policy concerns including whether samples are anonymized, whether future testing will be reported back to subjects, who shall have access to stored samples, and the level of consent obtained for collection, storage and future use of samples. All of our respondents indicated that they stored their samples for future use. Encouragingly, 90% of respondents indicated that they discussed the issue of storing samples in their consent forms, though only 73% of the consent forms we reviewed actually did so. Pleiotropic genes like ApoE and the potential for pleiotropy in other genes complicates using stored samples because subjects might falsely assume that the use of their samples is limited to the particular condition being investigated, when, in fact, the sample could be used for a variety of additional conditions. At a minimum, researchers should tell their subjects that tissue samples will be stored for future use and indicate that the samples could be used for research on conditions not studied in their current protocol. Tiered consent reflects this approach. It "allows individuals to choose the type of specimen(s) if any, they want to donate (e.g., tissue, blood, or urine), the type of research the specimen can be used for (e.g. a specific research project, general research, or genetic research), and/or whether their medical records and outcomes data can be accessed."

As IRBs are asked to review more genetic studies and more clinical studies that include a request for a genetic sample, they must begin to routinely address and discuss the ramifications of pleiotropy for research subjects. IRBs should routinely ask investigators conducting genetic research or requesting genetic samples if the gene(s) being investigated are known to have pleiotropic implications. If the studies involve such genes, IRBs should mandate that investigators include a section in the consent form and in the consent process which notes the pleiotropic nature of the gene(s) being investigated and the possible implications for the research subjects. Consider, for example, the following sample wording: "The ApoE gene being studied in this Alzheimer's disease research study has been associated with several other health conditions including coronary artery disease (heart disease), the risk of stroke, and multiple sclerosis (a progressive
nervous system condition). By enrolling in this study, you may also learn your likelihood of developing those conditions and as research advances, other conditions may also be identified. You may face discrimination and stigmatization based on these conditions. You may also experience stigmatization on the basis of your perceived likelihood of developing Alzheimer's disease, which is the principle aim of this study."

For genetic research where the gene is not known to be pleiotropic, it may be useful to acknowledge that genes under study may be found to have correlations with other diseases or conditions not understood. This could be analogous to what is written in pharmaceutical research where the researchers enumerate the known risks associated with the pharmacological agent and then state that there is also the possibility of other unknown risks of harm. In genetic research, the researchers could state in the risk section that 1) the genes discovered in this research may be known to correlate with other health conditions; or 2) the genes under study in this research project may be found to correlate with other health conditions.

Whereas IRB approval and informed consent are mandatory tools aimed at protecting human subjects, certificates of confidentiality (COCs) are optional. They are designed to protect both researchers and research subjects involved in human research from forced disclosure of results. Of our respondents, 10 (23%) indicated that they had obtained a COC. If the pleiotropic implications of a genetic test may yield information that could pose a significant threat to the research subjects, then researchers should consider applying for a COC as an added measure to protect subject privacy.

Our study had several limitations. First, the study was a retrospective review of ApoE studies in the literature. Although the study design had the advantage of obtaining information from a wider range of studies than would have been possible had we restricted our sample to studies that we could observe, the design had the serious disadvantage of using consent forms as a proxy for the entire consent process. This means that we may be understating researchers’ discussions about pleiotropy because it’s possible that they provide more information about the implications of ApoE for various health conditions in the consent process that what is found in the consent forms.

A second limitation of our study is that we had an overall response rate of 30%, which is below average for surveys of health care providers. We feared that some researchers might perceive our research as a threat to the privacy of their subjects, and we obtained a COC to try to encourage participation. We do not know whether this helped or caused even greater alarm—why would one need a COC unless the research posed risks to confidentiality? Despite the low response rate, the frequency of the topics and the demographics were the same in the overall sample and in the responses we received (Tables 1 and 2) which suggests an appropriate representation.

A third limitation is that our search strategy to increase the number of studies enrolling children did not achieve its goal, and we had very few studies that enrolled children. The implications of ApoE research in children are complicated by the subject’s age, their inability to consent for themselves, and the interval between predictive information and possible presentation of many of the conditions associated with ApoE. There needs to be more empirical investigation of what parents understand when they authorize their child’s participation in genetic research, and particularly in genetic research with pleiotropic potential.

