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Ethical considerations in the collection of genetic data from critically ill patients: What do published studies reveal about potential directions for empirical ethics research?

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Critical illness trials involving genetic data collection are increasingly commonplace and pose challenges not encountered in less acute settings, related in part to the precipitous, severe and incapacitating nature of the diseases involved. We performed a systematic literature review to understand the nature of such studies conducted to date, and to consider, from an ethical perspective, potential barriers to future investigations. We identified 79 trials enrolling 24 499 subjects. Median (interquartile range) number of participants per study was 263 (116.75–430.75). Of these individuals, 16 269 (66.4%) were Caucasian, 1327 (5.4%) were African American, 1707 (7.0%) were Asian Pacific Islanders and 139 (0.6%) were Latino. For 5020 participants (20.5%), ethnicity was not reported. Forty-eight studies (60.8%) recruited subjects from single centers and all studies examined a relatively small number of genetic markers. Technological advances have rendered it feasible to conduct clinical studies using high-density genome-wide scanning. It will be necessary for future critical illness trials using these approaches to be of greater scope and complexity than those so far reported. Empirical research into issues related to greater ethnic inclusivity, accuracy of substituted judgment and specimen stewardship may be essential for enabling the conduct of such trials.
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Introduction

Genetic variation influences disease predisposition and severity as well as treatment response.[1–4] The use of genetic information to aid diagnosis, stratify risk and guide therapy has potential to impact most facets of medical practice, including care of critically ill patients.[1,2,5] Substantial public and private investment has produced both more complete understanding of genomic structure and variation, and refinement in techniques to facilitate acquisition and analysis of genetic data.[6] As a result, genetic information is increasingly collected both as part of epidemiological studies to delineate genotypic–phenotypic relationships, and as an adjunct to therapeutic trials.[7] As in most sectors of medicine, there is substantial interest in applying genomic techniques to the study of critically ill patients.[5]

Collection of genetic material from the acutely ill poses logistical and ethical challenges not encountered in non-urgent settings. Conditions prompting intensive care unit admission are frequently precipitous and life threatening, and the care provided is highly technological. Neither patients nor family members have typically had the opportunity for education regarding the nature of the disease process, expected outcome, treatment alternatives or research opportunities. Furthermore, patients in intensive care units are frequently incapacitated and unable to provide informed consent permitting medical intervention or research participation.[8–12] Finally, many therapies, such as for sepsis, myocardial infarction or stroke, must be administered quickly after diagnosis.[10] If critically ill patients are to be enrolled in studies in which genetic material is collected, permission must often be obtained in a timely manner from surrogates (for example, family members, guardians or domestic partners), many of whom are being confronted with complex and serious medical issues for the first time. How the exigencies of acute illness affect perceptions of genetic data collection among patients, surrogates, clinicians and oversight bodies is largely unstudied.[13,14]

This commentary focuses on ethical considerations associated with the collection of genetic material from critically ill adults enrolled in clinical investigations. It is reasonable to question the extent to which such investigations occur. Although the ethical aspects of such studies would be identical whether rarely or commonly conducted, these issues might be viewed as esoteric or nugatory by oversight bodies and other stakeholders if such studies are infrequent, but a pressing policy concern if commonplace. Analogous to systematic literature reviews performed to evaluate methodological issues pertaining to the conduct of genetic epidemiology studies in critical illness,[15] we performed a review to quantify the frequency of such studies, and to provide background for discussion of the ethical and social challenges such investigations pose.

