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Volume XII, Spring 2021



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Letter from the Editor

As a global pandemic and racial equity have taken center stage in our national consciousness, bioethics has become deeply personal. Each of us has been forced to consider how our individual actions contribute to—and whether they are obligated to contribute to—collective well-being. We have interrogated the privileges that have allowed some of us to stay silent and insulated while others' bodies asymmetrically bear risk.

The past year has reminded us that science and medicine are inseparable from the people they affect and aim to serve. We have been given front-row seats to the development of COVID-19 vaccines, novel in both the technology they harness and the speed at which they were actualized. But the story does not end with successful development. The next act will chronicle how COVID-19 vaccines will interact with people and societies and whether those interactions can manage to advance justice. Can these vaccines be distributed, both domestically and globally, in a manner that does not coerce, exclude, or discriminate? Alexandra Deutsch, an associate editor of the *Journal*, opens this volume with a critical examination of a past experiment in inoculating the global population against smallpox. Next, an editorial by Daniel Peltyszyn, our former managing design editor, presents a case for mandatory vaccination. I hope you will find the dialogue between these two pieces engaging and relevant.

The following articles in the 12th issue of *The Rutgers Journal of Bioethics* continue to deal with the human consequences of incorporating technological advancements into society. Christina Ren discusses how individuals interpret, grapple with, and construct meaning from genetic disease risk scores. Dr. Allie Dayno argues for newborn screening reform to better serve disadvantaged families. Drs. Janet Dolgin and Renee McLeod-Sordjan analyze the moral and legal liminal space occupied by cryopreserved embryos. The genetic testing and assisted reproductive technologies examined in these articles do not exist in a vacuum but instead interface daily with healthcare professionals and patients, whose lives are personally impacted.

I am so grateful to each contributing author for placing their trust in us to make their voice heard, and to each member of the *Journal* staff for being thoughtful, adaptable, and present throughout the publication process. I also must thank the Society and our publisher for the integral roles they have played in bringing this issue to life.

I hope that Volume XII of *The Rutgers Journal of Bioethics* contributes meaningfully to an ever-growing dialogue about the interface between science, medicine, and humanity. By analyzing the imprint of technology on human experience, we can design and implement medical technology to better serve all people.

Cindy Song
Editor-in-Chief, *The Rutgers Journal of Bioethics*

Letter from the Society

We at the Bioethics Society aim to provide the student body at Rutgers with an open forum where they can express their views on complex and controversial topics in bioethics. Our mission is to foster debate and bring to light issues that undergraduates will often face only after they have joined the workforce. Over the course of the past year, we have covered a diverse range of issues including the right to genetic privacy, access to healthcare for prisoners and the transfer of consent to surrogate decision makers.

At the surface, these topics may seem inconsequential, yet they get at the heart of the field of bioethics, asking the most difficult questions in medicine and biotechnology. Should privacy in healthcare extend to our genetic makeup, even if it hinders scientific advancement? What are the rights of the disenfranchised in healthcare, if any, and how do we guarantee them these rights? How do we ensure that the limits our institutions impose upon us to protect our health do not encroach upon our civil liberties? Our discussions give members the opportunity to explore diverse angles and viewpoints from which to answer these essential questions. In doing so, we are creating not only more compassionate healthcare providers and scientists, but critical thinkers well equipped to handle the challenges of technology and medicine.

In the past year, we have been forced to rapidly adapt to the COVID-19 pandemic. As in person meetings and events were cancelled, the Bioethics Society moved to an online format. Despite this shift, the Society was able to connect with passionate members of the Rutgers community who were excited to share their thoughts. As the pandemic changed how we engaged with each other, we thought about its effect on millions of healthcare providers and scientists. Many of the topics we considered, like healthcare prioritization and disease risks of the incarcerated, became critical questions to answer in our current situation.

As times continue to change, we expect new, complex bioethical questions to arise. Thanks to the support of our dedicated executive board and members, we know that there will always be a place at Rutgers for students to discuss and attempt to solve these questions. As we look to the future, we move forward with hope, knowing that these same dedicated members of our society will go on to become leaders of their fields, leading with compassion and wisdom. Finally, we would like to thank the *Journal* executive board for their hard work in putting together Volume XII of *The Rutgers Journal of Bioethics*. We encourage you to thoughtfully consider the points made in this volume and to join in these important conversations with us.

Rishabh Hirday & Rushabh Mehta
Presidents, Bioethics Society of Rutgers University



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Editorial

Questioning the Motives and Methods of Imperialist Vaccination Programs

by *Alexandra Deutsch*[†]

Since Edward Jenner's 1798 invention of the smallpox vaccine, his discovery and the public health programs that disseminated it have saved millions of lives and served as lasting examples of international cooperation and philanthropy [1]. However, some of these smallpox vaccination programs were motivated by and furthered non-humanitarian goals, especially those programs introduced by empires to their colonial subjects. While "imperial medicine" prevented and cured diseases and established frameworks for public health, it also strengthened the colonizer's hold, deprived indigenous peoples of their culture, and enforced a white savior myth that asserted the intellectual, medical, and moral supremacy of Western physicians over their indigenous counterparts. In this essay, I will first explore three early, non-coercive smallpox vaccination campaigns implemented by colonial powers in Latin America, the American West, and southern India. These campaigns furthered

the empires' own goals in the regions and, in the case of Great Britain in India, reinforced racist stereotypes that could prove harmful to the health and autonomy of the indigenous population. I will then explore the World Health Organization's (WHO) 1973 Smallpox Eradication Program (SEP) in eastern India and Bangladesh and show how the racism and self-righteousness of American physicians led to coercive smallpox vaccinations. By discussing these four examples, I aim to begin a dialogue regarding the bioethics of imperialist vaccination campaigns and encourage people to reexamine the motives and methods of vaccination programs.

In one of the world's first vaccination campaigns, Charles IV of Spain tasked the physician Francisco Xavier Balmis y Berenguer to lead the Royal Philanthropic Expedition of the Vaccine in 1803. Balmis's mission was to bring the smallpox vaccine to New Spain and the Philippines while training local doctors in its administration and establishing vacci-

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nation Boards that would lay the foundations for future public health institutions [2, 3]. The Expedition vaccinated over 30,000 people and was praised for its humanitarian purpose, widespread success, and public health legacy [4, 3]. However, it was not motivated by only philanthropic intentions. At the time, smallpox was diminishing the colonial population that worked in New Spain's mines—the source of its gold and other precious metals [3]. Saving New Spain from smallpox meant saving Spain's economy.

In the same year that the Expedition set sail, the British Medical Board in southern India shifted from a policy of variolation to one of vaccination and faced “non-acceptance” by the indigenous population [2]. Variolation was a centuries-old medical tradition that was frequently integrated into religious customs [2]. However, because it used the smallpox virus to impart immunity, it was a far more dangerous inoculation technique than vaccination, which used the cowpox virus [5]. Brimnes (2004) attributes southern Indian “non-acceptance” to a number of factors. First, there were religious concerns: vaccination was far less ritualized than variolation, and the arm-to-arm nature of early vaccination (in which the contents of a cowpox pustule on one person's arm were transferred to an incision on another person's arm) and its use of the cowpox virus led to religious unease in the Hindu population. They were concerned about the vaccine being exchanged between people of different castes and the use of animal matter, which some worried could violate their religious commit-

ment to vegetarianism [2, 5]. Second, the indigenous population was leery of placing their physical wellbeing into the hands of foreign oppressors. Some Indians even referred to the scars that remained from smallpox vaccination as “the Company's chop” and considered them marks of colonization [5]. Finally, there were concerns about the safety of the smallpox vaccine, which could cause blindness, convulsions, quadriplegia, and brain damage [2, 6]. However, the British narrative did not frame indigenous “non-acceptance” in these terms. Because of the groundbreaking nature of vaccination and its positive effects on the public health, the British believed their role was that of benevolent modernizers struggling against what they often termed “indigenous prejudice and superstition” [2]. In turn, this framing enforced a power dynamic that legitimized the British colonial government's belief that it had a right to rule the colony [2, 5]. Such righteousness, built on an asymmetrical power structure compounded by racial and religious discrimination, was a harbinger of later smallpox vaccination programs in India and Bangladesh.

