Seeing Beyond the Margins: Challenges to Informed Inclusion of Vulnerable Populations in Research

Sarah Gehlert and Jessica Mozersky

There is general agreement that some individuals and groups are vulnerable to exploitation in medical research and therefore require special protections. In three reports issued during the 1970s, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research identified fetuses, pregnant women, children, and prisoners as vulnerable populations requiring special protections, and a 1998 report from the National Bioethics Advisory Commission identified dementias, delirium, schizophrenia, major depression, mental retardation, bipolar disorder, other psychotic disorders, and substance abuse disorder as conditions that may affect decision making capacity.[1] Beyond these recognized groups, less consensus exists about who belongs under the "vulnerable population" rubric.

We focus on persons who arguably are recognized less consistently as vulnerable, that is, those who are disadvantaged or marginalized due to social circumstances and, therefore, susceptible to coercion and exploitation in medical research. We include (1) members of racial and ethnic minority groups, (2) persons living in poverty who are socially excluded, and (3) persons with low levels of education and consequent low literacy and numeracy skills, including low health literacy in this group. These three groups frequently overlap because of the extent to which socioeconomic status and race/ethnicity are confounded in the United States. For these groups, vulnerability can manifest in multiple ways, including lack of access to potentially beneficial medical research efforts due to social, structural, or historical barriers and marginalization, as well as challenges associated with informed consent. We do not claim that all members of these groups necessarily remain vulnerable across time and context. Our purpose is to highlight how individuals belonging to these groups are more likely to be vulnerable and structurally excluded from research endeavors than others.

Current precision-medicine efforts, including the collation of data from multiple sources, offer the potential to improve population health, better understand risk, and reduce health disparities. This drives the U.S. Precision Medicine Initiative *All of Us* Research Pro-

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gram.[2] Including diverse populations is key to achieving the Precision Medicine Initiative's aims. Precision medicine relies on gathering multiple sources of data such as electronic health records and nonclinical sources of data collected using mobile devices. While in theory this offers the potential to increase the inclusion of vulnerable individuals by gathering data from multiple non-traditional source, vulnerable individuals may be structurally excluded from data collection in the first place. This occurs because they do not have access to health care providers who use electronic health records or access to the necessary technologies and connectivity, such as smartphones and consistent internet services that can collect or transmit data.[3] At the same time, these changes in the types and methods of how data are collected require new approaches and models of informed consent, which may present particular challenges for vulnerable populations.[4] In the light of such precision medicine and big data efforts, it is essential to consider how persons who are vulnerable as we define here could face harms and the exacerbation of pre-existing disparities.

We begin by providing the rationale for including racial/ethnic minorities and those of low socioeconomic status or educational attainment under the "vulnerable population" rubric. In the remainder of the paper, we describe the underrepresentation of these vulnerable populations in research, the harms that can result from exclusion, and finally describe recent strategies to improve informed consent. Throughout, we address two distinct but interrelated issues: underrepresentation and informed consent. Identifying and addressing the barriers to participation in research is related to the need to ensure informed consent, since informed consent is ethically necessary before participation can occur. As such, ensuring that vulnerable groups are given the opportunity to take part in research by eliminating structural barriers is a necessary first step to informed consent.

I. The Need to Expand Our Definition of "Vulnerable"

In the United States, race/ethnicity, low socioeconomic status and educational level, all of which contribute to vulnerability in research, intersect with one another in complex ways. This is especially true for African Americans, for whom increases in professional status do not always lead to increased longevity in the same way that they do for white Americans.[5] Members of racial and ethnic minority groups are more likely than white Americans to live in poverty. Forty-three million persons lived below the federal poverty line in 2015 ($24,257 or less for a family of four), and the numbers varied by race and ethnicity.[6] While 9.1 percent of non-Hispanic whites lived in poverty, the percentages for Blacks, Asians, and Hispanics were 24.1 percent, 11.4 percent, and 21.4 percent, respectively.[7] In that same year, a white woman could expect to live 9 years longer at birth than a black male.[8] Many Americans live in abject poverty, including the over 1.5 million families whom Edin and Shaefer identify as living on less than $2.00 per day and food stamps.[9] Those living in abject poverty largely operate outside the mainstream of society, lacking access to health care or the Internet entirely, for instance, and are therefore easily overlooked by researchers as a result of their absence from

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contexts in which investigators customarily identify and recruit research participants.[10]

Earlier work by Olshansky and colleagues,[11] and more recent work by Case and Deaton,[12] point to the salience of education for health. Olshansky et al. found that the trajectory of increasing education on life expectancy differed by race. Although white Americans could expect gains in longevity with increasing levels of education, the pattern differed for racial and ethnic minorities. Case and Deaton found similar results but noted an increase since 2012 in mortality from all causes among whites with high school educations or less since 2012, illustrating the negative impact of low levels of health education among white Americans and racial and ethnic minorities.

