

# Perspectives on choice of law challenges in multistate precision medicine research

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## ABSTRACT

Federal law establishes minimum standards for protecting human research participants, but many states have enacted laws that may apply to research. Precision medicine research in particular implicates state laws that govern an array of topics, including human subjects research, genetic testing, and both general and genetic privacy and discrimination. Thus, the determination of which state's laws apply, and under what circumstances, can substantially alter participant rights and protections. To shed light on this topic, we conducted interviews with experts in law, human research protections, and precision medicine research. Our goal was to better understand their experiences with choice of law issues, the effects of state law variation on research practices and stakeholder groups, and approaches to addressing such variation. Interviewees were aware of state-based variation in laws that could be applied to research. However, the extent to which they perceived such variability as problematic differed, as did their perceptions of stakeholder roles and responsibilities for addressing state law variation, and their estimations of requisite knowledge among IRBs and researchers. These divergent perspectives create an ethical and legal quandary, and further empirical and normative work is needed to fully characterize the implications of substantive differences in participant rights and protections.

**KEYWORDS:** Informed consent, Legal rights, Human subjects protections, Research ethics, Precision medicine research, Choice of law

## I. INTRODUCTION

Through the combined study of individual variation in genes, environment, and lifestyle, precision medicine research offers the potential for discoveries that will

improve human health.<sup>1</sup> Spurred by the declining cost of next-generation sequencing,<sup>2</sup> widespread use of electronic health records,<sup>3</sup> proliferation of wearable devices and health apps,<sup>4</sup> and other technological advances,<sup>5</sup> the immense scale required for such research is now within reach.<sup>6</sup>

These same characteristics, however, escalate the challenge of protecting research participants. In contrast to traditional clinical trials (for example, to evaluate the effect of a new drug, device, or other intervention), precision medicine research can be open-ended in nature and indefinite in duration. It commonly relies on the use of specimens and data collected under broad consent for unspecified future use. Thus, a tremendous volume, diversity, and complexity of data can be amassed in the absence of predefined research questions, with actual uses ceded to data access committees or procedures.<sup>7</sup> Furthermore, precision medicine research entails informational risks and harms that are evolving over time along with the scientific and sociopolitical environment.<sup>8</sup>

Federal law establishes minimum standards for protecting human research participants, but many states have enacted laws that may apply to research and may impose requirements or afford protections that differ from other states' laws.<sup>9</sup> Precision medicine research in particular implicates state laws that govern an array of topics—including human subjects research, genetic testing, and both general and genetic privacy and discrimination—which, in turn, can have a significant impact on research practices, including consent disclosures, confidentiality considerations, and offering individual research results to participants, to name just a few.<sup>10</sup> Thus, the determination of which state's laws apply, and under what circumstances, can substantially alter participant rights and protections in precision medicine research.

In non-research settings, 'choice of law' questions are often addressed in advance through contractual agreement,<sup>11</sup> but research settings are unique in at least two ways.

- 1 Francis S. Collins & Harold Varmus, *A New Initiative on Precision Medicine*, 372 N. ENGL. J. MED. 793 (2015); Euan A. Ashley, *The Precision Medicine Initiative: A New National Effort*, 313 JAMA 2119 (2015).
- 2 Ashley, *supra* note 1; National Human Genome Research Institute, *The Cost of Sequencing a Human Genome* (2021), <https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost> (last accessed March 28, 2022); Demosthenes E. Ziogas, et al., *Next-Generation Sequencing: From Conventional Applications to Breakthrough Genomic Analyses and Precision Oncology*, 15 EXPERT REV. MED. DEVICES 1 (2018).
- 3 Julia Adler-Milstein & Ashish K. Jha, *HITECH Act Drove Large Gains in Hospital Electronic Health Record Adoption*, 36 HEALTH AFF. (MILLWOOD) 1416 (2017).
- 4 Sabriya Rice & Darius Tahir, *App-Based Studies Bring Promise, Peril*, 45 MOD. HEALTHC. 8 (2015); Jessilyn Dunn, et al., *Wearables and The Medical Revolution*, 15 PER. MED. 429 (2018).
- 5 Bertalan Mesko, *The Role of Artificial Intelligence in Precision Medicine*, 2 EXPERT REV. PRECIS. MED. DRUG DEV. 239 (2017).
- 6 Benjamin S. Glicksberg, et al., *The Next Generation of Precision Medicine: Observational Studies, Electronic Health Records, Biobanks and Continuous Monitoring*, 27 HUM. MOL. GENET. R56 (2018); Lucila Ohno-Machado, et al., *Genomics and Electronic Health Record Systems*, 27 HUM. MOL. GENET. R48 (2018).
- 7 Christine Grady, et al., *Broad Consent for Research with Biological Samples: Workshop Conclusions*, 15 AM. J. BIOETH. 34 (2015).
- 8 Laura M. Beskow, et al., *Thought Leader Perspectives on Benefits and Harms in Precision Medicine Research*, 13 PLOS ONE e0207842 (2018).
- 9 Leslie E. Wolf, et al., *Protecting Participants in Genomic Research: Understanding the 'Web of Protections' Afforded by Federal and State Law*, 48 J. L. MED. & ETHICS 126 (2020).
- 10 Leslie E. Wolf, et al., *The Web of Legal Protections for Participants in Genomic Research*, 29 HEALTH MATRIX 1 (2019).
- 11 John F. Coyle, *The Canons of Construction for Choice-of-Law Clauses*, 92 WASH. L. REV. 631 (2017).

First, in the ethical conduct of research, informed consent is typically understood as a continuing relational process,<sup>12</sup> not a contractual document.<sup>13</sup> Even if it were a contract, federal regulations prohibit consent forms from including exculpatory language through which participants waive any legal rights.<sup>14</sup> A choice of law clause could result in at least some participants losing state law protections, and therefore appears to violate this provision. Second, federal regulations expressly do not preempt state laws that provide additional protections to human subjects.<sup>15</sup>

Because multistate trials have traditionally relied on local review and oversight by an Institutional Review Board (IRB), the problem of centrally accounting for and reconciling state laws has received little attention—and the transition to single-IRB review<sup>16</sup> under National Institutes of Health (NIH) policy<sup>17</sup> and the revised Common Rule<sup>18</sup> does not resolve this issue.<sup>19</sup> This change may avoid some of the inefficiencies and inconsistencies<sup>20</sup> associated with multiple IRB review by placing this responsibility with a single IRB, but they do not alleviate the need to comply with multiple states' laws, nor do they provide guidance on how to address potentially conflicting requirements. Thus, the nature and scale of precision medicine research, coupled with federal requirements for single-IRB review, are likely to bring choice of law issues rapidly to prominence.

To help inform these issues and contribute to the development of ethical policy and practice around state law variation in multistate precision medicine research, we conducted in-depth qualitative interviews with key informants across the US.