Isenberg (2017) discusses another empire's indigenous vaccination program. In the 1830s, doctors from the U.S. Office of Indian Affairs vaccinated between 39,000 and 54,000 Native Americans against smallpox in the American West. Similar to New Spain and India three decades earlier, this vaccination program was not coercive yet not completely humanitarian, either. The U.S. government hoped that the program would protect American set-

tlers from smallpox outbreaks, strengthen the relationship between the U.S. and Native Americans, and stake a claim on land disputed by nations such as Mexico and Great Britain. It is also important to note that the vaccination campaign happened concurrently with the implemen-



Hicks, J./Centers for Disease Control and Prevention. (1973). *Child with smallpox, Bangladesh*. Photograph. Retrieved from <https://phil.cdc.gov/details.aspx?pid=3265>.

tation of the Indian Removal Act, which dispossessed Native Americans of their land through coercive means [7]. The simultaneous nature of these programs raises more questions about the bioethics of imperialist vaccination programs.

Vaccination programs that are implemented in the name of humanitarianism but clouded by imperialist goals, racism, or self-righteousness risk more overt unethical practices. This is demonstrated in the WHO's 1973 Smallpox Eradication Program (SEP), in which American physicians and epidemiolo-

gists violated the autonomy of eastern Indians and Bangladeshis through coercive smallpox vaccinations. Although WHO personnel were meant to cooperate with local health workers, they often took the lead in identifying infected individuals, quarantining those individuals' close contacts, and vaccinating all villagers [8]. Foster et al. (2011) maintain that one of the qualities that rendered the SEP in Bangladesh so effective was “[n]ot accepting no as an answer” [9]. By this, Foster et al. (2011) refer to WHO personnel's determination and initiative in the face of administrative inadequacy and financial deficiencies, but this determination also applied to their behavior when confronted with indigenous noncompliance and resistance. In Greenough (1995), T. Stephen Jones, one of the WHO personnel in the eastern Indian state of Bihar, and Stanley Music, a WHO epidemiologist in Bangladesh, recount breaking into houses and forcefully vaccinating individuals in “military style attack[s] on infected villages.” As Jones once described: “I was a white man in that society, and I could do things that others couldn't do... and get away with it” [8]. Indeed, although a legal case was brought against Music for his actions, it was later dismissed.

The power and violence that WHO personnel wielded in eastern India and Bangladesh came from a utilitarian desire to do good, however, they disregarded local norms and religious beliefs as “irrational,” “archaic,” and “ignorant[t]” [8]. Joshua Pryor, another WHO epidemiologist in Bihar, viewed indigenous medical practices as “high level quackery” and suspected local health workers



Yanibel, H. (2020). *Statue, Dominican Republic*. Photograph. Retrieved from <https://unsplash.com/photos/UR35ArRoNaw>.

of laziness, stupidity, and a “lack of sense of responsibility” [8]. These sentiments echo the British colonial authorities’ views on variolation in the nineteenth century. Jones remembers feeling “religiously fervid” in the service of this utilitarian ideal that advocated vaccination for everyone, regardless of consent or immune status. He recalls feeling like a “crusader” and admits that he “did some very excessive things in the name of righteousness” [8]. By stigmatizing indigenous individuals and their customs, the British colonial authorities and WHO personnel “inherently violate[d] the dignity of the stigmatized” [10]. By using coercion to vaccinate unwilling villagers, WHO personnel violated patient autonomy, raising serious questions about whether those personnel failed in their ethical obligations.

These four smallpox vaccination programs were conducted to protect individuals from the scourge of disease.

Bester (2015) argues that ensuring sufficient vaccination levels in a population is a government’s ethical imperative [11]. In this way, each program fulfilled its ethical obligations. However, as Das et al. (2000) argue, the good deeds and goodwill of the vaccinators do not eliminate lasting questions of intent, consent, sovereignty, and culture [12]. The bioethics of public health policies often raise questions about the autonomy of the individual, and questioning the motive of the vaccinator adds to this complex query [13]. By asking these questions about our past, we may find answers to our current and future concerns regarding vaccine distribution and administration in a pandemic and post-pandemic world.

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Compulsory Vaccinations Can Be Ethically Justifiable

by Daniel Peltyszyn[†]

Infectious diseases pose an existential threat to human existence. However, our response to this threat is underwhelming if one considers vaccination rates a proxy for infectious disease preparedness. Vaccination, in particular, represents a safe, well-studied form of protection against specific transmissible pathogens.

Despite the proven efficacy of vaccines, immunization rates remain low for certain preventable diseases. For example, the Centers for Disease Control and Prevention (CDC) estimates that only 37.1% of adults over 18 received an influenza vaccine for the 2017-2018 flu season [1]. That same season, influenza claimed the lives of an estimated 61,000 Americans [2]. Relatedly, only 21.5% of adults aged 18-26 received the recommended number of doses of the HPV vaccine in 2018 [3]. Consequently, the CDC estimates that “about 45,300 HPV-associated cancers occur in the United States each year” [4]. These two examples demonstrate a pattern in

which significant morbidity is an outcome of insufficient vaccination against preventable diseases. Additionally, these less than favorable vaccination rates mirror a concerning trend in public opinion in the United States in which fewer people recognize the importance of vaccination. According to a study conducted by the Gallup Poll in 2019, only 84% of Americans say it is important that parents vaccinate their children, down from 94% in 2001 [5].

That said, not all vaccines are associated with such low administration rates. According to the CDC, 91.5% of children between 19 and 35 months of age received at least one dose of the MMR (measles, mumps, rubella) vaccine in 2017 [6]. This relatively high immunization rate is still not high enough to prevent local outbreaks of disease. Between December 2014 and February 2015, an outbreak of measles emerged in California, linked to Disney’s theme parks. This outbreak led to over 100 cases of measles, and, of those affected, nearly half



Boilly, L. L. (1827). *La vaccine*. Lithograph. Retrieved from <http://resource.nlm.nih.gov/101393085>.

were entirely unvaccinated against it [7]. This event indicates that even seemingly small, localized pockets of unvaccinated individuals can bring about significant disease incidence.

Drastic differences in immunization rates against various infectious diseases exist, at least in part, due to legislation or workplace-level expectations. Some employers, especially those in the healthcare industry, require their employees to receive the annual flu vaccine. Similarly, children attending public or private schools must be immunized to some extent. In New Jersey, for example, students in grades kindergarten through 12 (K-12) are required by law to be vaccinated against polio, chickenpox, hepatitis B, meningitis, tetanus, diphtheria, acellular pertussis, measles, mumps, and rubella [8]. While medical exemptions from vaccination exist and are acceptable for those who qualify, most states

allow religious objections to vaccination. Some states, including Pennsylvania, Ohio, and Texas, permit personal objections to vaccination apart from traditional religious beliefs [9].