Finally, we add two caveats. First, we do not mean to imply that research involving the determination of ApoE alleles is unethical. Although this research may not be useful for individuals, it has important population implications and may help elucidate correlations between what appear to be disparate conditions. Second, we do not mean to imply that ApoE research in the pediatric setting is inherently unethical. Children should only be enrolled in research when their participation is absolutely necessary to answer an important scientific question about the health and welfare of children.

There are disorders and conditions associated with ApoE that can only be studied in children (childhood nephrotic syndrome) and other conditions that may have different implications in children and adults (e.g., head trauma).

**Conclusion**

To our knowledge this is the first empirical study investigating written informed consent practices for research involving a gene that is associated with more than one health condition. We found that the pleiotropic implications of ApoE research were not routinely incorporated into informed consent forms although these implications are relevant to research subjects and should be included in the consent form and discussed in the consent process. Greater exploration of pleiotropy is needed to clarify what is necessary for a voluntary and informed consent for genetic research, particularly with respect to the potential impact that genetic information may have for subjects and families for health conditions beyond the specific research focus.

Investigators and IRBs must understand the pleiotropic potential of genes. They must give serious consideration to the ramifications of pleiotropy on the actual and perceived risks to research subjects. This is particularly true if a study involves a gene with known pleiotropic implications. This information should be
explicitly discussed in the consent forms. IRBs should also develop specific language for consent forms to alert prospective genetic research subjects that the study in which they are being asked to enroll may have clinical implications for conditions beyond the scope of the study. Consent forms for genetic research that is not known to have pleiotropic implications should state that 1) the current research may discover that the genes associated with the condition under study are associated with other health problems; or 2) future research may discover that the genes under investigation have clinical relevance other conditions.

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References


3. We thank an anonymous reviewer for pointing out these three distinct ways that pleiotropy can present special risks.


Hematological Agents 2004;27(2):137-134.


24. See ref. 11, Clayton 2003; see ref. 21, Rothstein 1997; see ref. 21, Burke 2002.


30. See ref. 26, Hamvas 2004; see ref. 27, Epps 2003; see ref. 27, Apse 2004.


Appendix 1.

1. Were the blood (or tissue) samples used for the ApoE testing obtained specifically for this research project?
   a. Yes    b. No    c. Not sure

2. Were the blood (or tissue) samples stored for future use?
   a. Yes    b. No

3. Did the study enroll children (defined as younger than 18 years)?
   a. Yes    b. No

4. Who gave consent or permission for ApoE testing? (circle all that apply)
   a. Adult subject  b. Child subject  c. Parent  d. Surrogate (legally authorized representative, family member)
   e. Waived consent  f. Other (specify ______________________)

5. Were the ApoE results de-identified such that you the researchers could not answer what alleles a particular subject or family member had?
   a. Yes    b. No    c. Not sure

6. In general, do you support reporting back of ApoE results to the participants or their proxy decision makers?
   a. Yes    b. No    c. Not sure

7. Were ApoE results reported back to participants in your study?
   a. Yes, routinely  b. Yes, if asked  c. No, the samples were anonymized  d. No, in the protocol we explained that the results would not be reported back  e. Other ______________________

8. Were ApoE results reported back to family members in your study? (circle all that apply)
   a. Yes, routinely  b. Yes, if asked  c. Yes, if the family member gave consent for the subject’s participation (e.g., parent or legal authorized representative)  d. Yes, but only with the permission of the research subject  e. No, the samples were anonymized  f. No, in the protocol we explained that the results would not be reported back  g. Other ______________________

9. Did you get a certificate of confidentiality (COC) for this research?
   a. Yes    b. No    c. Not sure, do not know what this is

10. Person responding to this survey
    a. Principal or co-principal investigator  b. Research associate  c. Administrative staff  d. Other

If you send us a copy of the consent, you may choose to answer the next 6 questions or we can review the consent form to obtain this information. You can send the consent as an attachment to this e-mail; by fax 773-834-5964; or by snail mail [5841 S Maryland Ave MC 6098 Chicago IL 60637]. If you choose to answer these questions, circle all answers that apply.