Racial and ethnic minority group members report health care experiences that differ from those reported by white Americans. African American women, for example, report unequal power relationships with providers, even when providers are themselves minorities.[13] Although less has been written on the topic, such power imbalances likely also characterize the health care experiences of those living in poverty, especially those who are visibly poor, who may feel compelled to participate in the face of perceived power differentials. Implicit in the principle of autonomy is a universal notion that individuals have a right to make decisions for themselves, free from coercion, though some groups have historically had less control over their lives than others. Respect for autonomy may be more difficult to realize in certain contexts. African Americans and American Indians in the United States have experienced histories of racism that may affect their views of and trust in medicine, science, and research. Researchers and providers who respect individual autonomy may nevertheless be unable to overcome the barriers to trust. Justice directs our attention to concerns regarding equity, fair access to research, and the beneficial knowledge that such research may produce.

Regardless of racial or ethnic identity, those living in poverty may feel compelled to participate in research because they need money or treatment.[14] In other words, the benefit of needed treatment may otherwise be unavailable or reimbursement for participation may outweigh their trepidation from lack of trust. These considerations have the potential to function as coercive forces. As Sears points out, "One can be 'autonomous,' yet be exquisitely vulnerable to contextual influences."[15] The bioethical principle of autonomy is not a fully adequate construct for informed decision making because it does not speak to the pressures exerted by contexts — pressures that can render one vulnerable due to particular circumstances.[16] For instance, the autonomy of a pregnant woman when abortion is inaccessible or illegal is considerably more constrained than for that very same woman when abortion is accessible. Because the principle of autonomy is grounded in the assumption that decisions are made at the individual level, that principle may neglect the fact that decision making may be constrained by such factors as economics, gender, family, and community. In some cases, decisions may not be up to the individual at all.[17] In fact, the principle is grounded in the assumption that certain baseline features necessary for rational choice and decision making — agency, lack of structural constraints, and others — are already in place.[18]

Those with low educational attainment and consequent low literacy and numeracy skills, including low health literacy, may find the language of consent documents difficult to comprehend, though a capacity for such an understanding is fundamental to ensuring ethical participation. Paasche-Orlow, Taylor, and Brancati found that the majority of consent forms provided by Institutional Review Boards were written at reading levels significantly higher than the national average.[19] Levels of educational attainment vary by race, ethnicity, and geography in the United States. In 2015, 54 percent of Asian Americans aged 25 years or older had a bachelor's degree or higher. This was true for 36 percent of whites, 22 percent of African Americans, and 15 percent of Hispanics.[20] According to the U.S. Department of Agriculture, 33 percent of urban residents had a college education in 2015, but this was the case for only 19 percent of rural residents.[21]

Fewer years of education are associated with less exposure to science and mathematics, a function of the educational system. Less exposure to science and mathematics early in life lowers the likelihood that one will understand information about research later in life. Groups cut off from the mainstream of society — some racial and ethnic minorities, persons of lower socioeconomic status, and rural residents — are much less likely to be exposed to media reports of scientific advancements and research. Most news comes from local sources, such as neighborhood or community newspapers, that are less likely to include content on science. Even if science and research are mentioned, it is likely that those with low levels of education will have less exposure to science content and terms, making comprehending what is being said or discerning the quality of research more difficult. Such individuals may disregard the research they encounter because the nature of local broadcast reporting on science lends itself to an erosion of trust in the credibility of findings. If these individuals are asked to participate

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in research, it is less likely that the language and process of informed consent will be accessible to them.

Despite a lack of consensus on who constitutes a vulnerable population, the considerations presented above indicate that members of racial and ethnic minorities, individuals of low socioeconomic status, and people with low levels of education can all be vulnerable in research settings. In the following section, we address the harms that can result from underrepresentation of vulnerable populations in research.

II. Underrepresentation of Vulnerable Populations in Research

Despite the fact that clinical and biomedical research studies with adequate representation of diverse subpopulations have provided many valuable insights, vulnerable populations remain underrepresented in research.[22] In an effort to increase participation of women and ethnic minorities in clinical trials, the National Institutes of Health Revitalization Act of 1993 established a mandate that funded research would be based on "valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial."[23] A 2014 review of publications in a major cancer journal by Chen and colleagues found, however, that only 20 percent of randomized controlled studies analyzed results by race or ethnicity. The authors concluded that increases in minority populations, coupled with their disproportionate cancer burden, heightened the need for greater representation of minorities in clinical trials.[24]

Despite the fact that clinical and biomedical research studies with adequate representation of diverse subpopulations have provided many valuable insights, vulnerable populations remain underrepresented in research.