Given the ongoing coronavirus disease 2019 (COVID-19) pandemic, some entities are mandating specific vaccinations. On August 19, 2020, Massachusetts public health officials announced that all children over six months old who attend child care, pre-school, K-12, and universities must be immunized for influenza [10]. Many universities, including Syracuse University, Indiana University, Cornell University, Purdue University, Johns Hopkins University, and the University of North Carolina at Charlotte, have issued similar vaccination mandates [11]. Even before the onset of the COVID-19 pandemic, some states had already passed or considered legislation that would do away with exemptions from vaccination based on religious or personal beliefs [9]. Given the potentially controversial nature of such a measure, let us consider what compulsory vaccines might look like from an ethical standpoint.

ETHICAL CONSIDERATIONS

New vaccines undergo a rigorous approval process overseen by the Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research. This process includes a “clinical development” phase that is itself divided into three stages. During each of these stages, the vaccine is progressively administered to a larger population until it is ultimately approved for widespread distribution [12]. For the purpose of this

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thought experiment, let us assume that a given vaccine is safe and effective at preventing infection by a particular pathogen. What might obligatory vaccination look like from a bioethical perspective?

Autonomy

As it pertains to patients in a healthcare setting, autonomy refers to patients' right to make decisions regarding their own health care options. Compulsory vaccinations constitute an infringement on this right, thereby violating the bioethical pillar of autonomy. This violation likely requires little further elaboration, as compulsory vaccination, whether mandated by legislation or some other authority, eliminates patients' ability to control their own health-related choices. Despite this infringement on patient autonomy, are mandatory vaccinations still justifiable?

Beneficence & Non-maleficence

Beneficence generally refers to the intention of doing good, while non-maleficence refers to minimizing potential

harm. While an individual vaccine's efficacy might be brought into question, the concept of vaccination itself has been validated. Historically successful vaccination efforts offer the most robust support for widespread, compulsory immunization. In particular, the worldwide immunization campaign against smallpox ultimately led to the World Health Assembly formally announcing the disease's eradication on May 8, 1980 [13]. Similar present-day vaccination campaigns might also successfully eliminate, if not eradicate, other communicable diseases. Therefore, as far as compulsory vaccination is concerned, the intention of doing good is present, thereby upholding the bioethical pillar of beneficence.

The concept of beneficence extends beyond simple intention to include acts mandated by moral obligation. The Belmont Report, which establishes ethical guidelines to protect human research subjects, maintains that beneficence includes the obligation "to secure [humans'] well-being" [14]. This statement



RF Studio. (2020). *Person holding injection*. Photograph. Retrieved from <https://www.pexels.com/photo/person-holding-injection-3825529>.

raises an interesting point regarding the practice of vaccination. Decades of immunology research have demonstrated that vaccination is safe and effective at preventing or reducing the severity of disease. Therefore, bearing such research in mind, the present-day institution of medicine is bound by a moral obligation to vaccinate as a means of securing the public's well-being. Compulsory vaccination fulfills that obligation for individuals who receive the vaccine and for those who cannot be vaccinated but benefit from herd immunity.

Despite the strong historical record of immunization, a non-negligible proportion of the population questions vaccines' safety and efficacy. While these concerns vary in nature, they often revolve around fear of unwanted allergic reactions, false threats of medical risks like autism, pharmaceutical companies' motives, and distrust of science [15]. Unfortunately, when enough like-minded people are in the same place simultaneously, the consequences can be significant, as seen in the 2014 outbreak of measles in California referenced earlier.

The question remains whether the general public has a foundational understanding of the principles of vaccination and an awareness of the rigorous vaccine approval process. Should people be given a choice to vaccinate or not vaccinate, considering that they might hold a misinformed opinion? The FDA's multi-step approval process for new vaccines provides ample opportunity to identify serious safety concerns, well before the vaccine is widely distributed and available to the general public. Therefore, once approved, the final product has

been demonstrated to be safe and effective. Consequently, I would argue that compulsory vaccinations satisfy the bioethical pillar of non-maleficence, under the condition that the vaccine has undergone the meticulous vetting process. Additional resources should then be funneled into public health education to alleviate the public's concerns.

Justice

With respect to bioethics, justice refers to the concept of fairness and the appropriate allocation of resources, including but not limited to, medical supplies, equipment, and personnel. The impact of mandatory vaccinations on this bioethical tenet can be trickier to predict, as several important questions need to be addressed. Firstly, and perhaps most importantly, on whom does the financial burden of mandatory vaccination fall? Will the individual patient be responsible for the cost, or will the vaccination program be government-sponsored? In the United States, a monumental 27 million people do not have health insurance [16]. Will they be expected to cover the cost of the vaccine out-of-pocket?

Another major consideration involves the appropriate distribution of the vaccine and questions regarding access to healthcare. For patients living in rural areas, will the vaccine be readily available? On average, Americans in rural communities live more than 10 miles away from the nearest hospital, as compared to 5.6 miles in suburban areas and 4.4 miles in urban areas [17]. Do the individuals living in these communities have the time and means of transportation to receive the vaccine?

Finally, how will compulsory vaccinations be enforced? If some individuals learn that their neighbor or colleague managed to circumvent vaccination, they will likely be less inclined to receive the vaccine themselves, especially if they question its safety. Will authorities implement formal sanctions, or will mandatory vaccinations simply be “mandatory?” In that case, is there even a point in pursuing such vaccination campaigns, given the likelihood of widespread non-compliance? For such a variety of factors, the effect of compulsory vaccination on the principle of bioethical justice is difficult to anticipate.

CONCLUSION

History reminds the present that vaccines have the potential to provide significant protection from infectious diseases. Only 100 years ago, smallpox was still rampant throughout the United States. Now, 40 years after its global eradication, smallpox no longer poses a threat. Despite its apparent benefits, vaccination is seemingly taken less seriously by the general public. Compulsory vaccinations offer a potential solution to this problem, but they would likely face fierce resistance from a portion of the public questioning their safety and efficacy. Medical exemptions would still be permitted for individuals with legitimate contraindications to vaccination, while exemptions based on religious or personal beliefs would be eliminated. From a bioethical standpoint, mandatory vaccination unquestionably infringes on patients’ right to autonomy, and its relationship with bioethical justice depends on numerous factors. However,

the well-studied science and the robust, government-regulated vaccine approval process serve as safeguards against unwanted medical risks that are often fabricated or blown out of proportion by skeptics. Therefore, I would argue that the benefits of mandatory vaccination—most especially the ability to curb the spread of communicable disease and to minimize disease morbidity and mortality—justify the practice, as long as special attention is paid to concerns regarding healthcare costs and accessibility.

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Psychosocial Impact and Behavioral Outcomes Associated With Receiving Polygenic Risk Scores

by Christina Ren[†]

To date, clinical genetics is primarily focused on identifying rare genetic variants that confer a large effect on disease risk. However, the genetic basis of common complex diseases is largely determined by the cumulative effect of many common variants across the entire genome. While individually each of these associated single nucleotide polymorphisms (SNPs) has a small impact on disease risk, their combined effect, calculated as a polygenic risk score (PRS), is large. The generation of PRS data and their predictive ability for disease risk is rapidly evolving and improving. As polygenic testing is implemented more broadly, there is a critical need to assess how this new type of genetic information is being communicated to people and how individuals respond to the knowledge of their probabilistic susceptibility to disease. With the availability of polygenic testing pushed to the forefront of genomic interpretation for complex conditions, genetic counselors need to consider how to apply and manage this information in various settings.

Recent efforts have shown that polygenic risk scores for common diseases like breast cancer, coronary artery disease (CAD), and type 2 diabetes can now identify a substantially larger fraction of the population than is found by rare monogenic mutations, at comparable or greater disease risk. For instance, data suggests that 8% of the general population has over a three-fold increased risk for CAD [1].

