Enrollment by Surrogate Authorization into Stroke Genetic Research

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Abstract

Continued clinical and translational research is necessary to address unmet clinical needs in stroke and cerebrovascular disease. Ethical and scientific challenges confront these research efforts. Genetic stroke research faces a number of specific challenges related to the legacy of genetic exceptionalism and the reality that stroke frequently impairs decision-making capacity. Maximizing scientific rigor and protecting human subjects have frequently and often erroneously been cast as opposing efforts. In this article, we review the challenges facing stroke genetic research and propose potential approaches given the current state of guidance and regulations. We consider the rationale behind including those with decisional impairment and several options to allow participation of these individuals. Appropriate infrastructure and processes should be established to ensure that genetic information poses minimal risk to individuals, just as has been done to minimize physical risk in non-therapeutic research.

Keywords

Research ethics, stroke genetic research, informed consent, decisional incapacity, surrogate consent

Disclosure: Donna T Chen, MD, MPH, receives support for her work in research ethics, in part funded by a grant from the National Institutes of Health (NIH) to the University of Virginia General Clinical Research Center, M01-RR000847. James F Meschia, MD, has been the principal investigator on several National Institute of Neurological Disorders and Stroke (NINDS)/NIH-funded grants, including the currently funded Siblings With Ischemic Stroke Study: SWISS (R01 NS39987). Bradford B Worrall, MD, MSc, is funded in part by NINDS K08-NS045802. None of the authors has any commercial conflicts of interest to declare.

Acknowledgements: The authors would like to thank Margaret Foster Riley, JD, for critical review of an earlier draft of this manuscript. The opinions expressed are the authors' own. They do not reflect any position or policy of the University of Virginia, Mayo Clinic, or the NIH.

Received: February 17, 2009 **Accepted:** May 6, 2009 *DOI: 10.17925/USN.2009.05.01.41*

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Stroke is a major public health burden worldwide that demands continued research to improve treatment and prevention. However, stroke presents a number of practical and ethical challenges to research due to its unpredictability, apoplectic onset, and potential to render individuals incapable of providing informed consent. Disagreements regarding appropriate safeguards for subjects are as old as acute stroke research[1–3] and continue to spark debate.[4,5]

Discussions of ethical issues in genetics research frequently treat gathering and using genetic information as exceptional.[6] The view that genetic information must be handled differently and risks in genetic research are unique arose from a heritage of research into single-gene disorders—generally rare conditions where the relationship between genetic variation and disease is seen in deterministic terms.

Notions of genetic exceptionalism developed from concerns about what happens with information that someone 'has the gene,' including concerns about the potential for personal and familial distress were the information to be discovered inadvertently or without sufficient counseling, and about the potential for stigmatization or discrimination if that information were to get into the wrong hands. Concerns that individuals must be in a position to protect themselves against such risks reinforced the more general sense of importance placed on individual control over genetic information.

However, in the genomic era, understanding of the role that genes play in disease and circumstances surrounding the discovery of genetic contributions to risk for developing a disease has changed dramatically. The majority of genetic studies focus on complex disorders in which a specific genetic variant alters the probability of getting a disease, but does so in the context of many other risk factors. In this situation, any piece of genetic information is ultimately less informative, and thus the risk for psychological distress, stigmatization, or discrimination resulting from discovery of genetic information decreases. The ethics and policy communities remain divided as to how to treat this new form of genetic information,[7,8] and by extension how to assess the level of risk in genetic studies.

Different standards for enrolling individuals unable to consent for themselves may depend on whether or not the research provides a prospect for directly benefiting enrolled participants. In the US, the ability to obtain a blood sample or cheek swab from someone for genetic research is uncertain when a medical condition such as a stroke

Table 1: Hypothetical Studies of a Population at Risk for the Malignant Middle Cerebral Artery Syndrome