Materials and methods

We performed a systematic review of clinical investigations involving collection of genetic data in the related clinical conditions of sepsis, septic shock and/or organ failure. We limited our review to studies of these conditions because we felt that this subgroup was sufficiently representative of all critical illness genetic studies in terms of trial characteristics and ethical issues posed to allow meaningful inference. Studies for potential inclusion were identified through a Medline search (English language, human, 1996–2007) using the terms 'sepsis,' 'septic shock,' 'organ failure' and 'organ dysfunction' as key words or subject headings. Related subject headings identified by these terms were also used. The subset of studies potentially involving genetic data collection was identified by selecting those studies also using 'genetics,' 'polymorphism,' 'variant' and combinations of these terms as subject headings or key words. Related subject headings identified by these terms were used. Bibliographies of review articles retrieved by this search strategy were examined to identify additional relevant citations. Two of the authors (BDF, CRK) reviewed the abstracts of all manuscripts identified by this strategy, included those that were clinical studies in which genetic material was obtained from critically ill adults (age $\geqslant$ 18 years), and extracted the following information: genetic variant studied, clinical entity studied, study location, whether study was single or multi-institutional, number of participants and ethnicity of participants. Several citations described the same study population, which we accounted for in the total number of subjects reported as well as their ethnic composition. This study was approved by the Human Research Protection Office of Washington University School of Medicine.

Results

Our search parameters identified 79 studies enrolling 24 499 subjects reported over the 11-year period (1996–2007).[16–92] (Figure 1, Table 1). The median (interquartile range) of subjects reported in each study was 263 (116.75–430.75). Of these individuals, 16 269 (66.4%) were Caucasian, 1327 (5.4%) were African American, 1707 (7.0%) were Asian Pacific Islanders and 139 (0.6%) were Latino. For 5020 participants (20.5%), ethnicity was not reported. Thirty-seven studies (46.8% enrolling 12 409 patients) were conducted solely or partly in the United States,[18,20,22,28,36–40,42,45,47,50,52,53,55,56,58,60–63,67–70,72,75,77,81,82,87,90–92,94,95] 34 studies (43.0% enrolling 10 096 patients) were conducted exclusively or partly in Europe,[16,19,23–27,29–35,43,44,46,48,49,54,57,59,65,66,73,74,78,80,83–86,89,93] and the remainder were conducted in Asia, South America or Australia.[17,41,51,64,71,76,79,88] Forty-eight studies (60.8%) recruited subjects from single centers,[17,18,22,24,26,27,29,31,33–42,44,47,50,52,53,55–58,60,61,63,64,70,71,73,75–77,80–89,92] 16 (20.2%) were multicenter,[16,20,21,25,28,30,32,43,46,54,59,67,69,90,91,94] with the remainder not specifying the number of participating centers.[19,23,45,48,49,51,62,65,66,68,72,74,78,79,93] All studies examined a relatively small number of genetic markers; none used genome-wide scanning techniques.

Discussion

Genetic information is often perceived as exceptional, associated with risks and requiring protections distinct from other types of data.[96,97] Reasons underlying genetic exceptionalism include the possibility that genetic information is predictive and might re-categorize an individual from healthy to at-risk of disease, infer information about family members or produce emotional duress.[96,98–101] These perceptions may underlie the findings that individuals from many backgrounds—the general population, patients at-risk for hereditable disease and clinicians practicing in ambulatory settings—have expressed reluctance to permit collection of genetic information.[102–104] The manner in