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Polygenic risk profiling, therefore, has the potential to provide personalized disease risk to individuals. This information could be valuable in informing appropriate preventative interventions and screening, assessing benefit from lifestyle changes, predicting treatment response outcomes, and modifying familial disease risk [2]. Together, these actionable measures may lead to clinical decision-making changes and improved individual and population-level health. Polygenic testing is now becoming increasingly available, with several commercial genetic testing laboratories, direct-to-consumer, and researchers offering polygenic risk score (PRS) testing [3, 4, 5, 6, 7].

The recent widespread implementation of PRS has sparked an emerging body of research assessing how individuals respond to receiving such polygenic risk information. This paper will focus on 1) reviewing current literature on the psychosocial impact and behavioral outcomes associated with receiving PRS, 2) exploring the psychosocial challenges and concerns of utilizing PRS, and lastly, 3) discussing how genetic counselors can incorporate PRS into practice as applications continue to expand in the coming years.

PSYCHOSOCIAL IMPACT OF RECEIVING POLYGENIC RISK SCORES

There are two primary areas in which researchers have assessed the psychosocial impact of receiving PRS. The first area involves inviting individuals from families with a high risk of specific disease but whose previous genetic testing results were uninformative. For these individuals, the etiology of high familial disease risk remains unexplained. A second research area aims to model how groups of higher-risk individuals can be identified in the general population for population screening. Population screening does not require individuals to have a previous personal or family disease history.

1) Individuals at High Risk of Cancer With Previous Uninformative Genetic Testing

An active area of research for utilization of PRS information is in clarifying individual genetic risk from families with a personal or strong family history of cancer. Thus far, less than 30% of familial breast cancer cases can be explained by a pathogenic variant in a moderate-to-high cancer risk gene [8]. Currently, polygenic factors can help explain an estimated additional 18% of the genetic component in familial breast cancer risk [9]. The Variants in Practice Psychosocial Study (ViPPs) led by researchers at the Peter MacCallum Cancer Centre in Australia have invited 400 women with either a personal or family history of breast cancer from six familial cancer centers (FCCs) to receive their personalized PRS generated from 180 single nucleotide polymorphisms (SNPs) [10]. Those included in the ViPPs study included 200 women with a low polygenic breast cancer score and 200 women with

a high polygenic breast cancer score. Genetic health professionals (genetic counselor or medical geneticists) at participating FCCs conducted in-person genetic counseling sessions to return the personalized breast cancer PRS. Participants were asked to complete three questionnaires to assess short- and long-term psychological and behavioral outcomes over 12 months (before receiving, 2 weeks after, and 12 months after receiving their result). Subsets of these participants were invited for interviews to explore women's experiences receiving their PRS qualitatively. Responses of unaffected and affected women at different levels of polygenic risk were compared. A series of papers have published these follow-up studies as part of ViPPs [11, 12, 13].



Samkov, I. (2020). *Person in black long sleeve shirt and silver ring*. Photograph. Retrieved from <https://www.pexels.com/photo/person-in-black-long-sleeve-shirt-and-silver-ring-6436185>.

The most recent study from Yanes et al. showed that women at high risk of breast cancer who previously received uninformative genetic testing results are highly motivated and receptive to new genetic information that clarifies and reduces uncertainty about their risk level [12]. When asked about their decision to receive their PRS upon invitation, most spoke about their desire to know and their belief that “knowledge is power” [12].

For unaffected participants, their relatives' uninformative BRCA1/2 result had been unsettling for them. They faced a great deal of uncertainty about their risk level and how to manage their breast cancer risk. Therefore, many were motivated to receive their PRS, even if that meant being told they were at higher risk for breast cancer:

“You should have MRI's, oh no you shouldn't, you should have this screening... oh you have got this lump and it's probably nothing. You know there's heaps of uncertainty around it [breast cancer risk]... as I said to my partner on the way in there, I hope they just tell me high-risk and I can just have a solid answer, so I kind of wanted certainty from it...” –Brittany, 36 years, Unaffected/Low PRS [12]

Prior lived experience with breast cancer was critical in informing how women responded and made sense of their PRS. Those who had a breast cancer diagnosis felt that receiving a high PRS result helped give an etiological explanation for why they went through such a traumatic and challenging event. Their previous uninformative genetic testing did not explain their diagnosis. Some also expressed that their high PRS result absolved them from past blame for their diagnosis. However, confronting reawakened memories and lived experiences of a breast cancer diagnosis can be distressing for affected individuals [11, 12]. Learning about an ongoing increased recurrence risk of primary breast cancer can also be initially shocking for some. Many also hoped that, since PRS is personalized to the individual, their relatives would have a lower risk for the disease:

“...I suppose the fact that they were saying that, you know the variables can cluster in one person I guess gave me some reassurance that just because I have high risk of something, they [sisters] are not going to as well, and same with my children.” –Melissa, 42 years, Affected/High PRS [12]

For unaffected participants who received a high PRS, all women described not being surprised due to their strong family history of breast cancer. For them, it validated their previous existing risk perception. No individuals reported levels of distress, and many were relieved to have information to help them make sense of their background familial breast cancer risk. Some expressed that for some time, they felt they were “off the hook” because their affected relatives had tested negative for BRCA1/2, even though these were uninformative negative results:

“...once my sister got sick [breast cancer]... I knew something was wrong with the BRCA1 and 2 ... in '97 it wasn't that I was lead [sic] to believe, but it seemed very clear cut: you either carry the gene or not. So my assumption was I was just like anyone else in the general population for that small period.” —Julie, relative risk (RR)¹ 1.5 [11]

Women who received a low PRS felt optimistic about their result, but some struggled to put this information into context, given their breast cancer family history. Some relied on the multifactorial nature of breast cancer and that

¹ Relative risk (RR) of breast cancer in the average general population is 1.0. A relative risk above 1.0 indicates an above average of breast cancer [11].

PRS was just one contributing factor in reconciling the difference between PRS and family history. Others felt they needed additional information like their affected relative's PRS. One individual who received a low PRS did not feel reassured about her risk unless her mother, who had breast cancer, also underwent polygenic testing and had a high PRS. Indeed, there is no good “true negative” for polygenic risk. PRS is derived from a combination of maternally and paternally inherited variants that can “cluster unevenly” in any one individual in the family by chance. The probabilistic nature of PRS is uniquely different from the binary approach of identifying monogenic pathogenic variants. For monogenic variants, familial variant testing can determine whether an individual either has the variant(s)



National Cancer Institute. (2020). *DNA genotyping and sequencing*. Photograph. Retrieved from <https://unsplash.com/photos/fd0b-B14cFc>.

or not. All participants understood that a low PRS meant that their risk was lower than that of the baseline risk for the general population (12%), but that it did not mean they had “no risk” [12].

Interestingly, receiving PRS information had little impact on participants' behavior with respect to breast cancer risk management. Instead, participants' prior lived experiences more strongly influenced their management and screening decisions. Those who received high PRS felt validated and that it was important for them to stay vigilant and continue breast screening. All participants with low PRS said they would continue with their current cancer risk management recommended by their clinician [12]. Since guidelines for increased screening for individuals with high PRS is not yet established, it does not seem that unaffected participants with high PRS have discussed chemoprevention and increased surveillance options in addition to their current risk management strategy.

These findings from ViPPs are mostly consistent with previous PRS studies in other familial cancer settings, including unaffected men with a family history of prostate cancer and no identified hereditary cancer risk. In

the ongoing PROFILE study led by the Institute of Cancer Research in the U.K. assessing the impact on prostate screening and genetic profiling, the psychosocial arm of the study found that participants did not experience distress and were reassured upon learning about their PRS risk information [14, 15]. Like the ViPPs study, receiving personalized PRS did not influence their prostate screening intentions, and family experience with affected relatives was the strongest influencing factor in participants' risk perceptions. Therefore, interpretation can vary even between men who received similar PRS risk—one man interpreted a two-fold increased risk as evidence that he would get prostate cancer. At the same time, another felt reassured by “only” a two-fold risk as it was much lower than he had anticipated [14].