Hypothetical Study 1
A study looking for genetic risk factors for the malignant MCA syndrome. Other than blood collected for DNA analysis, all research data are abstracted from clinical data and all patients receive standard clinical care. Patients are followed to determine who develops the malignant MCA syndrome. Those with and without the syndrome are compared to identify specific genetic variants associated with the syndrome.
Hypothetical Study 2
A study looking for a predictive serum biomarker for the malignant MCA syndrome. Other than blood collected for analysis, all research data are abstracted from clinical data and all patients receive standard clinical care. Design is otherwise identical to study #1 except non-genetic biomarker profiles are compared between the two groups.
Hypothetical Study 3
An early-phase study of a potential pharmacological treatment with a novel mechanism of action that is purported to restore autoregulation. Based on *in vitro*, animal, and healthy volunteer data, there were no major safety concerns, but there are substantial theoretical cardiac risks for lethal arrhythmias, especially in a stroke population that may have clinical or occult cardiac disease. A pharmacogenomic component is included in the protocol looking for genetic markers of risk for the malignant MCA syndrome *per se*, of clinical response to treatment, slow metabolism of the drug, and risk for cardiac complications.
Hypothetical Study 4
A study looking for genetic risk factors for the malignant MCA syndrome that includes serial MRI perfusion studies that would not otherwise be feasible to obtain outside of the study. If these perfusion studies were available for clinical decision-making, they might allow earlier diagnosis of compromised cerebral blood flow. Without profound renal impairment, the risk associated with the MRI perfusion study is low.[43]

MCA = middle cerebral artery; MRI = magnetic resonance imaging.

renders that person unable to make decisions and give informed consent (decisional impairment). Some ethics guidelines and local laws suggest that individuals with decisional impairment can only be enrolled in research if the research has prospect of benefit and there is a legally authorized representative to assess risk–benefit level and act as surrogate decision-maker. Stroke genetics research *per se* cannot offer the prospect of direct medical benefit. Decisions about the permissibility of surrogate authorization in stroke genetic research depend on national and international ethical guidance, laws, institutional policies, and local interpretations of each. However, when research on genetic risk factors is coupled with research on therapeutics or diagnostics, the calculus can change.

Example of International Guidance for Ethical Medical Research—Declaration of Helsinki

Since its original adoption in 1964 and in subsequent amendments, the Declaration of Helsinki has been recognized internationally as an important document framing ethical principles for medical research. The Declaration succinctly defines human subjects research, outlines basic requirements for ethical conduct of research, and specifically addresses research involving vulnerable populations, including those who lack capacity. The current version has several sections that are directly applicable to genetic research on stroke given the potential for decisional impairment.[9] It disallows no-prospect-of-benefit research with decisionally incapacitated individuals unless specific criteria are met, as outlined in item #27:

> "For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden."[9]

The Declaration goes on to require assent of the incompetent person if possible (#28) and further outlines the necessity requirement that the research "may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population" (#29).[9] Emergency research is allowable provided informed consent is obtained as soon as possible from the subject or a legally authorized representative. Other international guidelines dealing more explicitly with genetic information outline very similar requirements.[10,11]

Examples of Genetic Research Scenarios in Stroke

Consider the malignant middle cerebral artery (MCA) syndrome—seen in about 10% of all MCA infarctions and characterized by rapid and dramatic edema, herniation, and death.[12] The malignant MCA syndrome has a case fatality rate of 40–100%, compared with 5–25% of all MCA territory infarctions.[13] Accurate prediction of which stroke patients will develop the syndrome is limited. The challenge of identifying individuals destined to get the malignant MCA syndrome is substantial and clinically important given the recent data supporting early use of hemicraniectomy, a high-risk surgical intervention shown to improve survival rates when used early in the course of malignant MCA syndrome.[14] Research aimed at improving prediction of MCA syndrome would significantly advance physicians' abilities to target appropriate preventive interventions to high-risk individuals.

Table 1 outlines four hypothetical studies of a population at risk for the malignant MCA syndrome. Various interpretations of the Helsinki principles could deem some of the hypothetical studies to be ethically impermissible. For example, with clean needles, sterile syringes, and antiseptic technique, hypothetical study 1 poses minimal physical risk to a participant since phlebotomy for genetic analysis can readily be piggybacked onto a clinical laboratory draw, adding no additional risk for bruising, infection, or discomfort. The amount of blood taken for research over the course over the hospital stay would typically be about 15cc. This physical risk would be identical to the biomarker study described in hypothetical study 2.

Level of risk for genetic research is debated, as are appropriate safeguards.[15,16] The Declaration of Helskinki defines a cut-off at "minimal risk and minimal burden." For studies such as hypothetical studies 1 and 4 (see *Table 1*), while meeting the other criteria for enrolling decisionally impaired individuals, a determination that genetic research poses more than minimal risk could render the study impermissible.