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- 12 Graeme Laurie & Emily Postan, *Rhetoric or Reality: What is the Legal Status of the Consent Form in Health-Related Research?*, 21 MED. L. REV. 371 (2013).
  - 13 Natalie Ram, *Assigning Rights and Protecting Interests: Constructing Ethical and Efficient Legal Rights in Human Tissue Research*, 23 HARV. J. L. TECHNOL 119 (2009).
  - 14 45 C.F.R. 116(a)(6) (2019).
  - 15 45 C.F.R. 46.101(f) (2019) states 'This policy does not affect any state or local laws or regulations (including trial law passed by the official governing body of an American Indian or Alaska Native tribe) that may otherwise be applicable and that provide additional protections for human subjects.' Similarly, HIPAA, GINA and the ADA expressly establish a floor, not a ceiling; see <https://www.hhs.gov/hipaa/for-professionals/faq/preemption-of-state-law/index.html>, <https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination>, and <https://adata.org/faq/does-ada-override-federal-and-state-health-and-safety-laws>, respectively (last accessed March 28, 2022).
  - 16 Ann-Margret Ervin, et al., *NIH Policy on Single-IRB Review—A New Era in Multicenter Studies*, 375 N. ENGL. J. MED. 2315 (2016).
  - 17 National Institutes of Health, *Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research* (2016), <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html> (last accessed March 28, 2022).
  - 18 Jerry Menikoff, et al., *The Common Rule, updated*, 376 N ENGL J MED 613 (2017).
  - 19 Robert Klitzman, et al., *Single IRBs in Multisite Trials: Questions Posed by the New NIH policy*, 317 JAMA 2061 (2017).
  - 20 Bärbel Kastner, et al., *Clinical Research in Vulnerable Populations: Variability and Focus of Institutional Review Boards' Responses*, 10 PLOS ONE e0135997 (2015); Laura A. Petersen, et al., *How Variability in the Institutional Review Board Review Process Affects Minimal-Risk Multisite Health Services Research*, 156 ANN INTERN MED 728 (2012); Jonathan Mansbach, et al., *Variation in Institutional Review Board Responses to a Standard, Observational, Pediatric Research Protocol*, 14 ACAD EMERG MED 377 (2007); Catherine C. Vick, et al., *Variation in Institutional Review Processes for a Multisite Observational Study*, 190 AM J SURG 805 (2005); Rita McWilliams, et al., *Problematic Variation in Local Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360 (2003); Jon M. Hirshon, et al., *Variability in Institutional Review Board Assessment of Minimal-Risk Research*, 9 ACAD EMERG MED 1417 (2002).

## II. METHODS

### II.A. Participants

We conducted qualitative interviews with US experts from stakeholder groups likely to have diverse experiences and perspectives related to determining whether and how different, potentially conflicting, state laws apply in research involving multiple states. Specifically, our recruitment focused on experts in:

- *Law*: Legal scholars and institutional legal counsel at major academic medical centers and independent IRBs
- *Human research protections*: Leaders of IRBs at major academic medical centers, independent IRBs, and relevant national professional organizations
- *Precision medicine research*: Senior investigators associated with prominent multi-state endeavors in precision medicine research

We identified prospective interviewees based on their role and expertise through our professional networks, literature and web searches, and referral sampling.<sup>21</sup> We used stratified purposive sampling to recruit similar numbers of experts with and without a legal background, with the goal of interviewing 10–12 per group, the number expected to reach saturation (the point at which no new information or themes emerge).<sup>22</sup>

### II.B. Instrument Development

Based on our prior work on state law variation,<sup>23</sup> as well as personal experience assisting national endeavors, such as the *All of Us* Research Program<sup>24</sup> and the ADAPTABLE Study,<sup>25</sup> with related issues, we developed a semi-structured interview guide to elicit experiences with choice of law issues, the effects of state law variation on research practices and stakeholder groups, and approaches to addressing such variation. After refinements based on five pilot interviews, the final instrument ([Appendix A](#)) comprised 13 main questions. The Vanderbilt University and Georgia State University IRBs deemed this research exempt under 45 Code of Federal Regulations §46.104(d)(2)(ii).

### II.C. Data Collection

We emailed prospective interviewees an invitation to participate, including a study information sheet. Among those who expressed interest, interviews were conducted by phone or video conferencing between February and September 2020 by two research team members with both legal and qualitative research training. At the beginning of

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21 Emily E. Namey & Robert Trotter, *Qualitative Research Methods*, in PUBLIC HEALTH RESEARCH METHODS (Greg Guest & Emily E. Namey eds., 2015).

22 Benjamin Saunders, et al., *Saturation in Qualitative Research: Exploring Its Conceptualization and Operationalization*, 52 QUAL QUANT 1893 (2018); Kirsti Malterud, et al., *Sample Size in Qualitative Interview Studies: Guided by Information Power*, 26 QUAL HEALTH RES 1753 (2016); Greg Guest, et al., *How Many Interviews Are Enough? An Experiment with Data Saturation and Variability*, 18 FIELD METHODS 59 (2006).

23 Wolf, et al. (2019), *supra* note 10.

24 Joshua C. Denny, et al., *The 'All of Us' Research Program*, 381 N ENGL J MED 668 (2019).

25 Abigail Johnston, et al., *The ADAPTABLE Trial and Aspirin Dosing in Secondary Prevention for Patients with Coronary Artery Disease*, 18 CURRENT CARDIOLOGY REPORTS 81 (2016).

each interview, we reviewed the study information sheet and obtained the interviewee's verbal agreement to participate and for audio recording. Interviews averaged ~1 h in length and participants were offered \$100 for their time.

#### II.D. Data Analysis

We uploaded professionally transcribed interviews into qualitative research software (NVivo 12) and used an overarching grounded theory approach and constant comparison to code and analyze the data.<sup>26</sup> Specifically, the research team iteratively developed a codebook based on key domains reflected in the interview guide as well as themes emerging from a review of transcripts. Two team members independently applied the codes to a starting set of transcripts, comparing the results and modifying code definitions in consultation with the team as needed, until reaching  $\geq 80\%$  intercoder agreement. The remaining transcripts were divided between the two coders, who maintained  $\geq 80\%$  intercoder agreement through constant comparison of ~30% of transcripts.

Narrative segments presented here are exemplary of frequently mentioned ideas; they are labeled with participant ID and primary perspective by which we identified them [law, human research protections (HRPs), research].

### III. RESULTS

#### III.A. Participant Characteristics

We interviewed 22 experts representing a range of perspectives and disciplinary backgrounds (Table 1). Half had a law degree and about half were women.

Despite concerted efforts to maximize racial and ethnic diversity, nearly all our interviewees were white and non-Hispanic. It is unknown how the demographic characteristics of our sample might compare to those of the underlying pool of subject matter experts, which is likely currently small given this somewhat narrow and specialized topic. Among the 44 experts we invited to participate in an interview, 22 accepted, 12 declined (7 Law, 5 Research), and 10 did not reply (1 HRP, 1 Law, 8 Research). Among those who declined, the most common reason was self-professed lack of knowledge.