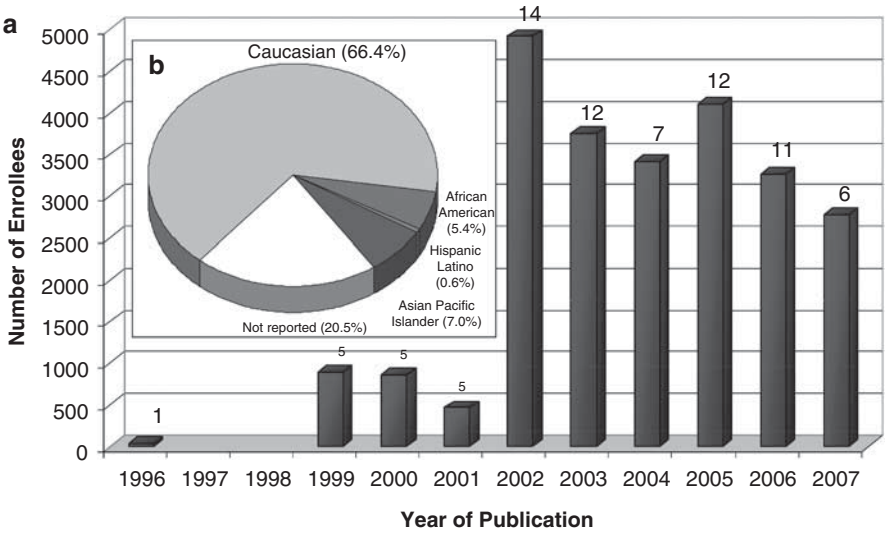

Figure 1 Studies performed in sepsis involving collection of genetic material (1996–2007). (**a**) Bar graph representing number of patients reported each year in studies performed examining genetic influences related to sepsis, severe infection or organ failure. The numbers over each bar refer to the number of studies reported that year. (**b**) Pie graph (inset) representing ethnic makeup of participants in these studies.

Table 1 Studies in patients with sepsis, septic shock or organ failure involving collection of genetic data

Author (ref)	*Study population*	*Participants*	*Genetic variant*
Mira *et al.*[16]	Septic shock	176	Tumor necrosis factor-2 (TNF2) allele
Tang *et al.*[17]	Post-operative intensive care unit (ICU), severe infection	112	TNF allele
O'Keefe *et al.*[18]	Severely injured	152	TNF allele
Majetschak *et al.*[19]	Blunt trauma	70	TNF allele (-α and -β)
Kerlin *et al.*[20]	Severe sepsis	1617	Factor V Leiden (fVL)
Yan and Nelson[21]	Severe sepsis	3894	Factor V Leiden (fVL)
Waterer *et al.*[22]	Community-acquired pneumonia	280	TNF allele
Schaaf *et al.*[23]	Pneumococcal sepsis	119	TNF and interleukin (IL)-10 alleles
Marshall *et al.*[24]	ARDS	2264	ACE allele
Majetschak *et al.*[25]	Blunt trauma, sepsis	110	TNF allele
Stuber *et al.*[26]	Post-operative, severe sepsis	40	TNF allele
Lowe *et al.*[27]	ICU, Sepsis	199	IL-10 allele
Lorenz *et al.*[28]	Septic shock	164	TLR4 receptor
Menges *et al.*[93]	Major trauma	61	PAI-1
Schroeder *et al.*[29]	Severe sepsis	197	Heat-shock protein 70; TNF
Gibot *et al.*[30]	Severe sepsis	212	CD14
Garred *et al.*[31]	Sepsis/SIRS	522	Mannose-binding lectin alleles
Hubacek *et al.*[32]	Severe sepsis	451	CD14
Ma *et al.*[33]	Septic ICU patients	120	IL-1
Schluter *et al.*[34]	Surgical ICU	533	IL-6
Arnalich *et al.*[35]	Severe sepsis	264	IL-1Ra, IL-1RN*
Stassen *et al.*[36]	Sepsis following trauma	61	IFN-γ receptor 1
Davis *et al.*[37]	Trauma	38	IFN-γ receptor 1
Barber and O'Keefe[38]	Sepsis following trauma	284	Lipopolysaccharide Binding protein allele
Barber *et al.*[39]	Sepsis following burns	159	TLR4 and TNF-a alleles
Sutherland *et al.*[40]	Sepsis/SIRS	252	CD14, mannose-binding lectin, TLR-2
Watanabe *et al.*[41]	Critically ill patients	300	TNF, IL-1, IL-6
Quasney *et al.*[42]	Community-acquired pneumonia	402	Surfactant protein B
Hubacek *et al.*[43]	Sepsis	454	Bacteriocidal/permiability increasing protein; Lipopolysaccharide-binding protein
Fang *et al.*[44]	Sepsis	354	IL-1β; IL-1ra