Because research risks and prospects for benefit are generally viewed collectively, and because adding a genetic study to investigation of a drug, device, or procedure increases the level of risk by a small amount, the added risk for the genetic component is generally perceived as easily offset by the potential for benefit, even when this potential is small—as can be the case with many early-phase investigational agents. Furthermore, it is unclear how far the prospect of benefit can be stretched. A diagnostic imaging test that may have clinical utility but is not part of the standard of care (as in hypothetical study 4) might be seen as adding sufficient prospect of benefit to justify the risk associated with the genetic component of the study.

Ethical Oversight of Research with Decisionally Impaired Adults

Local ethics committees and institutional review boards are charged with oversight of all human subject research but differ widely regarding permissible research and acceptable protections for research with decisionally impaired adults.[17] Similarly, wide variations are found in laws of individual countries worldwide and of individual states in the US, including silence on this issue in many jurisdictions.[18–23] This lack of clear guidance leaves many investigators and members of research ethics review committees (RERCs; called institutional review boards [IRBs] in the US) confused about how to proceed.[24]

Overarching ethical principles outlined in documents such as the Declaration of Helsinki or the UNESCO declarations avoid specificity on issues such as these. In the US, national regulations relating to the protection of human subjects in research are non-directive on the permissibility of enrolling adults lacking capacity to give informed consent other than in emergency research.[25] RERCs and IRBs are constrained by state and local laws, but many available resources do not fully address whether and how adults lacking capacity should be enrolled in research especially research that does not offer the prospect of direct, individual medical benefit.[26,27]

Weijer has recommended adopting component analysis to weigh potential benefits and harms in research that involve the critically ill and those lacking capacity.[28] This process requires separate analysis of the risks and benefits of the 'therapeutic' and 'non-therapeutic' interventions that invariably comprise critical care research. One difficulty with this approach is that even with aspects of research that offer prospect for benefit, defining them as 'therapeutic' or 'non-therapeutic' *per se* can be difficult. He argues that capacity to consent is defined by the context in which it is sought, and, in the emergent setting, even those with sufficient cognitive abilities to make rational choices can be rendered incompetent by circumstance. He suggests waiver of consent might be permitted in such circumstances, although he does not extend this option to research not offering prospect of benefit.

Coleman suggests that individuals derive personal benefit from being "governed by a policy that permits them to be enrolled in research without their personal authorization—even if such a policy puts them at risk for participating in studies that, when viewed in isolation, may involve more burdens than benefits."[29] This idea rests on the notion that we should all desire to be part of a community that allows enrollment of decisionally impaired individuals in research aimed at improving knowledge about the conditions that rendered them so because such a society values improving the care of the most gravely ill.

Consideration of Scientific Validity as a Key to Ethical Research

Ethical clinical research respects individuals in part by treating them as autonomous agents through the process of informed consent and providing other appropriate safeguards when individuals are unable to participate in decision-making. Scientific validity is also an ethical requirement of clinical research.[30,31] Before initiating enrollment, a study must be rigorously designed to address an important question and have the potential to advance knowledge. Any study of adults with decisional impairment must at a minimum satisfy the necessity requirement: that enrollment of such impaired individuals is scientifically necessary and that the research addresses the condition underlying their decisional impairment.[9,31] The corollary is that if scientifically valid results can be obtained only by enrolling those able to provide informed consent, persons who lack this capacity should not be enrolled even for research directed at conditions likely to produce cognitive impairment or if doing so would be logistically easier.