A number of factors contribute to underrepresentation of vulnerable populations in research. We have mentioned that individuals with low levels of education and low socioeconomic status may lack access to basic health care or research settings, and even if they do, they may not consider research valuable if they have not been provided with exposure to science, mathematics, and research as part of early educational experiences. Social isolation is another factor. Those living on the margins of society are less likely to encounter advertisements for research studies and may lack the means to respond (e.g., a call back number or transportation to get to a research site). Although most Americans have access to social media, that access varies by race, ethnicity, socioeconomic status, and geography. An analysis by Andrew Perrin of the Pew Research Center found that social media usage has risen for all groups but is much higher for those with high levels of education and household income.[25] The analysis also found that 65 percent of whites and Hispanics and 56 percent of African Americans currently use social media. Usage is higher in suburban and urban areas than rural areas (68 percent, 64 percent, and 58 percent, respectively). Viswanath and colleagues suggest that Internet access is less consistent over time for those of lower socioeconomic status because service is bundled with cable television and other offerings; coverage can lapse if bills are not paid.[26] Access for rural residents is limited by lack of broadband coverage in many rural areas of the country.[27]

Marginalized and vulnerable populations are more likely to be structurally excluded from large, preexisting data sets and electronic health records (EHRs), which are increasingly being used in precision medicine and other health research. Bayer and Galea argue against research approaches that rely solely on EHR data because they pose problems for the inclusion of marginalized individuals and groups that lack a consistent source of health care or fail to seek care entirely.[28] Drawing data from an EHR presumes that the record accurately reflects an individual's health care history: medications prescribed, admissions, test results, and features of the social environment that might affect care. This is problematic for two main reasons. First, patients may seek care from multiple sources over time, and the EHRs of those sources may not be linked. This is especially problematic for members of marginalized groups, who may lack the luxury of a consistent provider. Secondly, as Bayer and Galea note, EHRs seldom track factors like poverty and racial residential segregation, but such factors are known to affect individuals' responses to health care (e.g., adherence to treatment recommendations) and health outcomes.[29]

Srinivasan and colleagues acknowledge the challenges of collecting data from subpopulations that are difficult to access for research because they are dispersed geographically, operate outside the mainstream of health care, or are in some measure cut off from society itself.[30] They echo the importance of including subpopulations in research, specifically

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addressing studies that aggregate large data sets, and suggest analytical approaches that take small sample sizes into account. Yet, analyzing subpopulation data assumes that it has been collected in the first place, and recruitment of vulnerable populations remains an enormous challenge.

Public trust in science is generally low, with only 54 percent of the general population endorsing the statement that U.S. science is the best in the world or above average. In comparison, the statement was endorsed by 92 percent of U.S. scientists who were members of the American Association for the Advancement of Science.[31] Lack of trust in science may help to explain variation by race in research participation. Uptake in a large research project undertaken jointly by the National Human Genome Research Institute and the Henry Ford Center varied significantly by race, so that African American participants were less likely than whites to agree to genetic testing, to participate in the study's baseline survey, or to visit the study's website.[32] Race concordance seems to mitigate this tendency somewhat. In response to messages delivered by a race-concordant provider, African Americans were more likely than whites to change their perceptions of the lung cancer risk from smoking.[33] Lack of diversity among researchers may also contribute to the lack of attention and effort required to recruit more diverse and vulnerable individuals.

Providers' recruitment efforts may also explain low participation by vulnerable populations in research studies. Standard methods of soliciting participation, such as flyers posted in health care clinics and advertisements in mainstream media, may not reach socially and geographically isolated populations. For this reason, a number of researchers have turned to advertising in neighborhood newsletters, churches (e.g., through messages from the pulpit and health ministries or in church programs), and community-based organizations. Flyers posted in neighborhood locations frequented by urban minorities are more likely to reach potential research participants who live outside the mainstream of society. Alcaraz, Kreuter, and Bryan have met with success in recruiting urban African Americans of lower socioeconomic status by advertising in laundromats and currency exchanges.[34] Notice boards in grocery stores are a means of communication in rural areas. Flyers posted in emergency shelters or food pantries increase the likelihood of reaching those who lack permanent housing.

Some investigators have advertised in hair salons and barber shops or recruited participants through existing community advisory boards, whose members can act as liaisons between research staff and community members meeting eligibility criteria.[35] The use of community advisory boards works especially well when recruitment efforts are conducted by community members who themselves have participated in research studies, because their endorsement lends credibility and increases trust among those contemplating participation.

Alternative recruitment strategies are only the first step to including vulnerable populations in research. Isolated or marginalized individuals, such as those without permanent addresses or phone numbers, may face multiple additional barriers to taking part in research even once they become aware of opportunities. Researchers may also face challenges when trying to conduct research requiring multiple visits or longitudinal follow-up with marginalized individuals who may be hard to reach or transient.

III. The Harms of Excluding Vulnerable Populations in Research

One of the essential reasons for including vulnerable populations in research is that significant harms may result if they are excluded. Effective results-driven research to improve population health requires the inclusion of diverse subpopulations. If research samples are negatively skewed toward persons with higher socioeconomic status and samples that fail to reflect population averages of racial and ethnic groups and rural residents, they will yield inaccurate results. Risk estimates based on those findings may be erroneous, and the resulting interventions will fail to improve population health.