11. Was the issue of reporting ApoE results back (to the patient, surrogate, or family) discussed in the consent form?
    a. Yes    b. No

12. Were the multiple associations of ApoE discussed in the consent form? In other words, if the research was about ApoE and its relevance to cardiovascular disease, did the consent form discuss that ApoE is also relevant to Alzheimer Disease?
    a. Yes    b. No    c. Not sure

13. Were the familial implications of ApoE testing discussed in the consent form?
    a. Yes    b. No

14. Was the potential for discrimination (employment, health insurance, life insurance) discussed in the consent form?
    a. Yes    b. No

15. Was the issue of storage of blood (or tissue) samples for future use stated in the consent form?
    a. Yes    b. No

16. Were there restrictions on the stored samples described in the consent form?
    a. Time limit (certain period of time besides indefinite)  b. Type of research (e.g., related to a particular condition)
    c. Restricted to use by the researcher  d. Restricted to use within the original institution  e. Plan to re-consent subjects prior to future use of the sample  f. Other ______________________
Children, Research, and Guinea Pigs:
Reflections on a Metaphor

BY ELISA J. GORDON, AMY HARRIS YAMOKOSKI, AND ERIC KODISH

Despite extensive scholarly work examining the content and process of informed consent for adults, relatively little is known about informed consent discussions with parents and how parents make decisions regarding their children’s participation in clinical research. Some studies have investigated parental attitudes toward participation in a clinical trial and parental perspectives on the informed consent process, while others have focused on parents’ reasons for enrolling their child in a clinical trial and their decision-making process in general. What is known is that parents’ decisions about whether to enroll their children in clinical trials for cancer treatment are complex. Our work has shown that parents also frequently lack understanding about randomization and the difference between trial participation and treatment outside of the clinical trial. These studies have focused on the decision-making process, but still, the content of the consent discussions remains under examined.

One factor that has increasingly come under examination is the role of communication and the specific language used during consent discussions. One aspect of communication, framing, refers to how language and social interaction structure the reality of a given situation. People modify their interpretations of a given situation based on the expectations they bring with them and on unfolding social interactions that promote one account of what is going on over other possible accounts. Framing analysis is particularly well suited to studying informed consent interactions because it focuses attention on what is left out as much as on what is said and because it emphasizes the importance of examining the expectations that patient and investigator bring to the interaction.

Framing analysis applied to research on medical decision-making and specifically the informed consent process has shown that the specific language and framework in which physician-investigators discuss various options and survival statistics can influence adult patients’ decisions about participating in clinical research or accepting offered medical treatment. More recently, Sankar examined the use of frames during informed consent to research discussions as a way to explain the pervasiveness of the therapeutic misconception among adult participants in phase I clinical trials. Her inquiry revealed that when investigators discussed the study’s objective of reducing risk instead of determining toxicity, the investigators referred to the Food and Drug Administration’s (FDA) drug approval process to indicate that the study was safe. As these studies show, how consent discussions unfold and the language used to describe clinical trials are important for shaping participants’ understanding of treatment options and making medical decisions about participating in research.

Central to the process of establishing the frame is the language used within a scenario or to describe a scenario, such as informed consent for clinical research. In its investigation of the U.S. government’s sponsorship and conduct of studies of ionizing radiation during the Cold War, the Advisory Committee on Human Radiation Experiments identified a descriptive study in which patients and subjects were asked to compare the phrase “medical research” with “clinical trial,” “clinical investigation,” “medical study,” or “medical experiment.” Respondents rated the term “medical experiment” most negatively, citing the belief that experiments were more likely to be unproven, untested, and carry greater risk to patients. Similarly, Slevin et al. reported a study from 1995 on British patients’ attitudes toward participation in cancer drug trials wherein 72% of respondents thought that the prospect of getting “new” treatments was very appealing, while only 27% of the same group thought this was the case when the word “experimental” was substituted for “new.” Slevin and colleagues’ findings, while clearly demonstrating the effect of framing, should be understood within the context of a different historical and cultural relationship to research in the UK, where clinical trials were less common. More recently, scholars have examined the conflation of the terms “therapy” and “research,” and the concept of “benefit” in the context of gene therapy as a source.
of therapeutic misconception for patient/subjects. The metaphors are another form of language that can establish frames. Metaphor analysis is especially suitable for analyzing the meanings people attribute to their experiences. This is particularly the case given that metaphors pervade our everyday lives; specifically, our conceptual system that governs our thinking, actions, and even our bodily experience of the world is metaphorical. Metaphors pervade medical theory and practice. In the world of cancer and cancer clinical research, war and violent metaphors used by patients and health care professionals alike have been well analyzed. For example, patients and physicians rally to “fight” against cancer to be a “survivor.” When cancer patients and physicians engage in treatment discussions that include these terms, it promotes a worldview shared by both parties that establishes the expectation for patients to take on the fight by continuing with treatment. Metaphors therefore offer especially insightful entrees into patients’ experiences because they help people express subjective states, notably ones of dis-ease, which are phenomenologically difficult to convey.