#### III.B. General Experience with Choice of Law Issues

We began by asking interviewees about their general experience with choice of law issues. The frequency with which they reported encountering such challenges varied. Some said they seldom grapple with it simply because they apply each state's laws:

These generally are not issues for us . . . Our reference point is to tell people that they have to follow the laws of the state where the research is being conducted. (02, Law)

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26 H. RUSSELL BERNARD, et al., *ANALYZING QUALITATIVE DATA: SYSTEMATIC APPROACHES* (Sage Publications, 2nd ed. 2017); GREG GUEST, et al., *APPLIED THEMATIC ANALYSIS* (Sage Publications, 2012); Hennie Boeije, *A Purposeful Approach to the Constant Comparative Method in the Analysis of Qualitative Interviews*, 36 *QUAL. QUANT.* 391 (2002).

**Table 1.** Participant characteristics ( $n = 22$ )

	<i>n</i>	%
Perspective: <sup>^</sup>		
Human research protections	10	45%
Law	7	32%
Precision medicine research	5	23%
Academic degrees:*		
MPH	3	14%
Other master's degree (eg MA, MS, MBA)	8	36%
JD, LLB/LLM	11	50%
PhD	4	18%
MD	8	36%
Institutional affiliation: <sup>^</sup>		
Academic medical center	12	55%
Healthcare organization	3	14%
Law school	3	14%
Independent IRB	2	9%
Private law firm	1	5%
Professional association	1	5%
Gender:		
Women	12	55%
Men	10	45%
Race:		
White	20	91%
Other race	2	9%
Ethnicity:		
Hispanic or Latino	1	5%

<sup>^</sup> Primary perspective for which we identified interviewee; many could have been recognized in > 1 category.

\* > 1 per interviewee.

Others, however, described choice of law as a common problem they contend with regularly:

I can think of at least four or five different projects on my desk right now that implicate those [issues], and I've had many, many projects over the course of my career that have implicated them. So, I would say very frequently in my practice—maybe 50% to 60% of the time—a new project that I see will implicate an issue like that. (07, Law)

When discussing their experiences, interviewees recounted several broad types of challenges. First, they emphasized the complexities associated with assessing the 'location' where precision medicine research is being conducted:

I can traditionally say, 'I'm doing the research here'—and now you have to think about, 'Well, where?' . . . What we had to do in our system was, we added a series of questions about where the research's taking place . . . But I will say, even though we asked those questions, it's still sometimes hard to know what to do with the answers. (08, HRP)

Essentially all said the location of investigators and their institutions was a key consideration. Many also gave substantial weight to where participants are located:

A lot of times researchers tend to think . . . it's just the laws where their institution is that should be the only relevant thing or the mainly relevant thing. And that, of course, may be one answer, but as we know from telehealth and other contexts, that's not generally how state laws work. Most of the time, I would say, they are triggered based on where the subject or the participant is located. (07, Law)

They typically viewed the place where biospecimens and data are stored as important for security reasons but less so for choice of law issues:

It's not a huge issue, either from a regulatory or an ethical perspective. As long as they ensure us they have the appropriate security provisions in place, where it's actually stored doesn't come up. (01, HRP)

A few, however, spoke about growing issues related to data storage [such as 'the complexities of the cloud' (11, Law)], as well as downstream uses of data:

I think the challenge is recognizing that we can never anticipate all of the potential downstream uses of data, and all the potential nefarious things that could happen that would cause harms to participants . . . I don't have an answer to what should apply other than to say, I think we're seeing some of these rationales play out in the broader conversations in the US about consumer data or more comprehensive data protection legislation, specifically with this kind of notion of federal preemption. Should California's data practice policies apply to everyone everywhere? Or do we need something that applies to all NIH-funded research, for example, that says everyone's going to play by these rules? I think there are a lot of aspects to these challenges that haven't really been considered and discussed in ways that they should by the experts, by the scholars, by the researchers to really understand how those decisions would affect research and whether it would have a chilling effect on participation or a chilling effect on researchers' willingness to enroll individuals from different locations. (11, Law)

Another broad challenge interviewees described was the difficulty in determining whether and how state laws apply to research:

The area that's probably the most difficult is figuring out the applicability of laws that are not written specifically for research . . . A lot of those genetic statutes about privacy, they don't mention the word 'research.' Some do. Some have carve-outs for research. Some don't. A lot of times, it's really hard to figure out when those apply to a research project. (01, HRP)

As one noted, the rapidly evolving nature of precision medicine research may exacerbate this challenge:

You have to realize that there's an enormous amount of laws and regulations that lag behind the use case that you're in, and that were actually written for a different time and a different purpose... Almost by definition, you're trying to find a new use for genomics, you're trying to develop a future forward perspective on healthcare. (19, Research)

When discussing their experiences, interviewees also referenced general content areas in which choice of law questions arise, some with primarily pragmatic/operational impact and others with more substantive implications for participant rights and protections. Most commonly mentioned were genetics, including laws related to genetic privacy, return of genetic results, licensure of genetic counselors, and insurance discrimination; data-related issues, such as registries and databases, data sharing, and combining datasets; and informed consent from children, surrogates, and legally authorized representatives, as well as electronic consent. See [Appendix B](#) for specific examples.

### III.C. Risks Associated with State Law Variation

When discussing the effects of choice of law issues, interviewees tended to focus primarily on risks to institutions and to researchers (and the research enterprise):

There are a number of issues that you can conceive of where there might be relevant choice of law issues. I would doubt that any of them are going to be the major risk areas in a study, but it's part of the whole calculus of—not risk to participants so much—but risk to the researchers and institutions of not complying with something they may not have been aware of. (22, Law)

Although a few described 'a high level of liability [which] my institution has talked a lot about and struggled with' (13, Law), most assessed the risk level as low:

You've always got more uncertainty and hence potentially more risk, the more jurisdictions whose laws apply, because you may not know about them to be able to comply with them. How real those risks are is, of course, another question. In general, I think the answer to that is the risks are really quite low, probably not zero. (06, Law)

These interviewees offered several reasons why risks to institutions and researchers might be low. First, the traditional approach typically places the responsibility for knowing, following, and informing others of local requirements with each study site:

[Serving as the central IRB], you have reliance agreements and they set out the responsibilities, and our reliance agreement states specifically that the sites are responsible for being knowledgeable about their local laws and regulations that impact the research. So, we put that responsibility back on the sites. (02, Law)

Second, several described minimizing risk by taking a deliberately cautious approach to state law interpretation:

We shy very far away from doing anything that we think might be a problem for state law. That's why the institutional interpretation of [state] laws can be quite conservative. (05, Research)

Third, a few suggested that the risk of enforcement action by states in the context of research may be low:

In terms of enforcement risk from states, if you get this wrong and you do something that doesn't comply with state law, my sense is that in the research context, overall, that risk may be quite low. . . . I think a lot of researchers and IRB people sometimes [say],



“It’s research. It’s a research project . . . It’s something that is related to health and public health, or something important for the welfare of the residents of that state. So, what’s really the likelihood that they’re going to come down hard on us?” (07, Law)

Finally, many pointed to the historical lack of lawsuits as the basis for assessing the risks as low:

You never see lawsuits brought about research . . . Almost never . . . If it’s not [a study] where there is an intervention, but one where there’s just data, the chances that anybody is going to be motivated to bring a suit seem to be relatively low. (06, Law)

Interviewees recognized, however, the problem with relying on the lack of published court decisions:

There’s not a whole lot of lawsuits that have made it to court that involve research . . . And the ones that do tend to settle. So, it’s hard to get data about the actual case because they tend to settle with a confidentiality agreement. (01, HRP)

Furthermore, they acknowledged that a successful lawsuit is not necessary to bring attention to a grievance against researchers, institutions, or the research enterprise:

Just because you don’t necessarily have a private right of action doesn’t mean that you can’t try. It doesn’t mean that you can’t cause a really big public stink. It doesn’t mean that you can’t out, not just an individual researcher, but the institution where that researcher works, and really turn toward the court of public opinion to find some sort of resolution that might or might not involve monetary settlement. (11, Law)

Finally, some noted that, although the likelihood of harm may be low, the severity or magnitude could be high:

Is there a potential risk and liability? Yes, absolutely. And that’s going to come out when something bad happens. Most of the time, bad things don’t happen, but if we informed people the wrong way, or we didn’t pay attention to a state law and some research subject was entitled to those protections in their state . . . that is a big, huge liability issue, and it’s going to happen . . . When you look at risk/benefit, it’s the magnitude and the [likelihood], and I think the magnitude would be high. How often that would happen is probably going to be low, but it doesn’t mean that we shouldn’t worry about it. (09, HRP)

Regarding the effects on participants, several interviewees opined that variation among state laws does not change the level of research risk per se:

I’m not sure that I see much in the way of risks to participants. I think this is almost all related to risk to investigators for violating state law. But [the protocol] is vetted for risk level and that doesn’t really change based on state law. (17, HRP)

Interviewees did, however, express a range of views as to the impact of state-based variation on participant rights and protections. A few described such variation as ethically problematic:

I think ideally—and Lord knows we spent hours talking about this—if in [State X], our participants get higher protection because of some state law or some local policy, it does give me the creeps to say, “Well, if you’re from [State Y], you’re going to have higher risk because your state doesn’t have that.” For me, that doesn’t feel great. (03, HRP)

In contrast, some said that state-based differences are a fact of daily life, given our system of government . . .

Say that participants in one state had a greater right to recover damages in the case of an injury than participants in another state. Under just general state principles of tort law, I think that’s an ethical issue, but it’s more of an ethical issue with the lack of uniform standards on a lot of issues in our country due to the nature of the federal system. I don’t think it makes the research unethical . . . The disparity is just because the different states offer different levels of protection to their citizens. (22, Law)

. . . and may be substantively important:

I think each state has a reason for implementing the laws that they have . . . And respecting the people in that jurisdiction is important. From a safety perspective or rights or welfare perspective, if those states have felt strongly enough that they passed legislation to put these things into law, then there may be something unique about their patient population that requires additional protections or vulnerabilities or there may be cultural things that they would like to protect the rights and welfare of their people against discrimination, against insurability or lack of insurability or other similar nature things. (04, HRP)

Some interviewees suggested that the impact of state-based variation on participants was tempered by federal regulations that provide a reasonable set of minimum rights and protections for all:

Given that we have a floor of federal regulations—I’m sure they can be improved, but nonetheless—it seems hard to argue that research that was consistent with federal regs would be risky for participants in some states, but not others. (20, HRP)

#### **III.D. Approaches to Addressing Choice of Law Issues**

Interviewees described two basic approaches to addressing choice of law challenges. The first was to meet each state’s requirements. Indeed, some interviewees perceived no alternative:

It’s interesting the choice of law issue, because as a reviewing IRB, we have to be knowledgeable about the laws, but we don’t have much choice in applying them. (10, HRP)

More commonly, interviewees simply seemed to accept the need to accommodate state-based variation, particularly in the context of more pragmatic or operational issues. For example, discussing whether the age of majority is 18 in one state versus

19 in another, one interviewee recognized, ‘We call it conflict of law, but [in] most of these cases, they’re not conflict of law, they’re just different requirements’ (01, HRP).

A few, however, noted there may be limits to willingness to accommodate different state laws, depending on the impact on accrual goals. For example, referring to experience handling the disparate provisions of several large states, one interviewee noted:

This was a significant percentage of the sites and potential subjects who wouldn’t be involved in this study and that’s why we were committed in finding a solution to it. If it was going to be an overbearing, extremely time-consuming process for one site, somewhere in the upper Midwest that’s going to contribute 2 of 1600 patients, then we may say, “You know what, we’ll take our resources and use them in a more judicious manner.” (04, HRP)

The second general approach interviewees described to addressing choice of law challenges was to identify the most conservative or restrictive requirements and apply those across all sites:

What you tend to find is one state’s more conservative than the other states. And you go to the most restrictive law. (05, Research)

They acknowledged that such an approach is not without cost. For instance, describing the effect of meeting the higher bar when faced with differing state requirements for the use of a CLIA-certified lab to generate results that would be returned to participants, one interviewee said:

That actually ended up that the investigators decided to change their practices and switched to a different laboratory that was going to be conducting the study at a pretty substantial increase in cost so that they would be done in a CLIA certified environment . . . The majority of states didn’t say one way or the other on this matter. It was a few sites within a few states that caused global change for the entire study. (04, HRP)

Furthermore, several pointed to the possibility of sites not participating if they are unable or unwilling to meet a uniform standard:

[State law differences] can almost always be addressed by just going to the least common denominator. Everybody who’s enrolled has to meet the standards of the most stringent state . . . But occasionally you do have a team that says, ‘No, I’m not going to do that.’ That’s their choice and they may drop a site because of that—because it’s too difficult. (17, HRP)

Taken together, these discussions highlight the trade-offs involved in choosing between these approaches—meeting different requirements versus setting a uniform bar—including the feasibility of monitoring compliance with varying requirements versus pushing for uniformity when some sites may not be able to comply. As one interviewee summarized:

You’d have to be able to track where your participants are located, which rules would apply to them, and . . . think about how you can comply with one and not the other. Logistically,

is that going to happen? Or will that stop research? I think operationally, it could put a halt to a project. If [researchers] think about, well, this [is] multiple organizations in different locations, and we want them all to do the same thing—I think that’s one of the places where it becomes complicated. Because why wouldn’t they just get rid of a site that can’t comply? Or push the research in a different direction to avoid this inconsistency? (11, Law)

The difficulty in making these trade-offs is further exacerbated by variation in institutional policies, which interviewees often described as even more common than variation in state law. Although many acknowledged that institutional policies are not legally binding . . .