The impact of experiential knowledge and its precedence over any objective clinical estimates of risk in PRS studies assessing people's response is evident. As will be discussed in the last section on genetic counseling practice, it is critical to explore and reflect on patients' lived experiences to help contextualize the new genetic information provided [16].

2) Population Screening: Identifying At-Risk Subgroups in the General Population

Another area of application for PRS is population screening. If polygenic testing is extended to the general public, personalized screening programs based on genetic risk can be implemented, with increased screening and risk management strategies for those at higher risk. For example, in the ViPPs study, affected women who were diagnosed with aggressive cancers before becoming eligible for baseline population screening felt strongly that polygenic testing would have allowed them and others like them access to earlier screening and diagnosis [12].

To date, only a few PRS studies are assessing psychosocial responses that have recruited individuals to represent the broader public outside the high familial risk context. In an ongoing study called GeneRISK, led by a team at the Institute for Molecular Medicine Finland at the University of Helsinki, over 7,300 people have received information about their risk of heart disease based on both clinical factors and polygenic profiling [17]. About a third of participants were told they have a higher risk of developing cardiovascular disease (CVD). A follow-up questionnaire, 18 months after results were given, showed a vast majority of people found this genetic risk information useful and motivating. Of the over 5,100 who responded to the questionnaire, 89% said their personal risk information was easy to understand, 22% found the results to be unexpected, 29% said the results were of concern to them, and 89% said this information motivated them to take better care of their health [17].

Researchers conducting the GeneRISK study found that individuals with the highest PRS had the most positive changes in their health behavior in assessing behavioral outcomes. 36% of those with PRS risk for CVD greater than 10% had lowered their body weight, stopped smoking, or seen a physician. By contrast, only 21% of those with lower CVD risk had taken any of these risk-reducing behaviors [17]. A follow-up study, conducted 1.5 years after results were communicated to participants, found that these favorable behavioral changes were sustained—42.6% of individuals at high CVD risk made concrete health changes such as reported weight loss or smoking cessation, compared to only 33.5% of individuals at low or average CVD risk [18]. While this study certainly shows how communicating combined polygenic and clinical risk information for complex diseases like CVD can motivate individuals to make lifestyle changes, it is unclear how this might extend to broader populations in other countries like the United States.

Delivery of PRS to the general population has also been assessed in the context of melanoma risk. Recruited participants had no personal or family history of melanoma. Quantitative scoring of participant response found an overall positive experience that did not elicit high levels of distress or uncertainty [19]. This study also highlights how the perceived “severity” of a specific condition may impact different expected emotional and psychosocial responses. Given that melanoma was presented to participants as highly preventable through simple sun-related protection behaviors, there was less varying complexity and diversity of psychosocial reactions compared to other cancers like breast and prostate cancer as described previously [19].

PSYCHOSOCIAL CHALLENGES AND CONCERNS OF UTILIZING PRS

Much of the debate around PRS is centered around whether the calculation and interpretation of such scores yield accurate predictive ability for disease risk. While the generation of PRS presents one set of technical challenges, another critical component to consider in the implementation of PRS is the challenges and concerns posed in communicating and receiving PRS information to individuals, including the potential to 1) change perceived risk and impact objective physiological behavior (i.e., placebo and nocebo effect), 2) misinterpret the result, and 3) influence negative health behavior.

Learning About Genetic Risk Can Itself Impact Physiology, Behavior, and Subjective Experience

Previous reports have raised concerns that merely learning one’s genetic risk for disease impacts physiological, behavioral, and subjective outcomes. For example, a team of psychology researchers at Stanford found that when people were randomly assigned to receive either a genetic propensity for or

against either obesity or lower exercise capacity, it altered how they responded to fullness after a meal or to exercise [20]. In other words, the information itself can change an individual’s perceived genetic risk and impact outcomes irrespective of, and sometimes greater than, the effects associated with “actual” genetic risk.

Similar studies have found that when people receive results that impact perceived genetic risk, this affects self-perception and objective cognitive measures on conditions like Alzheimer’s disease, depression, and alcoholism [21, 22, 23]. The caveat and limitations of these studies are that the genetic risk only used single high-risk genotypes, like ApoE4 (a risk factor for Alzheimer’s disease), FTO (a risk factor for obesity), and CREB1 (associated with poorer aerobic exercise), that have relatively small effect sizes compared to their associated trait. Furthermore, research on how genetic information alters health outcomes has been limited to conditions in which psychological mindset can have a larger immediate short-term influence on physiology, rather than conditions that are less likely to be influenced (i.e., tumor growth in cancer or CVD). Studies focused on cancer and CVD support this notion since their findings demonstrated that receiving PRS did not negatively impact risk perceptions and health behavior, which contradicts these previous studies [15, 19, 17, 12].

Nevertheless, these reports highlight that receiving information about genetic risk is not innocuous and careful thought should be given to the potential impact of receiving PRS for a range of different conditions.

Possibility of Misinterpreting Results

Given the inherently probabilistic nature of PRS information, receiving such complex information may lead to a range of interpretations and potential misinterpretations. For example, individuals who receive a low PRS may interpret this result to mean “no risk.” On the opposite side of the spectrum, individuals who receive a high PRS may interpret their results as deterministic. Such fatalistic beliefs may increase an individual’s sense of distress and decrease feelings of self-efficacy and control. Current PRS studies detailed above have not found evidence of these misunderstandings, and participants demonstrate accurate knowledge and understanding of their risk level. Many were also astutely aware of the dynamic, evolving nature of PRS information, and that new genetic variants will continue to be identified that could change the sliding scale of these probabilistic results [14]. Limitations of these studies’ conclusions are that participants were mostly highly educated and of Caucasian ancestry, with many being active in cancer research studies, having received genetic counseling before, or being registered on a cancer research database [15, 19, 12]. More research is needed to assess responses within the broader population outside of academic institutions and

hospitals.

An ethical question remains on how PRS will be applied and interpreted for certain conditions such as psychiatric disorders. Using the term “risk” implies that the condition itself is not just a trait but a negative event to be avoided [24]. For certain conditions like cancer or cardiovascular disease, early treatment and preventative lifestyle modification are inherent mentalities of care. However, for psychiatric or neurodevelopmental disorders like schizophrenia, bipolar disorder, and autism, how this information is communicated without normative judgment is critically important to avoid stigma [25, 24].

Potential for No Change in Risk-Reducing Behavior

A previous meta-analysis of 18 studies found that communicating the genetic risk of disease did not affect risk-reducing health behaviors [26]. While these early studies between 1997-2015 have several limitations in quality, including the use of SNP rather than PRS genotypes, their conclusions are consistent with several studies on individuals receiving PRS information for cancer risk. Many found their results to be useful, validating, or reassuring, but learning about their results did not tend to change their risk management strategies [15, 19, 12]. There are several possible explanations. Perhaps study participants were already receiving the highest cancer screening level possible and did not feel the need to reduce screening. Another reason is that patients and providers perceive that PRS information is for emerging research purposes only and not yet validated to base clinical decisions from this result. GeneRISK is the one study reviewed in this article that did find measurable lifestyle behavioral changes after receiving PRS risk for CVD, especially for those who had a high PRS result [17, 18]. It is possible that, at present, PRS information may influence personal health behaviors like exercise and healthy eating but not yet clinical management like cancer screening. This was found in a previous study assessing individuals receiving genetic risk information on colon cancer [27].