In fact, if samples are not representative of the population to which results will be generalized, there are possible negative impacts on those who are inadequately represented. For instance, Manrai et al. described the misdiagnosis of an increased genetic risk for a heart disorder among African Americans, attributing the error to risk figures based on insufficiently diverse, publicly accessible exome data. They concluded that "disparities may result from errors that are related neither to access to care nor to posited 'physiological differences' but, rather, to the historical dearth of control populations that include persons of diverse racial and ethnic backgrounds."[36] Mancuso and colleagues noted that the numbers of both rare and common variants in prostate cancer heritability are much higher among individuals of African ancestry than among counterparts of European ancestry,[37] reinforcing the importance of including sufficient numbers of racial and ethnic minorities in research.

Another example of the harms of undersampling representative populations in research comes from genetic testing among African American women for mutations in *BRCA1* and *BRCA2*, which is used to

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predict risk for developing breast and ovarian cancer. Kurian estimated the prevalence of the *BRCA* mutations among U.S. women unselected for family history was 3.5 percent among Hispanic women, 2.2 percent to 2.9 percent among white women, and 0.5 percent among African American and Asian American women.[38] Kurian's prevalence estimates were based on two studies. The first study included 8,753 women under 65 years of age who were enrolled at the Northern California site of the Breast Cancer Family Registry.[39] A subsample of 288 African American women was randomly selected for the study, and 183 of them agreed to mutation testing (representing only 2 percent of the overall sample). This sample was derived from one geographic location and from those with family histories of breast cancer, raising questions about the generalizability of prevalence estimates, especially their generalizability for women without family histories of the disease. The second study, by Malone et al., yielded the same estimate for African American women as the first study.[40] The second study's sample was drawn from five large U.S. cities and included 1,628 women with breast cancer and 674 controls. Nearly one third of cases from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registries, and slightly over one third of controls, self-identified as African American. Although the geographic representation of the second study is preferable to that of the first and the use of SEER data is admirable, both studies problematically rely on self-identified race and ethnicity for group comparisons. According to ancestry informative genetic testing done by Kittles and colleagues, Malone et al.'s sample of self-identified African Americans from five cities varied greatly in their percentages of European admixture: from 10 percent in Atlanta to 35 percent in Seattle.[41] Combining all self-identified African Americans into a single category might therefore mask important subpopulation differences and could produce error in prevalence and risk estimates.

Estimates of the prevalence of mutations in well-known cancer susceptibility genes are used to determine risk for disease. In 2013, a working group of the American College of Medical Genetics and Genomics (ACMG) recommended that pathogenic variants detected in genomic sequencing tests in 56 genes be reported to individuals who have their genome sequenced, independent of the original purpose for the test.[42] *BRCA1* and *BRCA2* were among the cancer susceptibility genes recommended for mandatory reporting. Controversy arose about whether patients have a right not to know and should be able to opt out of such secondary analysis and resulting findings.[43] Particularly controversial was the ACMG recommendation that results be returned regardless of age, returning to parents or guardians their children's pathogenic variants in genes for adult-onset conditions.

Underrepresentation of African Americans in *BRCA* research, combined with the deficiencies produced by self-identified race, affects the accuracy of both prevalence and risk estimates, so that significant harms could accrue from returning *BRCA* mutation results to African Americans including children and adolescents.[44] *BRCA* mutations among African Americans are less well characterized, which affects the ability to predict risk of developing breast cancer based on genetic test results, and also leads to higher rates of variants of uncertain significance (VUS) for which the risk of developing the disease is unknown.[45] It is entirely possible that breast cancer will not develop, because the *BRCA* genes are not 100 percent penetrant. Here again, the penetrance among African Americans is less well characterized secondary to undersampling, further heightening concerns about returning information to caregivers of children. No management or prevention strategies can be implemented in children and adolescents, potentially adding to anxiety and stress among those who are identified as "at risk." The impacts of this knowledge on parent-child relationships and children's psychological development (for instance, in terms of self-image) are unknown. In response to the controversy about the ethics of mandating the return of certain genetic results, the ACMG revised its recommendations in 2014 to allow patients to opt out of the analysis of genes unrelated to the indication for testing.[46]

Recently, in an effort to understand how the results of genetic testing might affect treatment and management decisions, Kurian and colleagues surveyed breast cancer patients identified from two SEER registries and diagnosed in 2014 and 2015, asking them about genetic testing and merging their responses with SEER data.[47] Only about half of women who underwent genetic testing reported seeing a genetic counselor. Alarmingly, half of average-risk patients with a VUS result underwent bilateral mastectomy, which the authors suggest is due to surgeons' limited understanding of genetic test results, especially uncertain results such as VUS. As Kurian et al. noted, African American women are not only more likely to get a VUS result, but are also at risk of being given inaccurate advice about appropriate management options by providers as a result.

Vulnerable populations are thus doubly disadvantaged in research. If they are not included in research studies, the recommendations and practices that accrue from that research may ill fit them, hampering diagnosis and treatment. When coupled with consent

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language and processes geared towards individuals with higher levels of education and health literacy, this produces a perfect storm in which members of vulnerable subpopulations are neither included in research nor benefit from results that lack applicability to them.