It’s easiest if there’s a state law, because usually people aren’t going to question that and they’re not going to second guess that... When you get into institutional policies, there’s a lot more room about interpretation. (09, HRP)

. . . they also recognized that such policies may be deeply held and perhaps decisive with regard to site participation:

We’ve had a fair number of instances of institutional policies that prevented something from happening where otherwise we would expect the protocol to go through. In a few cases, it might have caused that site to just not be able to participate . . . I can remember one where it was really critical that they be involved, but they had a very strict policy at their site, which was very different from any other site, and we ultimately got [the lead institution] to accept that as a unique term—but it wasn’t over a state law. It had more to do with intellectual property rights that that particular institution required be preserved, which [the lead institution] wouldn’t have agreed to, but we got them to do it because it was really critical that this site be a part of it. (16, Research)

Interviewees’ discussion of consent form development illustrates these different approaches to preemptively addressing choice of law issues. They commonly asserted that many aspects of the consent form could and should be standardized across a multistate study, emphasizing the description of the research itself:

If you have one single consent form template, that should standardize the risks, the safety procedures, the monitoring. (02, Law)

Even so, they generally believed that at least some consent form elements must be allowed to vary. Information about research injury was a common substantive example. A few interviewees pointed to the Common Rule as enabling such variation because, rather than setting a uniform standard, it requires only that participants be told whether or not any compensation or treatment is available in the event of research injury:

Even at an independent IRB, the sites have control over the compensation language and the subject injury language. They can change that and that is specific site language you can’t take away from the site. A sponsor or a main site can’t tell a site in another state what the subject injury provisions will be for that institution. Because again, the regulatory

requirement is just whether there's compensation for research-related injuries, not that there has to be . . . So you get an element of variability even with a single IRB. (02, Law)

More broadly, several observed that US research regulations prohibit language in consent forms that requires or appears to require participants to waive any legal rights. Thus, if a standardized form contained a provision that contradicted a particular state's law, several interviewees raised the question of whether that would constitute such 'exculpatory language.' Furthermore, a few emphasized that consent forms are not contracts . . .

At least in contractual situations, typically the contract will have a choice of law provision in it. I don't know that I've ever seen a consent form with a choice of law provision in it nor do I think that would be a good idea. (06, Law)

. . . and that choice of law provisions typically found in contracts (eg stipulating one particular state's law that would apply) would be unlikely to favor participants:

Choice of law contracts provisions usually serve the party with the biggest bargaining power. So, they're unlikely to serve the interests of the research subject. (15, Law)

Beyond the general conception that at least some consent form language must be allowed to vary, interviewees expressed a range of opinions about the extent to which site-specific language should be accommodated. Some advocated that variation should be limited to that required by state laws per se:

For a particular study, I think having the same basic consent form is really, really important so that if you're joining from any state or wherever you're joining from, you are getting the same information. But at the same time, I would have an editable part if there were some state law that required something else. (03, HRP)

Others were willing to accommodate differing institutional interpretations of laws, as well as institution-specific policies:

We have state and local law requirements that I think it's better to accommodate, honestly. You'll have a very hard time coming to a [uniform] consent template because there's also issues that are embedded in local cultural considerations, the population that you might be targeting. So as much as possible, you have your template consent . . . that doesn't change. But I think you have to be able to accommodate some state law and institutional policy considerations. (10, HRP)

### **III.E. Responsibilities for Navigating Choice of Law Issues**

When we asked about responsibilities for navigating applicable state laws, interviewees seemed to agree on three basic aspects. First, it would be unreasonable to expect research participants to understand or negotiate choice of law issues that might affect their rights or protections:

A lot of studies have shown that patients have no idea what they're consenting to. They don't know their rights they're giving up. (15, Law)

Second, the move toward the use of a single IRB in multisite studies is generally positive . . .

I'm a huge proponent of single IRBs. They're a way to enable us to do research that needs to be done. (12, Research)

. . . but not a panacea for choice of law challenges and may, in fact, accentuate them:

There are laws created that people aren't super knowledgeable about. There's a ton of moving parts. To expect any one IRB to be able to digest all of the state law information, and get it right 100% of the time, is not great. It won't happen. (10, HRP)

Third, responsibility for knowing state laws lies primarily with each participating site, given the convergence of local context and legal compliance:

The only way to do this, realistically, is to give the responsibility to the local IRB or some individual or office at the local institution who can look at a protocol and provide that local context. You talk about local context in research review—to me, this is one of the most substantive components of that. So, it has to be a local site looking at it and saying, 'Is there anything about this protocol that we have concerns about, specifically because of the laws of our state?' (20, HRP)

I think it first lies in the local institutions, that if they're allowing research to be conducted at their institution, they have to ensure it's in conformity with local law. The fact that they've delegated oversight to the [single] IRB doesn't exempt them from the legal compliance job. (22, Law)

Beyond these starting premises, interviewees expressed different opinions regarding the roles and responsibilities for single and local IRBs and for researchers, and the processes among them. Several described the single IRB as having an active role in prompting participating sites about local requirements:

Most institutions have developed some type of local context form. We've developed it when we're reviewing IRB, and we've received them from other places where other institutions say to us, 'Tell us about these specific things. Tell us about the state laws on this . . . Here's a copy of the informed consent. These are the areas that we know state law can differ. Tell us what you need to say there to be in compliance with your state law.' (09, HRP)

Others portrayed the single IRB as having a more passive role, with the expectation that participating sites would raise concerns as needed:

What we do [as the single IRB] is require each institution to at least see and evaluate the studies and identify any issues that may be pertinent to their locale. We rely upon them to identify those issues on our behalf because we don't have legal counsel or other resources that are equipped to manage that type of work. (04, HRP)

Indeed, some described having a comprehensive process, as a participating site, to ensure their local requirements are identified and communicated:

What we require locally is something that we call an external IRB application. It's basically an application that still comes into our IRB system. But it is essentially a shell of an application that would be normally submitted to our IRB for review . . . We do a full regulatory review for local compliance with state law and institutional policy. We don't redo a review for patient and subject protections regulations because that's done by the reviewing IRB. We ask for appropriate documentation of those accommoda-

tions. But what we do is a full review of compliance with our local policy and state law. (10, HRP)

Interviewees typically expected that issues pertaining to applicable local laws would be documented in reliance agreements, along with associated roles and responsibilities:

There's a framework now with many of the reliance agreements where they address this issue of applying local law and, between the reviewing IRB and the relying sites, they spell out a process for who's going to identify what the relevant laws are, who's going to interpret them, who's going to communicate the requirements of those laws, and who's going to apply them to the research. (07, Law)

Despite identifying IRBs as having a key role in navigating choice of law issues, interviewees raised several concerns about them. They pointed to variability among IRBs and, perceiving them as 'charged with applying the federal regulations and reviewing ethical issues in a general sense' (22, Law), questioned their knowledge of state laws:

We definitely have to rely on the local institution to tell us and that I think of as good—but it's also a little bit scary because what if they don't have the resources to keep up, even on their own laws? (08, HRP)

Interviewees were also apprehensive that, without standard processes and adequate resources to address choice of law issues, there was the potential for missed information:

First, if you've seen one IRB, you've seen one IRB. Every IRB seems to be different. It's lots of variation in terms of what IRBs do and don't do. Second, I've never heard of an IRB . . . carefully saying, here are all the legal requirements that you particularly have to abide by . . . Some IRBs, under some contexts, will point out some laws, but I'd be really shocked if they purported to give you a nice, complete list of the laws that are relevant under their states. [Third], even if they did give you a list, there's no way in hell that the institution's lawyers are going to let them say this is a complete and full list of all the legal requirements you have to follow. (06, Law)