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Thus, studies that can obtain valid, generalizable results only by including individuals who lack capacity need to consider how to do so. This is the case with many neurological disorders and for most studies in stroke. Specific safeguards are delineated in the US federal guidelines governing research with children who are also considered to have diminished autonomy[25] and include limiting the type and scope of permissible research and utilization of legally authorized representatives as decision-maker for any potential enrollment. In the US, no comparable federally regulated safeguards are currently delineated for decisionally impaired adults, although these are being reconsidered.[32]

About 70% of acute stroke patients demonstrate a level of decisional impairment that requires surrogate authorization for treatment with thrombolytic therapy[33] or enrollment into clinical research.[5] Not allowing enrollment of these individuals into clinical research, including stroke genetics research, has the potential to substantially bias results.[34,35] Furthermore, merely attaching genetics studies to clinical trials of investigational treatments or diagnostics with stringent eligibility criteria may limit external validity and generalizability of the results.[36] We have previously suggested the type of scientific bias introduced by restricting enrollment to those able to provide their own consent to be akin to survival bias.[35]

Since research must be valid to be ethical, it becomes important to consider how it might be ethically acceptable to enroll individuals with decisional impairment. Options for stroke genetic research include research advance directives, awaiting return of capacity, and enrolling via surrogate authorization by a legally authorized representative. Unfortunately, research advance directives are rare[37,38] and even when available can be problematic to implement.[39] Awaiting return of capacity does little to address concerns about consent bias, especially in a disease such as stroke with a high case fatality.[35] Enrollment via surrogate authorization is perhaps the least likely to adversely affect generalizability and should remain an option for stroke genetic research. Research and experience suggest that, although imperfect, family member surrogates might be as acceptable in research as it is in clinical care.[40–42]

Conclusions

Enrolling via surrogate authorization for stroke genetic research should be seen as an acceptable alternative to excluding individuals based on concerns over decisional impairment and the lack of prospect for direct personal benefit. Genetic research involving complex disorders such as stroke poses little risk, and failure to include stroke patients with impaired decision-making capacity jeopardizes scientific validity. It is no longer prudent to rely primarily on individuals to ensure that their genetic information is adequately protected. Just as appropriate infrastructure and processes are required to ensure that risks from a blood draw are minimal, ensuring that genetic information poses minimal risk to individuals requires systemic attention toward implementing adequate laws, policies, and practices supported by appropriate infrastructure. ■