Bioethics scholars have increasingly advocated for the analysis of metaphors in bioethics and health policy. The meanings associated with metaphors may be explicitly discussed, but usually are tacitly maintained. As such, they may go unheeded. Metaphor analysis can render the tacit explicit and improve our understanding of the informed consent communication process. Analyzing metaphors can help to broaden our ethical analysis, which can then guide social change. Attention to metaphor can help parents and clinicians gain a better understanding of the ethical complexities inherent in the clinical research setting, which may foster more informed decision-making.

In the course of studying informed consent discussions for childhood leukemia clinical trials over the past six years, we came across the use of the term “guinea pig,” used metaphorically by both physician-investigators and parents. This paper focuses on use of the term guinea pig heard during the course of this research. We examine the way that both parents and physician-investigators independently and contemporaneously used this term to discuss participation in clinical trials and the meanings that they attributed to it.

**Guinea Pig Metaphor**

The term guinea pig has been examined briefly in the context of adult clinical trials. Corrigan interviewed a patient with hypertension who referred to himself as a guinea pig upon receiving a new drug. The author points out that the use of this term indicates that the patient understood his role as being an object of research. Gorelik and colleagues also came across this term in their investigation of the reasons why African American men and women withdrew or refused to participate in a stroke prevention study. They found that African Americans were concerned about experimentation, being a guinea pig, and that they were skeptical of government-sponsored research on African Americans. Similarly, the African American men in the infamous Tuskegee Syphilis study noted that they had been used by the government as guinea pigs.

The history of the term guinea pig reveals additional connotations that may shape the way parents and physician-investigators construe or frame what it means for children to participate in clinical research. As Lederer explains, the term was coined by George Bernard Shaw in 1913 to refer generally to the uncertain state of medical knowledge. The term was then picked up by the antivivisectionist movement in the early twentieth century, which was concerned about the medical profession prioritizing scientific goals over patient welfare. Lederer explains that to animal protectionists, animals and children were conceptually related by their mutual vulnerability to “ambitious investigators.” Interestingly, the historical conceptual linkage of children with animals predates Shaw’s time. In the nineteenth century, societies for the prevention of cruelty to animals often sought to protect children. Kipnis notes that the first prosecution for child abuse, in 1875, was brought under an animal protection statute. Although children are no longer viewed as counterparts to animals, as is evident in today’s separate protections specific to each group, they do share certain medical vulnerabilities with animals. Both children and animals are largely unable to verbalize their experiences with pain and both can be volunteered for experimental procedures by their guardians.

The historical meanings associated with words can endure, though often on more tacit levels. Indeed, the term guinea pig pervades popular culture, even in explicit ways. News stories continue to use the term to refer to past atrocities in human subjects research. The term is even used in the title of an electronic magazine, *Guinea Pig Zero*, which is devoted to helping “professional guinea pigs” stay apprised of risks...
and benefits of research participation through publishing report cards on pharmaceutical companies, and the quality of informed consent and technicians who draw blood at institutions. Thus, the popular use of the term guinea pig likely influences the way parents and physician-investigators use the term themselves to construe or frame what it means for children to participate in clinical research. It is unknown how widespread this term is used nowadays in the context of clinical research for adults or children. Nevertheless, understanding how the term guinea pig is used during informed consent discussions may reveal more about the meanings parents and physician-investigators hold about participating in clinical research. Before turning to our analysis, understanding the context of these conversations is central to unveiling the term's ethical import and highlighting strategies for improving the informed consent process.

Context: Parental Protection and Phase III Trials

In the same clinical conference setting in which the diagnosis of a life-threatening disease (leukemia) is disclosed, physicians talk to parents about the child's treatment and a randomized clinical trial (RCT). RCTs are commonly offered to parents in this context. In testimony to the Institute of Medicine, Children's Oncology Group Chair Dr. Greg Reaman explained that these clinical trials are "constructed such that the 'standard' therapy... determined from a previous study, is integral to the randomized design of the trial with one or multiple alternative regimens evaluating either improved response or equivalency of outcome with less toxicity."32

The language physician-investigators draw upon in the context of parental consent for children to participate in clinical trials is especially complex. Physicians must be sensitive to the needs of the individual child and parents while also advocating for the collection of data to advance knowledge about how to treat children with leukemia in the future. Physician-investigators who seek to enroll patients into clinical trials may therefore feel compelled to talk about research in such a way that minimizes any notion of children being used as a guinea pig in order to overcome the historic legacy and perhaps current notions that may still persist.