With regard to researchers' responsibilities for being aware of and complying with state law, interviewees articulated divergent perspectives. Some suggested that researchers have substantial obligations:

It's on the researcher to understand the full panoply of laws, tribal rules . . . whatever it is their patient population encompasses, the researcher has an obligation to understand what the rules are that might apply . . . From my perspective, the researcher has the obligation, and if they breach that obligation, then the lawyer in me will say it turns into a negligence standard. Did they exercise reasonable care in researching what protections are applicable? If that means every researcher has to have a lawyer on the team or consult with the lawyers at their institution, then I see that's an added administrative hurdle, but I think it's a necessary one. (15, Law)

However, perceptions of researchers' legal knowledge were mixed. Some interviewees had low expectations for researchers' legal acumen:

Having worked with a lot of investigators with legal questions, I don't want my investigators to be individually responsible for looking up state laws. That is not a good choice at the institutional level, because they don't know what they're doing. And that can't be their responsibility, because they cannot be held responsible for their interpretation of the law, it's way too complicated. That's not what their training is. (13, Law)

Others—particularly interviewees who were themselves precision medicine researchers—described researchers as well informed about the kinds of legal issues implicated in their work:

I just am so immersed in the field of genomics and clinical research and clinical care that I just have a general knowledge of these things. (19, Research)

They also underscored their detailed knowledge of their research protocols, and the crucial intersection between that expertise and prioritizing and resolving choice of law challenges:

Most of the burden has been born by the legal teams. To a certain extent, sometimes we get a little frustrated with that because we don't even know what's going on. They're arguing back and forth about something and they don't even tell us that this is an issue. All we notice is it's taking a long time and then we'll finally realize that that's happening and push on them and then it comes up that the thing they were arguing about didn't really make any difference to us. (16, Research)

A few confided that—absent clear leadership and guidance for handling choice of law issues—they would proceed with their research based on what they believed best:

We're academic researchers, we're not artists, we're not astronauts, we're not really brave in the sense of taking a lot of risks. But to accomplish what we need to accomplish, we do have to try to decide which written and unwritten rules to strictly follow, and which ones we are simply going to less strictly follow. Not necessarily break, but remain ignorant of, ignore. This is the equivalent of bravery in a researcher's life, and it's what you have to do to get stuff done. (19, Research)

Given the lack of shared vision and expectations for the roles and responsibilities of IRBs and researchers, and the processes among them, it is perhaps not surprising that some interviewees expressed concern about gaps in addressing choice of law issues:

I think there are some misconceptions along the way. Some people think this is the researcher's job. Some people think it's the relying organization's job. And when everybody thinks it's somebody else's job, nobody might be doing it, right? (10, HRP)

Of course, the catch 22 is, if it's too much work for the researcher and too much work for the IRB, then the research subjects get left in the dust. Because everyone throws their



hand up and says we can't figure this out or we shouldn't be responsible for figuring this out, so don't hold us to it if we haven't gotten it correct. (15, Law)

### III.F. Resources for Navigating Choice of Law Issues

Across discussions about responsibilities for addressing choice of law challenges, interviewees highlighted several kinds of resources needed. First and foremost was both time and expertise:

The time and resource burden of dealing with these issues is not insignificant . . . A lot of legal time and resources and money can get spent on these issues. A lot of internal administrative IRB time and other time can get spent on these issues. (07, Law)

Many described the need to consult institutional legal counsel . . .

We've gone to institutional resources, particularly in this case, the Office of General Counsel to try to get clarity and direction and advice . . . The last thing we want to do is put either any of our staff or the institution at risk by doing something that violates law or regulation. (20, HRP)

. . . although noted that even their time and knowledge may be limited:

In general, we have tried to make it work. We certainly have thrown a lot of questions to other people, other institutions. We've asked our legal counsel for some assistance, if we feel like we're not getting somewhere. We can barely ask our legal counsel to help us, I mean, they're so busy—interpret the state laws for us? If we started asking them to become experts in every state law and doing the research into that and how it applies, we couldn't do that. But they have helped out. (09, HRP)

Thus, some mentioned seeking advice from external legal counsel under certain circumstances. For example, in the context of a large-scale, long-term project, one interviewee explained:

This is beyond the usual expertise of in-house counsel . . . So, we contract with a lawyer who is part of a firm that specializes in health law and health law privacy. We would refer it to our retained counsel if there was a state law question. . . . When those questions surface, we encourage their counsel to talk with our counsel, and we say, 'Look, we will pay our counsel's bills to advise your in-house.' (12, Research)

Many interviewees advocated for a widely accessible database of state laws that either comprehensively catalogues relevant laws . . .

There needs to be some . . . central trusted resource that outlines the federal requirements—those are kind of more straightforward—but then go state by state. It literally lists every state. Has laws that are applicable in [each state] that deal with genetic research, that deal with reproductive health, and kind of go down a reasonable laundry list of types of research. . . . May be that can help IRBs streamline what they need to do. (15, Law)

... or calls out unusual state law variations:

It would be nice if NIH funded somebody to do a nice project laying out: here, in each of the US jurisdictions, are special peculiar laws that you should be aware of and concerned about, should the laws of that jurisdiction happen to apply to any of your research subjects. That would be a good way to become aware as a practical matter. (06, Law)

Several highlighted efforts by the Streamlined, Multisite, Accelerated Resources for Trials IRB platform<sup>27</sup> to develop these kinds of resources:

There's a separate group that is part of the CTSA that has actually developed software that I think hundreds of institutions are now using to record and document their institutional preferences and state laws so that they're more readily available. There's been a lot of work put into this ... and they've been an invaluable resource to us. (04, HRP)

Interviewees emphasized that such databases would need to be continually updated and include not only the laws, but also easy-to-understand information about their interpretation and application to research:

It'd be so nice if we could have a resource that we all could use, that would be low cost and it would be up to date and that would not just tell us what the law is, but how could you possibly operationalize that requirement so you're not having to figure all that stuff out. (08, HRP)

In addition to a database of applicable laws, many interviewees called for 'guidance on how to think through which state's law applies to different issues' (22, Law). They commonly named professional groups or other authoritative bodies that could take on this task:

Maybe this is where sort of overarching ethical bodies or some organization like AAHRPP or JCAHO or AAMC... or IOM or something, puts out points to consider or recommendations. (14, HRP)

As one interviewee noted, however, even these entities might lack the requisite expertise:

It's really a specialized field, of choice of law. Guidance would have to be developed by lawyers who have expertise in choice of law. So SACHRP could certainly consult with people like that, but the membership of SACHRP itself is not really the appropriate group to be resolving issues. (22, Law)

Interviewees also discussed the federal government's role in providing guidance or setting national standards, eg '[The] Common Rule should just be more expansive and incorporate more granular guidelines or regulations in order to simplify things' (15,

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27 Nichelle Cobb, et al., *The SMART IRB Platform: A National Resource for IRB Review for Multisite Studies*, 3 J. CLIN. TRANSL. SCI. 129 (2019).