Table 1 *Continued*

Author (ref)	*Study population*	*Participants*	*Genetic variant*
Quasney *et al.*[45]	Community-acquired pneumonia	289	Intracellular adhesion molecule (ICAM)
Gordon *et al.*[46]	Sepsis	213	TNF, TNFR
Sutherland *et al.*[47]	Sepsis/SIRS	228	IL-6
Heesen *et al.*[48]	Sepsis after trauma	58	CD14
Rauchschwalbe *et al.*[49]	Post-surgical sepsis	491	TNF allele
Stassen *et al.*[50]	Sepsis following trauma	66	IL-18 promoter
Dianliang *et al.*[51]	Acute pancreatitis/sepsis	324	TNF allele
Saleh *et al.*[94]	Sepsis	186	Caspase-12
Agnese *et al.*[52]	Surgical ICU	116	TLR4, CD14
Calvano *et al.*[53]	Surgical ICU	44	TNF allele
Frerkling *et al.*[54]	ARDS	490	Clara cell protein 16 alleles
Lin *et al.*[55]	ARDS	98	Surfactant protein alleles
Moretti *et al.*[56]	Post-operative major elective surgery	343	APOE alleles
Gong *et al.*[57]	ARDS	189	Surfactant protein B
Gong *et al.*[58]	ARDS	653	TNF
Gordon *et al.*[59]	Sepsis	527	MBL
Gong *et al.*[60]	ARDS	654	MBL-2
Gong *et al.*[61]	ARDS	640	IL-10 allele
Arcaroli *et al.*[62]	Sepsis	205	IRAK-1
Boudouin *et al.*[63]	Sepsis	692	mtDNA haplogroup H
D'Avila *et al.*[64]	Sepsis	85	CD14
Eklund *et al.*[65]	Bacteremia	147	C-reactive protein
Flores *et al.*[66]	Severe sepsis	535	CXCL2/MIP-2
Gao *et al.*[67]	Acute lung injury/Sepsis	449	Myosin light chain kinase (MLCK)
Garcia *et al.*[68]	Acute lung injury	430	PBEF, MLCK, PROCR
Lorenz *et al.*[69]	Sepsis	164	TLR2
Garnacho-Montero *et al.*[70]	Sepsis	325	TNF, IL-10
Nakada *et al.*[71]	Critically ill adults	411	TLR-4, CD14, TNF, IL-10
Nonas *et al.*[72]	Acute lung injury/sepsis	271	PBEF
O'Dwyer *et al.*[73]	Sepsis/ICU	57	DDAH II
Reise *et al.*[74]	Sepsis following abdominal surgery	172	TNF-β
Walley and Russell[75]	Sepsis/ICU	525	Protein C
Watanabe *et al.*[76]	Sepsis/SIRS	263	TNF, IL-1, IL-6
Wattanathum *et al.*[77]	Sepsis/pneumonia	550	IL-10
Zhang *et al.*[78]	Sepsis/pancreatitis	324	TNF
Zhang *et al.*[79]	Sepsis/pancreatitis	331	IL-1β, IL-10, CD14
Appoloni *et al.*[80]	Sepsis	34	TNF-1, TNF-2, IL-10
Barber *et al.*[81]	Sepsis/burn injury	288	IL-1β, IL-6, CD14, TLR4, TNF
Barber *et al.*[82]	Sepsis/burn injury	233	CD14-159 C
Domingo *et al.*[83]	Meningococcal sepsis	390	Fc-γ receptor IIA
Flach *et al.*[84]	Sepsis/multiorgan failure	60	TNF, IL-1, IL-6, IL-8
Reid *et al.*[85]	Multiple organ dysfunction syndrome	391	TNF, IL-10, transforming growth factor B1(TGF-B1)
Schroder *et al.*[86]	Trauma	232	TNF,IL-6
Spolarics *et al.*[87]	Trauma patients	87	Type A glucose-6-phosphate dehydrogenase (G6PD)
Eisen *et al.*[88]	Sepsis	431	MBL2
Garcia-Segarra *et al.*[89]	Sepsis	304	PAI-1, TNF-β, IL1-ra
Jaber *et al.*[90]	Acute renal failure	61	TNF-α, IL-10
Kellum *et al.*[91]	Sepsis/community-acquired pneumonia	1886	TNF, IL-6, IL-10
Silva *et al.*[92]	Sepsis/acute lung injury	56	HMGB1, LPS

which the exigencies of acute illness might influence such perceptions is poorly understood.[13] One of the most visible aspects of the debates pertaining to genetic exceptionalism focus on economic discrimination.[103,105] The recently enacted Genetic Information Non-discrimination Act (GINA) may mitigate many of these concerns.[106] GINA prohibits the use of genetic information by health insurers to determine eligibility or premiums, and by businesses for employment decisions (hiring, termination and so on). Although GINA's provisions extend to genetic data obtained

through clinical investigation, they are not all encompassing. For example, GINA does not proscribe the use of genetic data to determine eligibility for life, disability or long-term care insurance, nor does it affect underwriting based on current health status.