As with any kind of clinical trial, parents must make decisions on behalf of their child, who is in a vulnerable position as a minor without a full understanding of the medical condition or trial procedure. In their protective role, parents may be especially cautious about enrolling their children in clinical trials with uncertain risks and benefits at this time of profound fear, grief, and intense distress. At the same time, the context of newly diagnosed leukemia may make parents more willing to permit their child's participation in an RCT.33 The powerful poignancy of the moment, and the potential for confusion between the goals of research and the goals of treatment, make the informed consent process complex, rich, and worthy of careful analysis and reflection.

Study Background

...the observed 140 conferences between parents and physician-investigators regarding the leukemia diagnosis and the RCT option, and conducted 140 semi-structured interviews with these parents at six academic research hospitals throughout the country. The period of time between disclosure of the diagnosis of leukemia and the audiotaped conference and offer to participate in clinical trials ranged from a matter of hours to approximately two days. A total of 153 parents participated in interviews, and 66 physician-investigators participated in the informed consent conferences; each research site held on average 2.3 conferences. Parents were interviewed one to two times, once immediately after their informed consent conference, and again after they made a decision about participating if their decision was not made by the time of the first interview. Interviews were conducted to ascertain parental understanding and motivating factors regarding the RCT enrollment decision. Parents were eligible for participating in the study if their child was diagnosed with having acute leukemia and offered RCT participation. All conferences and interviews were audiotaped and transcribed verbatim. The conference and interview content was analyzed by systematically searching for themes and repetitions pertaining to the guinea pig metaphor emergent from the data.34 The themes were developed by grouping coded segments into larger domains, having all authors review the categorization schema for appropriate thematic fit, and then adjusting and reviewing the schema again until the authors reached consensus. Institutional Review Board approval was obtained from University Hospitals of Cleveland and the five other participating children's hospitals. Written informed consent was obtained for parents, and verbal consent was obtained for all physician-investigators.

Informed Consent and Guinea Pig Metaphor

The metaphor of being a guinea pig as analogous to participating in clinical research was explicitly stated by both doctors and parents in the context of the consent discussions between physician-investigators and parents. It was also used in parent interviews conducted with no physician present. The metaphor of guinea pig was used in 15 conferences (11%), and 12 parent inter-
views (9%). In seven of these 15 conferences, a family member first used the term guinea pig, while in the remaining eight conferences a physician-investigator was the first person to utilize the phrase. In parent interviews where the guinea pig metaphor was used, eight of the 12 were independent of use in the informed consent conference. In other words, eight parents did not say or hear the term during their meeting with the doctor, but did apply the phrase when responding to interview questions. There were no demographic differences between parents who used the term guinea pig and those who did not.

We do not contend that guinea pig is pervasive in consent discussions by our focus on the meanings parents and physician-investigators maintained about it. Rather, in contrast, we wish to highlight that it is a tacitly shared concept, and the vast majority of conferences did not mention the term. This absence of use may actually suggest intentional or subconscious efforts by investigators to avoid using the term guinea pig so as to prevent the complex set of ethical concerns raised by clinical trial design and participation from arising in parents’ thoughts during the discussion of participation in clinical trials, namely not being used for the good of others, not receiving an experimental drug that has not yet been tested on humans, etc. This emerging silence may in fact make the term worthy of closer inquiry.

The metaphor guinea pig was used in the discussions generally to refer to negative experiences associated with being in an experiment. However, parents and physician-investigators attributed overlapping and divergent meanings to the metaphor. These included legitimate concerns about randomization and consequent impersonal care, being used as a means to an end, sample size, testing on humans for the first time, withdrawal from research participation, experimental drugs being inferior, and insulting physician-investigators through using the term. In the following, we present these meanings with accompanying examples to demonstrate the various uses of the guinea pig metaphor in the context of childhood leukemia RCTs.

**Randomization – Impersonal Care.** Foremost and not surprisingly, parents conceived of being a guinea pig to mean being in an experiment, which has a negative connotation for several reasons.