IV. Methods of Fostering Greater Comprehension and Equity in Informed Consent

Many have questioned the feasibility of achieving true informed consent with vulnerable populations, given lower levels of health literacy, potential for coercion, and power differentials with researchers. Beauchamp describes the tension between two definitions of informed consent.[48] From a moral perspective, informed consent is conceptualized as autonomous authorization by an individual to participate in research based on an accurate understanding of the research and a lack of coercive influences. The second conception, more commonly used by federal regulations and institutions, is a legally or institutionally effective approval provided by an individual. Consent forms have become increasingly long and complicated to meet regulatory requirements and are often designed to serve the interests of institutions and sponsors.[49] They are often written in language that exceeds the recommended appropriate reading level for the general population.[50] Beauchamp suggests that informed consent in the moral sense cannot be achieved without a climate of exchange in the consent context. Creating this climate arguably is a greater challenge with individuals and groups with low levels of education and trust, and where power differentials may hinder the notion of a fair exchange between parties.

Although no approach has been used consistently to foster the comprehensibility of informed consent for vulnerable populations and to create a more equitable climate of exchange, a number of interventions have been proffered to achieve more effective consent materials and methods. These interventions can be grouped into five rough categories: (1) simplified consent forms; (2) checks on comprehension of content to identify obstacles to comprehension; (3) a modified consent process; (4) clinical associates; and (5) visual aids and graphics. The five groups are briefly defined, and examples provided, in the following paragraphs.

A number of authors have focused on shortening consent forms for vulnerable populations and decreasing the complexity of their language. Beskow et al., for example, argue for the use of plain language in consent forms for biobanking that includes the minimum of information needed to meet federal regulatory requirements.[51] They developed a simplified, two-page form and asked a community sample of patients with diabetes if it contained the information they would need to decide whether to take part in a biobank. Based on the results of that investigation, the authors recommended the use of a two-page form with easily available supplemental material for those who require more information.

Ittenbach and colleagues conducted a pilot study of individuals with low levels of education and income who were randomized to either a simplified or a traditional consent form for an immunization study.[52] While less than half of participants reported reading either consent form in its entirely, 73 percent responded that they understood the form very well. The two groups said that they read the risks and benefits of the study in similar numbers, yet more members of the group assigned to the simplified form reported understanding those risks and benefits. The authors also found a slight advantage for reading the simplified form over the traditional form for certain sections of the consent form, namely those that addressed risks and benefits, availability of alternative treatments to the one being tested, what to do if injured in the study, and compensation for participation. Although preliminary in nature, this suggests that shortening a consent form may increase comprehensibility of language meant to explicate key aspects of a research study by persons with low levels of education without impeding understanding.

A second group of interventions builds comprehension checks and checks for coercion to participate into the consent process. The latter is particularly important in research with persons living in poverty, who might have a high need for treatment or money. Teach-back is fairly commonly used to assess comprehension. An example of its use with low-literacy populations comes from the work of Kripalani and colleagues, who conducted a randomized controlled trial of a method for increasing medication adherence among inner-city patients with low literacy from a teaching hospital's clinics.[53] After receiving written informed consent materials and listening to a scripted study overview, participants were asked to explain the purpose of the study, timing of the follow-up interview, treatment to be received, and potential risks and benefits of participation, etc. Less than 40 percent correctly taught-back all items in their first attempt, and literacy was significantly associated with comprehension of consent. Those with a high school reading level were four times more likely than those a third grade reading level or less to comprehend the consent form.

Although not directly aimed at improving comprehension, Dugosh and colleagues developed and tested a standardized instrument for use in measuring per-

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ceived coercion among young adult misdemeanor-level substance offenders.[54] The seven-item scale, developed based on input from experts in criminal justice, demonstrated strong psychometric properties. 56 percent of 84 participants reported feeling some pressure to enter the study to help their court case and 57 percent reported feeling pressure to please the judge. While limited in generalizability, the study highlights the threat of coercion for vulnerable populations and the need to recognize it in informed consent. Placing extra emphasis on the voluntary nature of research and making clear that refusal to take part will not result in loss of any benefits could help combat potential coercion in research contexts that involve vulnerable populations or where coercion may be more likely.

A third group of interventions couples consent form changes with changes in the consent process aimed at assessing and addressing lack of comprehension. In a randomized trial of two advance directives with a diverse sample of older adults, Sudore et al. followed a consent form written at a sixth-grade reading level (yet congruent with most standard IRB templates) with seven true/false statements to assess comprehension of study procedures, risk, and confidentiality.[55] If comprehension was not achieved on one or more statements, the consent from sections corresponding to those statements were reread to participants up to three times. Over 70 percent of statements were answered correctly on the first pass, yet 23 percent of participants required three or more passes to achieve comprehension. The authors found that lower literacy scores (divided into adequate, marginal, and inadequate) were significantly associated with needing more passes in multivariable models, after controlling for other variables.