Concern about the potential exceptional nature of genetic data is mirrored in Institutional Review Board behavior. Institutional Review Board's affiliated with participating venues for multicenter genetic studies vary both in their view of the risks such studies pose, and the protections put in place.[7,107] Such variability is problematic. Recruitment of individuals to participate in genetic data collection at some sites but not others, or having differing consenting standards and processes in place at participating institutions, would be expected to introduce sampling bias. Our analysis of critical illness investigations suggests that the minority of these studies to date have been multicenter. Thus, while investigators conducting clinical research in which genetic material is collected may not have dealt with issues related to variable Institutional Review Board behavior to date, this issue is expected to gain relevance, as has been described for non-genetic studies in critical illness.[108]

Do racial or ethnic barriers to the collection of genetic material exist?

For studies using genetic data collection to be maximally informative, they must be ethnically and racially inclusive.[109,110] Our examination of studies conducted in acute illness suggests underrepresentation (and/or underreporting) of ethnic minority groups. The ethnic makeup of those studies wholly or partly performed in the United States (11 447 participants) was 74.0% Caucasian, 11.6% African American, 1.2% Hispanic-Latino and 0.1% Asian Pacific Islanders. For 13.0% of enrollees, ethnicity was not described. We do not know if this ethnic composition differs from that of studies conducted in similar populations in which genetic data was not collected or from the composition of the populations from which these patients were recruited. Nonetheless, the ethnic composition of participants seems to differ significantly from that of the US population (www.census.gov). On the basis of the current census data, African Americans, Latino-Hispanics and Asian Pacific Islanders comprise 12.9, 12.5 and 4.2% of the US population, respectively, with each of these constituencies experiencing rapid growth (www.census.gov). The Latino-Hispanic population alone expanded 57.9% between 1990 and 2000 (www.census.gov).

Low rates of participation of ethnic minority populations in clinical research is well documented and is described for studies involving collection of genetic data conducted in non-acutely ill individuals.[111–116] Fifty-eight percent of African–American respondents expressed a willingness to participate in a hypothetical study examining the genetic basis of tobacco addiction.[117] Similarly, African Americans were less likely than other ethnic groups to permit collection of genetic data as part of longitudinal studies examining health and nutritional status[118] and type 2 diabetes.[7] Several investigators have reported that relative to Caucasians, African Americans were more likely to believe that collection of genetic data would have negative ramifications.[119–121] The manner in which incorporation of genotyping might influence such perceptions, and possibly further hinder research participation in the context of critical illness, is unstudied. Attention to recruitment of diverse populations for clinical investigation is essential not only for understanding genomic influences on health and disease, but also for ultimately applying the knowledge created by these studies to all segments of society.

What concerns exist regarding future potential uses of genetic data?

We found that investigations involving patients with sepsis were generally of moderate size and involved study of a limited number of genetic loci. With the advent of techniques enabling genome-wide scanning, studies enrolling several thousand patients are needed to sufficiently characterize genotypic–phenotypic relationships.[122] Such studies have been conducted in the setting of non-acute illness.[123–126] Very large biobanks have been established to enable investigations of this scale.[127,128] Conducting comparable studies in the setting of acute illness will likely become common.

The use of biobanks and tissue repositories leads to questions regarding consent to permit future use of this material. The willingness of patients to allow their genetic data to be used for unspecified future studies is unknown in most contexts—including critical illness—and raises ethical and policy concerns. An expedient solution is to obtain comprehensive consent for any and all future unspecified research at time of specimen acquisition.[129] Helft *et al.* surveyed oncology patients who had contributed samples to a biobank using such a consent mechanism.[130] When presented with specific research scenarios, these donors expressed clear boundaries for use.[130] For example, a significant minority of respondents did not wish other research institutions, drug companies or for-profit entities to have access to their samples. More than one-third of the respondents were concerned about privacy and expressed a strong preference for sample de-identification. Compared with other ethnic groups, African Americans were less likely to permit future use for several indications. These findings illustrate an inherent limitation of blanket consent; subjects cannot be given sufficient information about the risks of a future undefined study so as to make an informed choice.