First, the very fact of randomization reinforces the notion that the arm of treatment that the child receives will be impersonal and unpredictable. For parents, this may undermine hope that the health care team will provide tailored treatment according to the patient’s own best interests. After stating that she felt like her child was going to be a guinea pig, one mother explained to the physician-investigator, “No one can control what comes down. It’s like somebody’s sending something down on our computers at work, we don’t know what’s coming. I don’t want to play that game” (CL-09 ICC). After validating this mother’s feelings, the physician-investigator revisited the guinea pig comment, using the term herself, to address the underlying fear: “Let me just say one thing about your comment about the guinea pig.” (CL-09). To which the doctor then added an explanation of the overall uncertainty of the effectiveness of treatment for the patient. During an interview, a different parent explained his dislike for the randomization process since he thought it renders one a guinea pig, and emphasized that giving patients a randomized treatment can be harmful because it does not take into consideration the patients’ own clinical condition:

> In my own opinion, I’m no doctor, don’t claim to be a doctor, but why would you want to hit somebody intensively with chemo if they’re not, 1, if they’re not able to handle it, you don’t know, that’s one of the unknowns, you don’t know if they can handle the intensified chemo, OK? Number 2, if you’ve got a low blast count, why do it anyway? Because when you start doing stuff like that, then it does become an experiment and you do become a guinea pig because you don’t really know what’s going to happen anyway, right? (CL-09 PI#2).

By contrast, one parent’s concerns about her child not receiving proper care were allayed through her trust in the large group of health care professionals involved in running the clinical trials. During the interview this parent stated, “I don’t think of her as a guinea pig so much because I think there’s too many people involved to think she’s not getting the right care” (CL-12 PI#1). For many parents and patients, participation in clinical trials promises the added benefit of increased monitoring of the medical condition.

**Using People.** Another reason that experiments may be perceived negatively is that they use people for the purpose of advancing knowledge. As one physician-investigator said in response to a parent’s concern, “And so the issue would be whether you would want to participate in something that would help us learn more about leukemia in general. I wouldn’t necessarily want you to think about this as... No one’s using him as a guinea pig” (CL-09 ICC). While communicating with family members via interpreter, another physician-investigator defended a child’s participation in the study in a way that ironically reinforces this meaning of experiment while humanizing the effort to make it more palatable: “I, I just wanna make it clear that we’re not using K. as like a guinea pig. Allowing her to be part of the study will help us to understand and help children in the future” (LA-16 ICC). Interestingly, other parents were
more receptive to their child’s participation in the study when the experiment was framed this way, as one parent recounted the discussion she had with the physician-investigator:

You know, there are some people that would just say, ‘you know, that I don’t want to be a guinea pig, leave me alone,’ you know, and they didn’t present it like that you know, that my child’s a guinea pig. They presented it as helping, that’s, to us that, that was a key factor. We’re helping somebody not be as sick as J. is, somewhere down the line (CIN-07 PI#2).

Testing on Humans for the First Time. The term guinea pig conjures other negative meanings of participating in an experiment. For some, it meant testing out drugs on humans for the first time. Yet in the phase III clinical trial context, the drugs themselves have already been tested on humans; rather, the method of administering the drugs was the focus of the investigation. One Medical Fellow attempted to address these negative concerns expressed by a mother and father in the following way:

Fellow: Right. So they’re not brand new drugs right off the shelf, no. We’re not experimenting with new drugs. We’re experimenting with new forms of giving the drugs and new timing and sometimes how the drugs are given. But it’s not a brand new drug. Mother: She’s not a guinea pig. Father: That’s what I was thinking when she was saying that. Not my daughter. No, no, no. Fellow: No, it’s not a new drug (PH-05 ICC).

Several other physician-investigators conveyed this idea, as in the following ways:

When we say it’s a study, I don’t want you to think that there’s anything experimental about it. It’s scientific in its experimental design, but all the medicines and the chemo drugs on there are not experimental, they’ve been used for years, and we have a lot of experience with all of the medicines on there. What’s new is the different combinations of them, and the frequency of them. And the other thing to remember is that we’re not, we don’t think of D. as a guinea pig and we’re not trying this versus that therapy (CIN-13 ICC).

A guinea pig to me is actually sticking a child and giving him some new medicine or something like that (LA-22 ICC).

Parents also expressed this idea through their comments about the research: “It wasn’t like they were testing the medicine on her. It was already tested on somebody. I didn’t want her to be like a guinea pig.” (CL-18 PI #2). “I think they probably think my son’s a guinea pig trying a new drug but it might cure him, you know what I mean?” (LA-24 PI#2).