A similar example comes from the work of Rounsaville et al. with young marijuana-dependent adults enrolling in a randomized treatment trial who were referred for treatment by their probation officers.[56] Participants were read a review of the study by a research assistant, including detailed review of the consent form, and given a written copy of the form. They then were given a four-question multiple choice quiz to assess comprehension of key information. When questions were answered incorrectly, relevant material was reviewed until it was clear that the participant understood the material.

A fourth group of interventions relies on clinical research staff to increase the transparency of consent. Steinke speaks of the utility of clinical research associates in guiding more vulnerable participants through the research process.[57] In terms of consent, this guidance involves assessing participants' understanding and ensuring that potential participants understand the study and what is entailed in participation using appropriate written, auditory, and visual materials, as needed. The advantage of the clinical research associate or similar individual is the longitudinal nature of their involvement compared to more time-limited interventions.

The final group of interventions adds visual aids and graphics to traditional methods of informed consent with populations with very low health literacy. An example of such a study, by Heerman, White, and Barkin, involved a trial to reduce childhood obesity among a group of racial minority parent-child dyads of low socioeconomic status.[58] Investigators used a multifaceted approach to enhance consent that involved using four visual aids while reading through the consent document. The visual aids employed white space, clear visual images, avoidance of jargon, and easy-to-read figure captions. Investigators' approach was informed by health communication strategies specifically for those with low literacy, and included teach-back methods and careful attention to children's behaviors to look for signs of dissension that might not be observed when the signed parental consent document is the only measure of informed consent.

No single approach overcomes obstacles to the comprehensibility of consent documents. This challenge is not unique to vulnerable populations. Given that nearly half of adults in the United States have an 8th grade reading level or less, and that many consent forms are written well above this average,[59] lack of comprehension likely affects many research participants but will be even more pronounced among vulnerable populations.

V. The Changing Standards in Acceptable Forms of Consent

The innovative models of obtaining consent described above still generally adhere to a variation of the standard model of informed consent: A researcher provides a physical document to a participant to read and sign, and that document generally relates to one particular study. Technological capabilities to collect and collate multiple forms of data, or big data, are challenging this standard model of consent in two key ways. First, the rise in technologies such as smartphones and increasing Internet access enable potentially new mechanisms of obtaining consent (i.e., "e-consent").[60] Second, the ability to collect new forms of data has led to revised proposals regarding the type of consent that is required (i.e., no consent, broad consent, and governance).

There is now potential to collect large amounts of data "passively," that is, by mining existing databases

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or electronic health records, or by the use of data collected via mobile phone apps, social media, or wearables.[61] The collation and analysis of big data offers the potential to improve population health, better understand risk, and potentially reduce health disparities. This potential is the driving force behind the U.S. Precision Medicine Initiative *All of Us* Research Program.[62] Yet the change in how data is collected may necessitate new approaches and models for informed consent.[63] Some have suggested that requiring consent for the collection of preexisting data that presents low risks to participants could hinder research efforts, by either creating unnecessary barriers to data collection by increasing the possibility that individuals will decline or potentially leading to selection bias as those who consent are fundamentally different from those who do not consent.[64]

Many academics agree that broad consent, defined as consent for a broad and unspecified range of future research, is a reasonable approach in many research contexts and more feasible than consent for specific use.[65] Importantly, empirical evidence regarding consent preferences that solicits the perceptions of vulnerable populations, including racial and ethnic minorities, is much more limited. While the majority of empirical evidence regarding consent preferences suggests that individuals want to be asked and given a choice about participation even when risks are minimal or involve preexisting data or samples, most studies have failed to include the voices of vulnerable populations.[66]

Brown et al.'s qualitative study compared views among African American and white women regarding their preferred models of consent for biobanking and found that the majority of both groups preferred broad consent.[67] African Americans participants emphasized the importance of being asked permission to use samples for future research. Not seeking consent, even for minimal risk research, risks further undermining public trust in research and science and further eroding participation by vulnerable populations. Catz et al. found that both African Americans and Hispanics had mixed feelings about genetic research, with concerns and fears about the risks of taking part, and that African Americans expressed the most concern about possible harmful uses of genetic information.[68] All individuals expressed a desire for more information, leading Catz et al. to call for new strategies for communicating genetic knowledge that are understandable and acceptable for diverse cultures, linguistic groups, and people with diverse educational levels. Kaphingst et al. found race/ethnicity and educational attainment to significantly impact knowledge regarding genomic sequencing, so that there was much less knowledge of genomics among minorities and those with low education.[69] The authors suggest that these differences in knowledge are partially attributable to differences in exposure to genetic information and information sources by race/ethnicity and education.

Trust is an important factor in determining whether people take part in research, and may encompass trust in the sociopolitical system, key actors, and institutions involved in medicine and research.[70] Many factors contribute to willingness to take part in research and preferred models of consent, highlighting the need to gather data regarding the views of vulnerable and marginalized populations and avoid assumptions about what forms of consent groups may prefer.