Reche, D. (2019). *Gray scale photo of man covering his face with his hands.* Photograph. Retrieved from <https://www.pexels.com/photo/gray-scale-photo-of-man-covering-face-with-his-hands-3601097>.

FUTURE MODEL OF GENETIC COUNSELING FOR POLYGENIC DISEASE

New Personalized Evaluation Framework With Similar Underlying Principles of Genetic Counseling

A future model of genetic counseling will require a personal evaluation accounting for both monogenic and polygenic risk. These two forms are not mutually exclusive and likely have an additive interaction. A recent seminal study found that polygenic risk can help further modify risk and explain the variation in outcomes for individuals positive for monogenic risk variants [28]. For example, for an individual positive for a BRCA1/2 mutation, the probability of breast cancer by age 75 can vary from 13% to 76% based on their polygenic background. For carriers of a Lynch syndrome mutation, the probability of colorectal cancer by age 75 can vary from 11% to 80% based on polygenic background [28]. Therefore, clinical risk estimation will likely improve with the integrated interpretation of monogenic risk variants alongside polygenic background, which has fundamental genetic counseling implications.

However, as genomic interpretation and technology evolve, the principles of genetic counseling that provide a framework enabling us to understand how individuals conceptualize risk and address the psychosocial needs of individuals remain critically important. Polygenic testing remains but a probabilistic risk factor tool. Genetic counselors are uniquely equipped to make meaning of these numerical risk estimates in the context of a patient's experiences, acknowledging that these embodied and empathetic lived experiences change how one internalizes new genetic information.

As the studies reviewed in this paper highlight, individuals who receive their PRS result face many of the same psychosocial responses and processes that patients seen in clinical settings have. Uncertainty, anxiety, fear, vulnerability, hope, and resilience are often attached to one's experience and are salient to constructing a story, explanation, or understanding meaningful to them. As polygenic risk score information becomes an increasingly important aspect of genome understanding and interpretation, keeping these fundamental values and psychosocial tools in mind while staying abreast with emerging science is how genetic counselors can serve patients best.

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Unwinding the Ethical Concerns of Newborn Screening in the Age of Genomic Medicine

by Allie Dayno[†]

The bioethical analysis of newborn screening (NBS) in the United States is not a new topic. Nevertheless, as newborn screening dives into the age of genomic medicine with pilot studies to assess whole exome sequencing at birth and support for expansion of the federal government's Recommended Uniform Screening Panel (RUSP), it is imperative to examine the principles of beneficence and equity in relation to NBS. Every newborn undergoes NBS; however, those children in marginalized and disadvantaged communities may face barriers that prevent them from gaining the benefits of early screening and diagnosis. The focus must be on awareness and education surrounding an equitable NBS process and on using evidence-based protocols for adding new conditions to the panel.

Within the initial 24 to 48 hours of life, a newborn baby undergoes their “first test.” A heel stick is obtained to collect a blood sample for the newborn screen (NBS) to check for possible harmful disorders before symptoms appear. The state-mandated NBS, a public health initiative, is now routine in every hospital across the United States. The implementation of tandem mass spectrometry, a technique using mass-to-charge ratios to identify molecules, allows screening of a large panel of genetic conditions with one blood sample. The American College of Medical Genetics (ACMG) Recommended Uniform Screening Panel (RUSP) has sanctioned expansion of newborn genetic screening using mass spectrometry technology [1]. This type of “multiplex testing” is used to screen for inborn errors of metabolism, such as fatty acid oxidation

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defects, amino acid metabolism conditions, and organic acid disorders [1]. Expanded screening opens up the process to screen newborns for metabolites indicative of rare genetic disorders that might not have known clinical significance or recognized treatment options. There has been support for more conditions to be added to the RUSP, and National Institutes of Health pilot studies are assessing whole exome sequencing at birth [2]. The technology has clearly arrived, but expanding newborn genetic screening in the age of precision medicine requires very careful consideration of how it will affect all children, their families, and society at large.

BENEFICENCE

Beneficence is the principle of doing good. Furthermore, it can be defined as “a normative statement of a moral obligation to act for the others’ benefit, helping them to further their important and legitimate interests, often by preventing or removing possible harms” [3]. The notion of acting “for the others’ benefit” and “removing possible harms” raises the question—who is the subject of this benefit? In terms of the NBS process, is it helping the individual infant, the family, and/or society as a whole? In December 2008, the President’s Council on Bioethics published a comprehensive report that examines “The Changing Moral Focus of Newborn Screening” [4]. The Council held meetings that brought together experts in the fields of public health, genetics, bioethics, and pediatrics to examine the ethical dilemma of expanding newborn genetic screening outside the traditional screening criteria. The report examines the shift in perspective of benefit and purpose of the NBS after the ACMG’s RUSP was introduced in 2005 [4].

Chapter two of the President’s Council on Bioethics NBS report focuses on the question: “Is the expansion recommended by the ACMG consistent with the classical ethical principles of screening, or does it represent a radical departure?” [4]. There seem to be two distinct perspectives on the definition of benefit with regard to the newborn screening process. One perspective is that NBS should directly benefit the individual child (with indirect benefits to family and society). This view represents the “classical ethical principles of screening” set forth by Wilson & Jungner (1968), which highlight the need for effective treatments of those conditions in the screening panel [4, 5]. Alexander & van Dyck’s (2006) position represents the conflicting point of view that an expanded approach to newborn genetic screening that includes conditions without a known prognosis or a proven treatment should be done for the broader benefit to families, society, and ultimately, biomedical research [6]. Identifying newborns with mutations in disease-associated genes can provide answers to families seeking to understand what is wrong with their child and, at the same time, generate data to develop a database that enables us to learn more about these conditions. This information could help lead to

possible discoveries of treatments to help those children afflicted by these genetic disorders and other advancements for future generations.

The President's Council on Bioethics argues that the 29 core conditions and the 25 secondary conditions within the RUSP brought forth by the ACMG in the early 2000s fall outside the traditional screening framework [4]. The ACMG (2006) used a two-step method involving a panel of experts to determine which conditions qualify for the RUSP [1]. Conditions were initially ranked based on criteria surrounding characteristics of screening tests, diagnostic services, and treatments [1]. The second step focused on evidence-based fact sheets for each condition that were evaluated by experts to determine if the disorder qualified for the core panel, as a secondary target, or was not appropriate for NBS [1]. The Council on Bioethics examines how the ACMG focuses on maximizing mass spectrometry—using its “full profile mode” to look for all possible “clinically significant” metabolic disorders in asymptomatic infants, regardless of understanding of the natural history of a disease or availability of effective treatment options [4]. The ACMG justifies this view based on the broader concept of benefit that mostly includes society at large and the biomedical research community [1].

The Council on Bioethics, healthcare providers, and public health officials criticize this expansion of newborn screening established by the ACMG due to lack of evidence-based studies, poor methodology in the development of the RUSP, harms of false positives, and lack of insight into the ethical and legal consequences in the ACMG working group's report [4, 7]. Jeffrey Botkin and collaborators, including Murray and Baily from the Hastings Center, offer their opinion in the 2006 article titled, “Newborn Screening Technology: Proceed with Caution” [7]. Botkin et al. argue that it is obvious that many children and their families have benefited from newborn screening since its initiation over 40 years ago; however, phenylketonuria (PKU) for example, despite being a “model condition,” still has its own faults with regards to the efficacy of its screening program [7]. The article mentions the need for



Feyissa, S. (2020). *Newborn baby hearing test* (edited). Photograph. Retrieved from <https://unsplash.com/photos/uVd1Z6Go74M>.