Law). Some, however, were circumspect about whether the federal government has the authority or even the will to act in this arena:

While it's helpful for the federal research regulatory agencies to acknowledge that these issues exist in multi-site studies... those agencies don't really have the authority to solve the issues that come up under state laws, and so . . . what can guidance from a federal level really do on this? (07, Law)

I can't imagine OHRP is going to do that since they deal with federal regulation and not state regulation. I have a feeling this is going to have to come from either an academic institution as a project that an investigator takes on or from one of the professional societies. (17, HRP)

Ultimately, interviewees indicated that guidance from the federal government or other authoritative group (eg a professional society) might be useful . . .

It would be very helpful for people that are engaged in these research specific questions to provide some sort of guidance, even if it's just a paper, in case courts would have to address this so that they wouldn't be doing it completely cold. (11, Law)

. . . but of uncertain effect:

I think guidance could be useful. It's not going to have tyrannical effect. It's not going to have any legal power. If a court of common pleas judge in [County, State X] has a suit brought in front of her from some [County] citizen who somehow was involved in a research project run out of [Institution in State Y] and thinks she has been harmed and wants [State X] law to cover it, the fact that a sort of guidance has been issued by a thoughtful expert committee may or may not have any effect on that judge's decision. (06, Law)

Thus, one interviewee suggested, 'There would have to be almost a consortium of state government representatives looking at this to produce any guidance that might really be reliable on how to address these issues' (07, Law)—but went on to elaborate the potential pitfalls of this approach:

It's quite apparent that many states don't really have a great understanding of the work that healthcare institutions are doing in the research space that implicates their own state laws, so it might be a bit of an uphill battle to get states to be aware of this—but maybe the pandemic will facilitate some of that. (07, Law)

Another predicted that raising awareness of inconsistencies between states (eg through a compilation of state laws) could prompt change at the state level:

In helping get change to happen, to be able to go to a state and say, "You're the only state with this requirement" or "It's in conflict with all of the other states because the legwork was done by this group. Can we try to get this changed? It's in conflict." Right? So a compendium of the laws, particularly ones that are in conflict, would be very useful. (21, Research)

Finally, interviewees recommended education about roles and responsibilities in understanding local laws and choice of law issues, including for researchers who might have expected that the single IRB model would be ‘the magic potion that everything’s going to be much more streamlined and faster and harmonized’ (08, HRP). Educating researchers was also thought crucial because of their role in ensuring the application of laws and policies in the day-to-day conduct of their work:

I think education for the investigators [to] explain all of this and say, “Here’s your job in this. You still have to carry out the study in accordance with the state laws, so you’ve got to keep your eye out if something has been approved by the reviewing IRB that doesn’t jive with your local.” (10, HRP)

### III.G. Future Issues and Directions

We asked interviewees about an emerging study design involving only one site that recruits participants directly from potentially any state (without a local site), eg over the internet or through social media. Known as ‘direct-to-participant’ research,<sup>28</sup> investigators capitalize on new technologies such as home biospecimen collection kits, data capture through mobile health devices and apps, and personal health records controlled by patients. This approach brings choice of law issues to the forefront, highlighting the challenges associated with defining the ‘location’ where the research is taking place. Many interviewees indicated that the investigator’s location would be controlling in terms of applicable law:

There has to be a PI, there has to be a site. There has to be a basic place that’s conducting the research. So in that situation, where it’s an internet survey or something like that, we would say that it’s the place... where the PI is located and the research is being conducted. (02, Law)

Some supported this position with reference to the regulatory concept of ‘engagement’ in research:<sup>29</sup>

If the investigators at [Institution] are the ones conducting the study, they’re the ones engaged in the study. They may be soliciting people from all across the country but the institutions and facilities where those patients seek their medical care are not engaged in the conduct of the study. (04, HRP)

Other interviewees, however, considered participants’ location to be a key consideration:

Is the participant leaving his or her home to do anything? If not, if they’re doing things from the convenience of their own home, then it’s hard to tell them that they should be availing themselves to rules that apply elsewhere. (11, Law)

28 Mark A. Rothstein, et al., *Legal and Ethical Challenges of International Direct-To-Participant Genomic Research: Conclusions and Recommendations*, 47 J. L. MED. & ETHICS 705 (2019).

29 U.S. Department of Health & Human Services, Office for Human Research Protections. *Guidance on Engagement of Institutions in Human Subjects Research* (2008), <http://www.hhs.gov/ohrp/policy/engage08.html> (last accessed March 28, 2022).

The importance of participants' location was especially prominent in situations where prospective participants are identified (and thus their locations known) in advance, eg through a disease advocacy organization:

It would depend on what your recruitment was. If you're just going on social media and saying, "Contact us if you're interested," we just do a single [site], "This is what we do." . . . As opposed to, if you were going to get the names of everybody in five different states who had a particular disease and actively recruit them, then we'd really want to know what the local situations were. (03, HRP)

Overall, interviewees underscored the unsettled nature of direct-to-participant research—as illustrated by one who said both 'I love this idea of research that isn't bound by the walls of a single institution' and 'It makes me nervous to suggest that an institution could do that' (20, HRP). Due to the difficulties of determining which laws might apply given the range of possible states involved, several predicted that choice of law issues might need to be worked out after the fact:

Part of the problem is that you don't know where all these people are when they go on the internet and they do whatever they're doing. But the one thing you do know is where the investigator is located. So I think . . . you hire a lawyer and figure it out if somebody's upset. (02, Law)

Beyond this particular emerging study design, interviewees commonly anticipated that navigating choice of law issues in multistate precision medicine research would involve increasing complexity and risk in the future:

I would suspect that the likelihood of these types of issues is higher when precision medicine, personalized medicine, genetics, genomics are involved just because I think more states are becoming more sensitive to those topics. (04, HRP)

Some of these things are just going to become more obvious as we get more experience and as more things go to a single IRB . . . When we start taking responsibility for what other IRBs would be doing or picking up, there's heightened risk there. Honestly, I think it's a matter of time before we have some exposé of something that went wrong and some IRB didn't pay attention to a state law. (09, HRP)

Several reflected on the continuing priority that should be given to participant protections, rights, and remedies:

[In] multi-site research, whose law and what law do you respect and need it to be identical across every site—or not? I don't think that's an answered question . . . To me it seems that there are two pieces. One is the legal question, which I can't answer, as I'm not a lawyer. The second is the ethical question: whether you should give a right or permission to one participant in a study that you do not give to another. We do it lots of times. We have different conduct for different individuals, even within the same study. But I think that one would, if one were aware of all these laws, [be] thinking about what the foundational principles are and whether it would be possible to apply the most protective [approach] in a good way . . . in terms of promoting the rights of individuals more forcefully. Whether that's possible to do, and why it is not if it is not. (18, HRP)

#### IV. DISCUSSION

States have enacted a significant number and variety of laws that are potentially relevant to precision medicine research.<sup>30</sup> Such laws could substantively influence a wide range of research practices, and thus have important implications for participants' rights and protections. To shed light on this little-studied topic, we conducted exploratory qualitative research with key informants—experts in law, human research protections, and precision medicine research—across the US. Our goal was to better understand the experiences of these professional stakeholder groups with identifying and determining which laws might apply in multistate research; perceptions of the risks posed by variation in state law to researchers, institutions, and participants; appropriate approaches to and responsibilities and resources for addressing state law variability; and expectations for the future in this realm.