Parents’ use of the term guinea pig has actually helped to communicate their (mis)conceptions of phase III clinical trials as testing a drug on humans for the first time. Parents’ statements underscore the need for clearer explanations about the purpose of phase III clinical trials in the consent discussions. Since the physician-investigator had not used the term guinea pig in the informed consent discussions with either parent, the parents’ statements reflect how they independently held connotations of this term. However, these connotations were not unique to parents: they were shared in the parent-doctor dyad in the course of their interactions, suggesting that the connotations fit within a broader cultural schema.

Sample Size as a Source of Reassurance. In some instances, the concern over being used as a guinea pig by participating in a study was discussed in light of the study sample size. For example, one physician-investigator clarified this point by stating, “So participating in a study does not mean again, that we’re using this child as a guinea pig. You need, hundred, 200, 300 children in each of the treatment groups to tell the difference” (LA-23 ICC). By referring to the fact that many other children are also participating in the study, the physician-investigator is attempting to reassure parents that their child is safe, much like safety in numbers, and not a pioneer in taking the drug for the first time. This form of reassurance reflects the physician-investigator’s struggle to advance the recruitment rate while simultaneously providing care to an individual child.

Freedom to Withdraw.

Parents became relieved to learn that their initial notions of participating in an experiment were not like being a guinea pig, in the sense that there is no way out of it, trapped like an animal in the trial, with no freedom to withdraw from it. When asked what things were most important to her decision about the clinical research study, one mother expressed her relief in the following way: “I just think, being able to get out of it, if we have to um, that we don’t really, that sort of makes us feel like he’s not being sort of a guinea pig, you know, that you have that option” (CIN-13 PI#2). Another parent conveyed her understanding of research in her follow-up interview: “That I can get out at any time I wanted” (CL-18 PI#2).

Experimental Drugs are Inferior. Parents may be concerned that experimental drugs are inferior to standard drugs. When one physician-investigator sought to allay parents’ fears about enrolling their child in a study, he/she reified this notion of ‘experiment’ when he/she stated, “So many parents will tell me that they’re very nervous about putting their child onto a study, because they are not interested in their child being a guinea pig, or receiving inferior therapy, or receiving chemotherapy that no one else is giving” (CIN-12 ICC).

Guinea Pig as an Insult.

Two
families conveyed their reluctance to use the term guinea pig out of fear of offending the physician-investigator. Parents expressed concern that by using the term, they were going to demean the research project because guinea pig has negative connotations, as noted above. As one parent stated during the conference, “I don’t want to insult it, but it feels like you’re telling, I feel like he’s going to be a guinea pig” (CL-09 ICC). Another parent also expressed his fear as follows: “I don’t wanna come out the wrong way and insult you guys but I don’t want you using my son like a guinea pig saying ‘Okay we wanna...” (PH-41 ICC). Physician-investigators responded to these two parents’ comments by assuring them that the child was not going to be used as a guinea pig. One physician-investigator emphasized this point by stating “each of the alternatives in one of these studies is state of the art treatment” (PH-41 ICC). The parents’ statements explicitly reflect the intersection of the power of language with social dynamics: how the consent discussions unfold, and specifically parents’ responses to it, are shaped by the social status differential between parents and physician-investigators.

Reflections

Examining the transactions taking place during these discussions of participating in research revealed insights into both parents’ and physician-investigators’ attitudes toward research. In approximately 11% of the parents’ and physician-investigators’ discussions, the experience was likened to being a guinea pig. Although this proportion in which the term was used may not seem particularly high, our focus is on the meanings that people espouse which are not always easy to articulate given their tacit nature. The fact that physician-investigators and parents conversed at ease about the term guinea pig, without having to explain what exactly they mean by the term, indicates that both parties held deeply shared meanings about it. The point here is not necessarily the frequency of its use, but rather the depth of the shared meanings that are subtly woven in the consent discussions about participating in research.

Through the use of this metaphor, a diverse array of interrelated meanings was revealed about parents’ and physicians’ attitudes toward research. Together, the meanings associated with guinea pig relate to participants’ concerns

Through the use of this metaphor, a diverse array of interrelated meanings was revealed about parents’ and physicians’ attitudes toward research. Together, the meanings associated with guinea pig relate to participants’ concerns about compromising their child’s care by clinical trial participation. The guinea pig metaphor suggests a fear of being randomized to a treatment that may not best suit their child and of having limited ability to withdraw from treatment.

The guinea pig metaphor suggests a fear of being randomized to a treatment that may not best suit their child and of having limited ability to withdraw from treatment. This concern about compromising their care emerges again in terms of not knowing the kinds of side effects children participating in research will experience from the treatment, and in the possibility of receiving inferior care by being randomized to the experimental arm of the trial.