“insurance coverage for ongoing specialty care and special diets” in addition to difficulty of following the PKU diet “because of its poor palatability, high cost, and limits on insurance coverage in many policies” [7]. NBS aims to improve health outcomes for children. Botkin et al. reveal how, even for a “model condition” like PKU, its success as an effective screening program should be tempered by the challenges of managing the children who screen positive for this condition [7].

The goal of NBS, to improve children's health outcomes, can be interpreted based on who the beneficiary is—whether that be the newborn children being tested, future children, or society as whole. Another variable in this ethical question concerns what is meant by “effective treatment.” The Council on Bioethics dissects the ACMG working group's conclusion: “...effective treatment was available that could prevent all (for 4 conditions), most (ten), or at any rate, some (fifteen) of the disease symptoms... Finally, for 25 of the 29 core conditions, the ACMG concluded that the available treatment was

efficacious at preventing mortality, independent of any reduction in morbidity” [4]. The concept of “effective treatment” can be interpreted in different ways. While a treatment might not prevent all disease symptoms, it could prove beneficial for “most” or “some” of the symptoms if averted through early detection and intervention.

However, what if that child with a genetic mutation remains totally healthy without any intervention? The Council on Bioethics highlights this potential for clinical uncertainty, especially amongst the secondary conditions, such as organic acid disorder 2-methylbutyryl-coenzyme A dehydrogenase deficiency (2-MBG), an extremely rare disorder most often found in individuals of Hmong ancestry, an ethnic group in East and Southeast Asia [4]. Symptoms can range from severe developmental delay, seizures, and cerebral palsy to no noticeable effects. According to the Council, “only five cases of 2-MBG had been described worldwide when the state of Wisconsin, in 2000, added 2-MBG to its mandatory newborn screening panel” [4]. Between 2000 and 2006, 27 infants in Wisconsin were diagnosed with 2-MBG, most undergoing modified diets; however, the Council notes, “parental compliance with this diet was quite variable. ... As of 2007, all of the Wisconsin children who had been diagnosed at birth with 2-MBG were normal, healthy, and asymptomatic” [4]. It is unclear whether the dietary modifications led to prevention of symptoms or whether the children would have remained asymptomatic without intervention. Many countries, such as the United Kingdom, do not believe these secondary conditions qualify for neonatal screening [8].

There appears to be some disconnect surrounding the definition of “effective treatment” and “clinical significance” between state governments that decide what to screen, public health officials who run the NBS process, and the primary care pediatricians on the front lines ordering the testing. The dilemma weighs the needs of a child against the benefit to society at large. It is evident that the NBS process is complex and that there are many stakeholders. It should be even clearer that all parties must come together, focus on the newborn infant population, and find common ground in order to establish equitable screening protocols that best serve the needs of this population and the families caring for them.

EQUITY

The words “equity” and “disparity” are often used within the healthcare field without much clarity as to what they really mean. The ACMG comments on the newborn screening landscape in its report: “It is important that universal access to this screening and its central public health focus are maintained, while efforts move forward to bring uniformity and *equity* to State screening efforts” [1]. The ACMG report uses the term “equity” in terms of uniform

screening programs such that each state should use the same panel to ensure early detection and treatment of genetic diseases [1]. Equity transcends uniformity; it encompasses the ability to recognize unique circumstances and perspectives to allow people to achieve their full potential.

Health inequities stem from unfair discriminatory policies that persist within a larger system. Institutional racism ultimately denies access to disadvantaged communities. Public health initiatives, such as NBS, must look inward to evaluate how their policies affect health outcomes in all groups of people. A webinar on www.babysfirsttest.org entitled “Health Equity in Newborn Screening” discusses equity concerns within current newborn screening programs in regards to follow-up testing and long-term care [9]. An example of health inequity could be a pregnant, non-English speaking, uninsured woman from a low socioeconomic background without access to prenatal care, resulting in inadequate education about the NBS process that possibly leads to a lapse in care for her newborn baby. A 2019 study suggests that newborn screening without Medicaid actually increases the infant mortality rate for African American newborns, compared to a minimal decrease in infant mortality among whites [10]. When NBS and Medicaid are available together, the study concludes that the change in infant mortality rate for African Americans and whites are “equivalent to about 1000 and 380 fewer deaths in a hypothetical cohort of four million births respectively” [10]. This finding highlights how the advantages of NBS are clear only when there are already policies in place to lift up those who are marginalized and disadvantaged. Health inequities like this must be addressed in NBS programs to overcome the unjust racial, educational, societal, and institutional barriers that some populations are faced with.

The Council on Bioethics acknowledges some of the similarities between state-run NBS programs, such as “privacy and confidentiality policies” that allow parents to decline screening, and dissemination of NBS educational material to inform parents about the screening process [4]. Nevertheless, there are important differences between each program. The Council on Bioethics highlights three main differences: “quality of parental education,” the price of the screening test, and the timing/number of initial screening tests [4]. There are more similarities than differences in general NBS practices across state lines; however, as Tarini & Goldenberg (2012) point out, there is “One Nation, 51 Programs” [11]. These differences in NBS practices between the states can cause inconsistencies in health outcomes for infants across the United States.

The capability to universally screen newborns for genetic conditions represents significant advancement in the age of genomic medicine, but this can only be beneficial for all infants if the screening tests are valid, results are clearly communicated, and patients and families have access to treatment, if

available. Screening tests bring with them false negatives and false positives. It is vital to investigate whether these results are clustered within certain populations and what negative effects they might bear. There is still debate today about which screening tests should be done and how the diversity of ethnic backgrounds impacts the selection of which genetic tests are most relevant.

Falling Through the Cracks: Cystic Fibrosis and Fatty Acid Oxidation Defects
Cystic Fibrosis (CF) is an autosomal recessive disorder caused by a mutation in chloride ion channels resulting in lung, pancreas, and digestive dysfunction. It is more prevalent in Caucasians, occurring in 1 in 2,500 to 3,500 white newborns compared to 1 in 17,000 African Americans and 1 in 31,000 Asian Americans [12]. Early diagnosis and intervention improve health outcomes. Since every newborn in the U.S. is screened for CF, equitable tests and follow-up protocols must be in place to provide adequate healthcare to all children, regardless of race, ethnicity, or socioeconomic status.

A 2008 article in the *Journal of Pediatrics*, entitled “Newborn screening for cystic fibrosis: a lesson in public health disparities,” describes the different methods for CF newborn screening and their different false negative rates between ethnicities [13]. For example, some states require two blood tests that show elevated immunoreactive trypsinogen, a substance released from the pancreas, before allowing an infant to undergo the diagnostic test for CF—a sweat chloride test [13]. Other states require one elevated immunoreactive trypsinogen level and one DNA mutation [13]. False negatives, or failure to identify someone who has the disease, have significant consequences given the severity of the disease. Ross (2008) discusses how “physicians are reassured by a negative screening test even though it is not meant to be diagnostic” [13]. Therefore, children with a false negative screening result, based on the screening protocol in that state, might not obtain a diagnostic workup for CF and continue along a diagnostic odyssey which would result in a delay in receiving appropriate interventions.

Prevention of false negative screening results in ethnic minorities is imperative to avoid health inequities. As ethnic heterogeneity in our society increases, Ross discusses the need for a diverse panel of mutations in states that use DNA testing as a screening criteria [13]. The delta F508 mutation is the most common CF-causing mutation. If mutations that occur at lower frequencies within minority populations are not tested for, there will be missed diagnoses of CF amongst children in these communities during the newborn period. Ross examines how the ACMG CF Carrier Screening Working Group created a panel of 25 mutations in 2001 [13]. Between 2001 and 2008, the panel expanded to include 20 additional mutations that occur at lower frequencies, usually within minority populations [13]. Nevertheless,

Ross emphasizes, “Adding mutations will improve sensitivity but decrease specificity. The selection of mutation panels, then, is not a simple medical decision” [13]. As more genotypes are uncovered and added to the DNA-based screening panel to reduce false negatives in minority populations, new questions arise regarding carrier status and diagnostic criteria for CF.