Several approaches have been proposed to obviate these concerns, including requiring donor re-contact for all future sample use, sample de-identification with the intent of carrying out future research without need for re-contact and use of tiered consents, that is, specifying the types of applications the samples might be used for and obtaining consent for specific levels of research.[129] As noted below, how these approaches might be implemented in the context of critical illness remains a challenge.

Considerations in obtaining informed consent

Obtaining informed consent in the context of critical illness genetic studies pose challenges. Although permission to

participate in clinical research in such settings is generally obtained from surrogates, available evidence suggests that the concordance between these proxy decision makers and the patients represented is poor.[8–10,131–137]

There is precedence for waiver of informed consent in investigations of emergency conditions under select circumstances ((21CFR50.24) Exception from informed consent requirements for emergency research). Specifically, the condition under study must be life-threatening and available treatments unsatisfactory. Furthermore, the urgency of the situation and the patient's incapacitation render it impractical to obtain informed consent from either the potential participant themselves or their surrogate. Such circumstances would rarely apply to studies involving collection of genetic data performed in the intensive care unit. The dilemma becomes whether to rely solely on patient's surrogate for consent, to obtain consent from the patient once their critical illness has abated or possibly a hybrid of these approaches. While for selected investigations, it would be appropriate to obtain participants' consent following recovery, and not rely on surrogate judgment, there exist practical limitations to this approach. For genetic epidemiology studies, subjects who either expire or who are lost to follow-up would not be enrolled, potentially eliminating an informative subset of genetic variants from analysis. Furthermore, such studies are dependent upon a robust clinical database to define genotypic–phenotypic relationships. Construction of such a database is ideally real-time and prospective. Collecting this data retrospectively, after a patient has recovered and provided consent, would likely be less accurate and detailed. Similarly, discarding prospectively collected data because a patient declines to participate would strain limited resources. Finally, a research design dependent upon gaining informed consent from patients once they have regained decision-making capacity would effectively preclude trials that base critical care therapy on individual genotype. Ultimately, the investigator is reliant upon the patient's surrogate to provide consent.

We are not suggesting that empirical investigation will negate or supplant the obligation to determine patient's wishes once incapacitation from acute illness abates. Furthermore, many aspects of genetic research, such as donor re-contact to delineate future sample use, would appear most appropriately addressed to the recovered patient. Nonetheless, gaining a fuller understanding of attitudes of surrogates regarding genetic data collection and of the accuracy with which these views reflect those of the patients represented potentially allows critical illness investigations to proceed in an ethically rigorous and resource sensitive manner.

Limitations

A limitation of our analysis is that we examined a narrow focus of acute illness, specifically sepsis and acute organ dysfunction. Some of our observations, such as those pertaining to ethnic representation, enrollment size and multicenter participation, might not be generalizable to other applications in critical care such as myocardial infarction or stroke. In contrast, considerations related to the accuracy of substituted judgment and archiving and future use of genetic data are more likely to be broadly relevant to critical care investigations and illustrate the challenges in conducting these studies.

Conclusion

The ethical implications of critical illness genetics research are poorly studied. It might be argued that the most 'conservative' ethical approach in this setting would be the use of research designs based exclusively on anonymized data sets. Although such investigations would be of undeniable value, they would have limitations. Specifically, studies based on anonymized data collection would preclude assessment of long-term (for example, post-hospitalization) outcomes and would constrain future analyses of archived samples. Obtaining maximal impact of critical illness investigation will require that the scientific community have access to non-anonymized data. Empirical research to more fully understand the views of patients and their surrogates regarding genetic data collection is necessary to guide investigators, oversight bodies and other stakeholders with a vested interest in conducting these investigations in the most ethically rigorous manner possible.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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