Framing enters into the informed consent discussions in terms of the presence and absence of the guinea pig concept, and how both parties respond to the metaphor. Accordingly, we question why so few conferences and interviews raised this term. It may be the case that the omission reflects a silencing of the notion. In all consent conferences, physician-investigators consistently downplayed the notion of children acting as guinea pigs by their participation in clinical research in the form of a generalized pattern. As their statements show, physician-investigators tended to directly hone in on the term, reiterate it, explicitly state (“deny?”) that the child will not be used as a guinea pig (or even that parents should not even think in such a way), and proceed to clarify research processes involved in the clinical trial that emerged as a source of confusion raised by the initial use of the term guinea pig. In some instances, physician-investigators clarified the research by emphasizing the treatment over the experimental component of the clinical trial. By downplaying this notion, physician-investigators promote a semblance of control for parents, which may putatively mitigate their own concerns about enrolling children in such trials. The practice of silencing discussion of a topic is sometimes done by those in powerful positions, such as the physician-investigators.16 That parents also expressed discomfort at the mere mention of the term guinea pig out of fear of insulting the physician-investigators lent support to the concern about the power to silence. We may then ask, what is at stake for physician-investigators and for parents by using this term? Physician-investigators may be especially cautious about using this phrase for
fear that parents may misinterpret or conflate the notion of a guinea pig with their children’s role in the clinical trial. Physicians may be sensitive to minimizing the stress parents experience given the emotionally charged context. Efforts by parents or doctors to eliminate discussion of a child being treated like a guinea pig suggest that the historical meanings of this term are still alive, albeit contested.

Practical Implications

Examining the meanings that both physician-investigators and parents of pediatric cancer patients attribute to the concept of being a guinea pig is important for better understanding the informed consent process and parents’ decision-making processes. Informed consent for pediatric clinical trial participation should be considered in light of the historical context of ethical discourse surrounding research on pediatric subjects. The ethical considerations about child participation in clinical research have historically been characterized by compartmentalization. However, the pendulum has in more recent decades swung closer to considerations of justice by fostering greater access to clinical trial participation as a way to find more effective therapies for children.37 If we eliminated the guinea pig metaphor in the context of clinical research on children, would this eliminate or minimize what it is that keeps children in this vulnerable status? In other words, does using this term intentionally or unintentionally reaffirm our ethical concerns about enrolling children in clinical research? Upon initial thought, one might set out to determine whether using this term intentionally or unintentionally reaffirms our ethical concerns about enrolling children in clinical research.

Whether or not parents and/or physician-investigators use the term guinea pig in the future, we show that parents maintained various concerns about the way clinical trials are conducted and how these features of trials may impact the welfare of their child. Accordingly, individual concerns about participating in clinical trials can easily be addressed without having to couch them in the catch-all term guinea pig. Future research is needed to determine how to clearly present information to parents and children in the consent process. Specifically, it would be important to conduct research that would assess the contexts and conditions under which some of the meanings associated with guinea pig are invoked and others are not. Additionally, examining the associations of concerns about randomization, using people to advance knowledge, testing drugs on humans for the first time, being free to withdraw from trial participation, and the status of experimental drugs compared to standard drugs with parent age, gender, ethnicity, and social class may reveal further factors influencing the consent discussion and outcomes.

Examining the tacit meanings of the term guinea pig has helped to reveal the complex set of legitimate concerns parents hold regarding clinical trial participation. It is certainly the case that randomization removes an element of personal care, regardless of the fact that the drugs provided are not experimental; the drugs are still being used in novel combinations, doses, frequencies, or duration in one treatment arm. Nevertheless, physician-investigators may help to allay parents’ anxieties about participation in clinical trials by noting, but not emphasizing, that there is usually greater clinical oversight of children enrolled in clinical trials than outside of them from the group of researchers responsible for the research and/or a data safety monitoring board that reviews clinical data as studies progress. By making explicit the multiple tacit meanings associated with guinea pig, we can help to increase physician-investigators’ awareness of its impact on parents’ understanding of clinical research. Increased awareness can foster transparency in consent discussions in the future. Improved transparency in the consent discussion does not remove inherent ethical tensions that parents must address between protecting the welfare of their own child and contributing to the welfare of future children. However, it is helpful in enabling parents to discern the trade-offs more explicitly and clearly.

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