More recently, some have suggested a governance model informed by deliberative democracy techniques.[71] According to Koenig, consent to governance involves agreeing to be governed by the deliberations of others who have been chosen for this purpose.[72] Koenig describes convening a group of "representative citizens" or creating a citizen-led Community Advisory Board to deliberate extensively about appropriate use of data and samples on behalf of participants as one mechanism to achieve governance. One advantage of the governance model is that participants may be assured that "like-minded" people, as opposed to just experts, had input into decisions about research. The governance model provides more flexibility and adaptability by enabling ongoing input as new findings arise rather than presuming all decisions can be made or anticipated upfront. Governance also helps to avoid the highly individualistic focus on autonomy and individual choice that dominates many informed consent discussions.

Lacking from recent discussions about new models of informed consent are the unique challenges, both

Of particular concern in consent for research with racial and ethnic minority groups, and often overlooked when informed consent is conceived as either an autonomous authorization by an individual or legally and institutionally effective approval by an individual, is the role that group identity may play in decisions to take part in research.

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ongoing and new, that these models may present for vulnerable populations. In the first instance, we need to work to eradicate the structural barriers that prevent vulnerable individuals from being included in research. From this perspective, ensuring informed consent becomes a secondary but related consideration. However, new models of consent such as broad consent or consent to be governed may pose additional challenges for certain vulnerable or marginalized populations. [73] We turn to this in the following section.

VI. Who Can Speak for Whom? Tension Between Respect for Individual Autonomy and Group Identity

Of particular concern in consent for research with racial and ethnic minority groups, and often overlooked when informed consent is conceived as either an autonomous authorization by an individual or legally and institutionally effective approval by an individual, is the role that group identity may play in decisions to take part in research. In the almost 40 years since publication of the *Belmont Report*, community research has steadily increased and taken on greater moral significance. In considering the effect of group identity on consent for research, Ross and colleagues (including S. G., first author of this paper) distinguished structured groups from unstructured groups.[74] Structured groups are those with defined social structures, often with identified leaders, whose identity is sustained over time and exists irrespective of research. According to this definition, racial and ethnic groups may be either structured or unstructured. Ross et al. consider American Indians as structured groups because they record group enrollment and have recognized leaders. Other racial and ethnic groups, like African Americans and Hispanics, lack defined leadership and internal cohesiveness, although they may be recognized as groups by third parties because of a shared trait. They, thus, are considered unstructured.

Ensuring informed consent among both structured and unstructured groups gains significance in light of the recent trend toward integrating massive amounts of existing data from a range of health care, commercial, social data and mobile devices, and other sources. The aim of most big data collection and analysis is to improve the ability to predict those at higher risk of illness and potentially intervene to treat or prevent disease with the goal of improving overall population health.[75] Including data that are gathered via nonclinical sources, such as social media and mobile devices, has the potential to increase the inclusion of those vulnerable individuals who either do not access health care or lack consistent providers. It likewise has the potential to provide sources of more social information than has been available in electronic health records. However, vulnerable individuals may be structurally excluded from data collection in the first place, because they do not have the necessary technologies and connectivity, such as smartphones and consistent Internet access that can collect or transmit data.[76] At the same time, agreement is lacking on how best to gain informed consent for the use of these data, or even if consent is necessary. Gaining consent for the use of available data from marginalized and isolated populations presents an even greater challenge.

Governance and consent to be governed has appeal as an alternative model particularly among structured groups with recognized leaders or councils. It is less clear how consent to be governed would work among unstructured groups who may lack a shared identity or set of leaders, raising questions about representation. Community-engaged and community-based participatory research based on established relationship between academics and community stakeholders may provide even greater representation of the key stakeholders in such situations.

The Ross et al. framework suggests that unintended negative consequences may follow a governance approach among both structured and unstructured groups. Risks to well-being and agency may accrue at three levels: (1) the level of the individual; (2) to individuals as members of groups, both as research participants and nonparticipants; and (3) to the group as a whole. An example at the second level comes from Native Hawaiian culture. An individual consents to have blood drawn for a research project. Because blood is associated with power in Native Hawaiian culture, the research participant risks stigmatization from the community.[77] Another example is a group leader who has an ongoing relationship with a research institution who wants his group to participate in a research project. Although other group members do not wish to participate, they feel pressure to so because the leader has promised the group's cooperation. At the third level of risk, a group's cohesiveness and structure may be compromised when, after the group engages in research, the leader disagrees with researchers about the direction and extent of participation. Group members who side with the researcher may lose respect for their leader, producing dissension within the group.