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1. Lindley RI, Thrombolytic treatment for acute ischaemic stroke: Consent can be ethical, *BMJ*, 1998;316:1005–7.
2. Alves WA, Macciocchi SN, Ethical considerations in clinical neuroscience: Current concepts in neuroclinical trials, *Stroke*, 1996;27:1903–9.
3. Doyal L, Informed consent in medical research: Journals should not publish research to which patients have not given fully informed consent-with three exceptions, *BMJ*, 1997;314:1107.
4. Chen DT, Why surrogate consent is important: A role for data in refining ethics policy and practice, Neurology, 2008;71:1562-1563.
5. Flaherty ML, Karlawish J, Khoury JC, et al., How important is surrogate consent for stroke research?, *Neurology*, 2008;71:1566–71.
6. Green MJ, Botkin JR, “Genetic exceptionalism” In medicine: Clarifying the differences between genetic and nongenetic tests, *Ann Intern Med*, 2003;138:571–5.
7. Kakuk P, Gene concepts and genethics: Beyond exceptionalism, *Sci Eng Ethics*, 2008;14:357–75.
8. McGuire AL, Fisher R, Cusenza P, et al., Confidentiality, privacy, and security of genetic and genomic test information in electronic health records: Points to consider, *Genet Med*, 2008;10:495–9.
9. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects, 2009.
10. UNESCO, Universal Declaration on the Human Genome and Human Rights, 1997.
11. UNESCO, International Declaration on Human Genetic Data, 2003.
12. Hacke W, Schwab S, Horn M, et al., ‘Malignant’ middle cerebral artery territory infarction: Clinical course and prognostic signs, *Arch Neurol*, 1996;53:309–15.
13. Thomalla GJ, Kucinski T, Schoder V, et al., Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging, *Stroke*, 2003;34:1892–9.
14. Vahedi K, Hofmeijer J, Juettler E, et al., Early decompressive surgery in malignant infarction of the middle cerebral artery: A pooled analysis of three randomised controlled trials, *Lancet Neurol*, 2007;6:215–22.
15. Knoppers BM, Avard D, Cardinal G, Glass KC, Science and society: Children and incompetent adults in genetic research: Consent and safeguards, *Nat Rev Genet*, 2002;3: 221–5.
16. Merz JF, Is genetics research “Minimal risk”, *IRB*, 1996;18:7–8.
17. Kim SY, Appelbaum PS, Jeste DV, Olin JT, Proxy and surrogate consent in geriatric neuropsychiatric research: Update and recommendations, *Am J Psychiatry*, 2004;161:797–806.
18. Lemaire F, Informed consent for and regulation of critical care research, *Curr Opin Crit Care*, 2008;14:696–9.
19. Lemaire F, The European directive 2001/20 for clinical research: Friend or foe?, *Intensive Care Med*, 2006;32:1689–90.
20. Reade MC, Young JD, Consent for observational studies in critical care: Time to open pandora’s box, *Anaesthesia*, 2003;58:1–3.
21. Liddell K, Bion J, Chamberlain D, et al., Medical research involving incapacitated adults: Implications of the EU clinical trials directive 2001/20/ec, *Med Law Rev*, 2006;14:367-417.
22. New Jersey, Access to medical research act, Act 26, 2008;14.1–14.5.
23. Saks ER, Dunn LB, Wimer J, et al., Proxy consent to research: The legal landscape, *Yale J Health Policy Law Ethics*, 2008;8: 37–92.
24. Lemaire F, Ravoire S, Golinelli D, Non-interventional research and usual care: Definition, regulatory aspects, difficulties and recommendations, *Therapie*, 2008;63:103–6, 197–101.
25. DHHS. Code of Federal Regulations (CFR), 45CFR46d. 2005; 2009.
26. Bankert EA, Amdur RJ, *Institutional review board: Management and function, 2nd ed*, Sudbury, MA: Jones and Bartlett, 2006.
27. OHRP, *IRB guidebook*, 1993, 2002.
28. Weijer C, Is clinical research and ethics a zero-sum game?, *Crit Care Med*, 2005;33:912–13.
29. Coleman CH, Research with decisionally incapacitated human subjects: An argument for a systemic approach to risk-benefit assessment, *Indiana Law Journal (forthcoming)*, 2008.
30. Emanuel EJ, Wendler D, Grady C, What makes clinical research ethical?, *JAMA*, 2000;283:2701–11.
31. Wendler D, Informed consent, exploitation and whether it is possible to conduct human subjects research without either one, *Bioethics*, 2000;14:310–39.
32. DHHS, Request for information and comments on research that involves adult individuals with impaired decision-making capacity, *Federal Register*, 2007;72: 50966–70.
33. Rosenbaum JR, Bravata DM, Concato J, et al., Informed consent for thrombolytic therapy for patients with acute ischemic stroke treated in routine clinical practice, *Stroke*, 2004;35:e353–5.
34. Stewart A, Davis P, Kittner S, Langenberg P, The effect on risk estimates of excluding cases from a case-control study of ischemic stroke, *Neuroepidemiology*, 1997;16:191–8.
35. Chen DT, Case LD, Brott TG, et al., II. Impact of restricting enrollment in stroke genetics research to adults able to provide informed consent, *Stroke*, 2008;39:831–7.
36. Rothwell PM, External validity of randomised controlled trials: “To whom do the results of this trial apply?”, *Lancet*, 2005;365:82–93.
37. Bravo G, Dubois MF, Paquet M, Advance directives for health care and research: Prevalence and correlates, *Alzheimer Dis Assoc Disord*, 2003;17:215–22
38. Chen DT, Case LD, Brott TG, et al.; for the ISGS Investigators, Impact of restricting enrollment in stroke genetics research to adults able to provide informed consent, *Stroke*, 2008;39: 831–7.
39. Muthappan P, Forster H, Wendler D, Research advance directives: Protection or obstacle?, *Am J Psychiatry*, 2005;162:2389–91.
40. Veelo DP, Spronk PE, Kuiper MA, et al., A change in the Dutch directive on medical research involving human subjects strongly increases the number of eligible intensive care patients: An observational study, *Intensive Care Med*, 2006;32:1845–50.
41. Bravo G, Duguet AM, Dubois MF, et al., Substitute consent for research involving the elderly: A comparison between Quebec and France, *J Cross Cult Gerontol*, 2008;23:239–53.
42. Kim SY, Kim HM, Langa KM, et al., Surrogate consent for dementia research: A national survey of older Americans, *Neurology*, 2009;72:149–55.
43. ten Dam MA, Wetzels JF, Toxicity of contrast media: An update, *Neth J Med*, 2008;66:416–22.