In our study, all interviewees were aware of state-based variation in laws that could be applied to research, including laws related mostly to pragmatic/operational issues, as well as those with more substantive effect. This included familiarity with the complications surrounding laws that were not written for research per se (eg privacy laws related to 'genetic testing'), as well as the complexities arising from the characteristics of precision medicine research in particular (eg the multiple places where the conduct of such research could be located). However, the extent to which our interviewees perceived state law variability as a problem in multistate precision medicine research differed depending on their assessment of the likelihood and magnitude of the risks, their opinions regarding the significance of the variation (whether it is simply a fact of daily life in the US versus ethically troubling), and their view of the appropriate approach to addressing it (apply each state's laws versus strive for uniformity).

These divergent perspectives create an ethical and legal quandary, and further empirical and normative work is needed to fully characterize the implications of substantive differences in participant rights and protections. Arguably, in the context of health-related research, the acceptance of state law variation as a fact of life in the US ignores the crucial ethical distinction that, although daily life typically involves activities in pursuit of self-interest and outcomes that accrue to the individual, research participation asks individuals to volunteer to take on risks for the collective good, with no promise of direct benefit. The collective good is generalizable knowledge for the benefit of society and, in the case of large-scale precision medicine research, the unified endeavor (and outcomes) to which people are asked to contribute transcends state borders.

Another of our findings further illuminates the quandary: Our interviewees observed that state law variation can influence study site selection, as willingness to accommodate more onerous state requirements may be a trade-off with that site's expected contribution to accrual goals. Such trade-offs could further disadvantage already marginalized groups; for example, if states comprising large rural areas have more onerous requirements, rural populations (and the health problems they face) will continue to be underrepresented in research. This finding also suggests an assumption that site location is the most relevant factor in determining which state's laws apply. However, our workshop with choice of law experts and research law and ethics

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30 Wolf, et al. (2019), *supra* note 10.

experts—during which we asked them to consider a range of ‘places’ (eg the place the participant currently resides, the place the wrong/harm occurred), as well as other traditional choice of law factors (eg the justified expectations of relevant parties, the certainty, predictability, and uniformity of results)—indicates that that determination may be more complex than is currently understood.<sup>31</sup>

Furthermore, our interviewees’ perceptions of stakeholder roles and responsibilities for addressing state law variation differed, as did their estimations of requisite knowledge among single IRBs, local IRBs, and researchers. This finding is consistent with a recent national survey<sup>32</sup> in which IRB administrators, chairs, and members were asked about the use of a single IRB for multisite studies. Approximately 80% expressed concern about the allocation of authority and responsibility across sites, and a substantial minority thought use of a single IRB would weaken human subjects protections. These concerns come amidst persistent questions about the purpose and function of IRBs more generally.<sup>33</sup>

One topic on which our interviewees agreed was that individual participants are the stakeholder group least situated to have responsibilities or knowledge concerning state law variation. Although IRBs ensure compliance with requirements to disclose research risks, neither IRB review nor consent forms typically encompass details concerning subsequent harms or specific protections, rights, and remedies (or lack thereof). Even to the extent that some of these issues are touched upon, decades of research have consistently documented significant gaps in informed consent comprehension.<sup>34</sup> Thus, assessing the level of ethical concern about state law variation based on an historical lack of lawsuits or public outcry is tenuous at best. If prospective participants were aware that their rights and protections differed from others contributing to the same national project, would they accept this as a fact of ‘daily life’ or find it troubling?

Given the large scale of many (if not most) precision medicine research endeavors, combined with recent federal requirements for single-IRB review, there is a critical need to foster multi-stakeholder deliberations and devise solutions on a national level. Our interviewees suggested a range of ideas—including some that could help ameliorate practical challenges associated with continuing to meet each state’s requirements (eg a database of relevant laws, authoritative guidance, and education), and others that might facilitate a shift toward more uniform rights and protections (eg harmonization efforts spearheaded by a consortium of state governments). It is likely that a multifaceted approach will be needed to address both immediate and longer term objectives, especially considering the swiftly evolving future landscape of precision medicine research.

In addition, although the focus of our project was state laws, our interviewees frequently highlighted the substantial challenges created by variation in institutional

31 Leslie E. Wolf, et al., *Addressing Choice of Law Challenges in Multi-State Precision Medicine Research: Experts’ Assessment of Key Factors* (submitted).

32 SANDRA H. BERRY, et al., *PROFILE OF INSTITUTIONAL REVIEW BOARD CHARACTERISTICS PRIOR TO THE 2019 IMPLEMENTATION OF THE REVISED COMMON RULE* (RAND Corporation. 2019).

33 See, e.g., Christine Grady, *Do IRBs Protect Human Research Participants?*, 304 JAMA 1122 (2010); Christine Grady, *Institutional Review Boards: Purpose and Challenges*, 148 CHEST 1148 (2015).

34 Laura M. Beskow & Kevin P. Weinfurt, *Exploring Understanding of ‘Understanding’: The Paradigm Case of Biobank Consent Comprehension*, 19 AM J BIOETH 6 (2019).

policies (not based in law). Such variation may sometimes be a genuine reflection of local context and community interests; but other times, the basis for and importance assigned to institutional preferences may be hard to discern. Efforts are needed to identify and critically examine these differences, with the goal of supporting beneficial research by reducing unwarranted variation.

Interpretation of our results is subject to several limitations. Our exploratory study with purposively selected key informants was intended to elucidate a broad range of qualitative perspectives and themes on an understudied topic. Due to time and resource constraints, exacerbated by COVID delays, we stopped after 22 interviews. Although no new themes emerged after the 20th interview, we may not have reached saturation by subgroup—particularly the Research group. Furthermore, we were unable to achieve our goal of enrolling a diverse sample. Thus, choice of law challenges in precision medicine research could be further clarified through additional qualitative and quantitative studies designed to maximize diversity. Future research should also integrate input from additional stakeholder groups, including two-way dialog to both educate and learn from research participants, marginalized communities, and the general public about these issues.

Finally, because of our modest sample size and the qualitative nature of our study, we did not attempt to assess similarities and differences by stakeholder group. Investigation of the extent to which perspectives differ between groups, as well as the origins and prevalence of such differences, may assist the process of identifying solutions and achieving consensus.

Ultimately, the goal should be to uphold the primacy of participant rights and protections that are fair and equitable, within the context of societal support for beneficial biomedical research.

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#### SUPPLEMENTARY DATA

[Supplementary data](#) are available at *JLBIOS* online.