According to Ross et al.'s definition, African Americans are an unstructured group, yet there is evidence that more isolated African Americans make health care decisions based on their group identity more than their individual identity. Salant and Gehlert analyzed data from 18 focus groups conducted in 15 predominantly African American neighborhoods on

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Chicago's South Side to explore understandings of the breast cancer risk of African American women.[78] Three dominant themes emerged. First, collective memory, or nostalgia about traditional ways of life, was observed when discussing breast cancer causality. This theme focused on external sources of risk, such as a disproportionate number of toxic waste dumps in African American neighborhoods, rather than on risks from individual behavior. Second, the study noted community candidacy: how individual communities are "constructed" for disease by powerful others. Third, community victimization was a prominent theme. Respondents expressed the sense that dominant economic and political powers neglect the interests of poor communities and that scientists and governments withhold cures and scientific breakthroughs or experiment directly on communities that lack the power to oppose them. This view of science and research through a community lens highlights the deficiencies of the principle of respect for individual autonomy in ensuring informed consent. As new approaches to consent are considered, including broad and possibly no consent for pre-existing data, we must remain attuned to the potential greater harms to groups already marginalized and structurally excluded from research.

V. Conclusions

Although the importance of including vulnerable populations in research is widely accepted, how to achieve such inclusion remains a challenge. Ensuring that informed consent is comprehensible presents no less of a challenge. Although a variety of interventions show promise in increasing the comprehensibility and bidirectional communication that should accompany informed consent, consensus is lacking on which interventions (e.g., shortened consent forms, the use of clinical associates, etc.) should be used in which situations (e.g., with individuals with low levels of health literacy or with groups whose trust has been compromised by historical racism). Yet, current regulations provide little guidance.

We have argued that the notion of individual autonomy may be too narrow for some vulnerable populations by virtue of its failure to acknowledge their unique histories and current circumstances. Individual autonomy has a different meaning for members of structured groups like American Indians versus unstructured groups with complicated histories that foster group identity like African Americans. This is not to claim that individual autonomy and consent are unnecessary for members of structured or unstructured groups. Our goal is to highlight how focusing solely on autonomy neglects the equally important consideration of the potential impact of individual participation in research on a group as a whole.

New ways of thinking are required to ensure broad participation in research and selection of appropriate methods for obtaining informed consent, namely methods aligned with the source of vulnerability and level of risk. These new ways of thinking might produce guidelines for aligning informed consent models and processes with the characteristics and needs of subpopulations. Broadening our lens to achieve this perspective requires that ethicists, clinical scientists, providers, social and behavioral scientists, community stakeholders, and information scientists work together to devise adequate and sustainable solutions.

Grady and colleagues eloquently describe the promise of big data (i.e., data collated from multiple biomedical, clinical, and social sources) to improve the nation's health.[79] Yet, while combining existing data from multiple sources may at first blush seem innocuous, with the potential gain far outweighing the costs, few have taken the time to calculate how these costs will be distributed across the population. Arguably, those living at the margins of society rather than in its mainstream have more to lose in terms of power when their data are compromised. Likewise, those unable to afford or access consistent health care services will, almost by definition, have less to gain from the benefits of big data.

It is encouraging that the few studies that have been undertaken to solicit the attitudes and perceptions of research and informed consent of vulnerable populations have yielded consistent results, namely that peo-

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ple want to be notified when their data are used. There likewise is evidence that racial and ethnic minorities will participate in research when its purpose and benefits are explained to them comprehensibly.[80]

New ways of thinking are required to ensure broad participation in research and selection of appropriate methods for obtaining informed consent, namely methods aligned with the source of vulnerability and level of risk. These new ways of thinking might produce guidelines for aligning informed consent models and processes with the characteristics and needs of subpopulations. Broadening our lens to achieve this perspective requires that ethicists, clinical scientists, providers, social and behavioral scientists, community stakeholders, and information scientists work together to devise adequate and sustainable solutions.

One means of building trust with communities is to establish ongoing relationships through either community-engaged research (CEnR) or community-based participatory research (CBPR).[81] The two differ in the degree to which community stakeholders participate in the research process. In the case of CBPR, community stakeholders are involved as partners in decision making from the formation of research questions through the interpretation and dissemination of results. In contrast, CEnR can involve less formal and ongoing involvement. Both CBPR and CEnR can involve community and academic partnerships to design informed consent forms and processes for specific research projects and identify the best way to advertise a project and develop a process of recruitment that are based on finding a balance between the requirements of the research project and attitudes and exigencies of the vulnerable population involved.[82]

Both cross-disciplinary team science and ongoing community participation in research have the potential to increase research literacy and trust among vulnerable populations. Over time, these gains can make the determination of which approach is best for which vulnerable population less arbitrary and help to build a science of informed consent that is inclusive of all.

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81. See Ross et al., *supra* note 65; L. F. Ross et al., "The Challenges of Collaboration for Academic and Community Partners in a Research Partnership: Points to Consider," *Journal of Empirical Research on Human Research Ethics* 5, no. 1 (2010): 19-31; L. F. Ross et al., "Nine Key Functions for a Human Subjects Protection Program for Community-Engaged Research: Points to Consider," *Journal of Empirical Research on Human Research Ethics* 5, no. 1 (2010): 33-47.
82. See *id.*

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