Screening newborns for fatty acid oxidation defects (FAOD) also demonstrates inherent challenges in NBS itself, based on the complexity



Science in HD. (1954). *Medical examination of Marshallese people*. Photograph. Retrieved from <https://unsplash.com/photos/QERDepT9Zf0>.

and heterogeneity of this group of disorders, which can be further complicated by ethnic, socioeconomic, and environmental factors. With the advent of mass spectrometry, FAOD are screened using ratios of acylcarnitines within dried blood spots, which can be indicative of abnormalities of fatty acid breakdown in the mitochondria for cellular energy. During one

of my clinical rotations, I encountered a four-year-old boy from North Philadelphia with developmental delay presenting to the hospital with recurrent hypoglycemic episodes and elevated creatine phosphokinase, an indicator of muscle breakdown, suggestive of a FAOD not properly identified on the NBS. How did this boy fall through the cracks of the NBS system? If identified when he was a newborn, proper diagnosis and interventions could have prevented his recurrent symptoms and changed the trajectory of his medical condition, possibly reducing his pain and suffering and that of his family. The literature reveals case studies that are similar to my experience, further highlighting the challenges with screening for FAOD, such as valid acylcarnitine ratios, timing of dried blood spot collection, influence of stressors (such as infection) on pathophysiology, and confirmatory biochemical plasma levels [14, 15].

Ideally, NBS should not miss diagnosing infants with harmful genetic conditions. Yet, there is not a one size fits all approach. Each disease process is unique, and the more we learn with regard to genomics, the more we appreciate the heterogeneity of disease processes and underlying etiologies. Additionally, every patient is unique and brings to the testing encounter a different baseline based on their genetic makeup, environmental and

socioeconomic situation, health status, and belief system. Families, such as the one I met on my clinical rotation, may face barriers, such as low health literacy, inability to access healthcare and poor follow-up, that can impede timely diagnosis and intervention for their newborn. Evidence-based protocols and valid assessment algorithms are necessary for conditions like FAOD that are screened by mass spectrometry. Even with such protocols in place, the NBS process still needs to recognize the vast diversity of the newborn population it is serving and the obstacles some families face.

Advocacy, Advocacy, Advocacy!

Public health initiatives do not occur in a vacuum. Policy decisions are made by people or groups of people who are influenced by their unique experiences and the broader context of the world around them. The medical community—pediatricians, geneticists, researchers—must promote thoughtful, equitable, and fair NBS policies to improve the health of all children. Additionally, family members of someone affected by a specific genetic disease are major advocates who have a significant impact on the decision-making process. Each condition has its own advocacy network, usually made up of several organizations that are committed to the same cause. For example, the main advocacy organization for CF is the Cystic Fibrosis Foundation. Its website has a page dedicated to advocacy that explains all the ways to get involved and raise awareness in order “to ensure that the CF community receives support from federal and state decision makers across the country” [16]. There are numerous similar examples that demonstrate the power of advocacy and how it can sway legislation in one direction or another. For example, Vince and Robin Haygood, parents of a child with a fatty acid oxidation defect, greatly influenced Mississippi’s genetic advisory committee and other state legislators to expand NBS to 30 disorders using mass spectrometry in 2002 [17].

Advocacy is a driving force in the setting of public policy. One must consider who is represented amongst the voices in these powerful groups, especially since genetic variation is clustered within ethnicities. Advocacy for NBS policies does not stop at universal screening. It is also about equal access to comprehensive care and research funding to find treatments for these disorders. Farooq et al. (2020) revealed “from 2008 through 2018, federal funding was greater per person with CF compared with SCD [Sickle Cell Disease]” [18]. Consequently, there are over 100 comprehensive care centers for CF [18]. Meanwhile, for sickle cell disease, a condition that disproportionately affects Black children, ten federally funded centers were lost in 2008, resulting in dependence on institutional support for comprehensive care [18]. Recommendations from the Communities of Color and Genetics Policy project stress the importance of representation within advisory com-

mittees, community-based organizations, non-discriminatory policies, and trust in public health agencies to ensure that all voices are heard [19].

ETHICAL CONCLUSION: EDUCATION AND EVIDENCE-BASED PROTOCOLS

The above ethical analysis of expanded universal NBS dives into concerns surrounding beneficence and equity. On a macro level, NBS programs are similar across state lines and benefit children by identifying serious rare diseases and intervening early to prevent harm and preserve health for newborns. However, a screening test is just a screening test. False negatives can lead physicians to be incorrectly reassured their patient does not have a condition on the panel. Conversely, if the screening results are positive, patients and their families must receive follow-up testing, education, interventions, and long-term care. The NBS is a process. Therefore, the focus now must be on education for the existing program and pilot studies to support an evidence-based approach to expansion of NBS to include conditions that benefit individuals, their families, and future generations. The pilot studies include both an objective approach and ethical considerations in the analyses of their findings to help guide the recommendation of which genetic disorders would be appropriate to add to the NBS panel for all states to use. There are excellent education materials online, such as www.babysfirsttest.org; however, more education is needed for primary care pediatricians and parents, especially those with low health literacy, mistrust in the healthcare delivery system, and/or additional barriers to accessing healthcare. Pediatricians play a central role in this process and must be able to explain what conditions are on the panel for their state and how the NBS process works because they coordinate most of a child’s care after birth. It is vital to support families throughout the newborn screening process, understanding their unique perspective, in order to allow their infant to thrive. It is not about doing less newborn screening, it is about doing fair, equitable, efficient newborn screening.

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The Determination of Embryonic Status: Merging Context and Whim

by Janet Dolgin[†] and Renee McLeod-Sordjan^{††}

The collapse of moral arbiters in American society has led to the theoretical and practical resolution of familial matters in courts of law. In recent years, assisted reproductive technology has aided many individuals in delaying and achieving parenthood through cryopreservation of embryos. A conservative estimate suggests that there are presently well over hundreds of thousands—probably over one million—cryopreserved embryos in the United States. While embryos are generally not accorded an ontological status of personhood, the abortion debate has implicitly shaped legal discourse. Cryopreserved embryos are genetic extensions of procreating persons who desire parenthood at some point in time. The complexity of societal and cultural norms of parenthood creates complex indecisions regarding the use, donation, and/or disposal of cryopreserved embryos. Legal decisions, occasioned by disputes about the disposition of cryopreserved embryos, illustrate the apparent need to determine embryonic status. This article focuses on legal cases that have entertained the uncertainty of embryonic status in society and highlights the protections afforded to individuals in their pursuit of life, liberty and parenthood.

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The ontological status of cryopreserved embryos is at issue in an increasingly wide set of contexts. While embryos are generally accorded a lesser ontological status than fetuses, the abortion debate has implicitly shaped discourse about embryonic status. Efforts to determine embryonic status have played a key role in a variety of legal disputes. These include disputes between maternal and paternal procreators of the embryo (progenitors) and disputes between a progenitor or progenitors and embryo storage facilities, fertility clinics, and clinicians.

That courts are being asked to settle disputes about the status—and thus, often the fate—of cryopreserved embryos reflects widespread social uncertainty and disagreement about the status of embryos (and of fetuses). Various positions—that embryos are persons, that they are property, that they enjoy an intermediate position between the two, that they are merely a form of human tissue, or that they enjoy a status not yet, or only recently, determined—suggest the depth of social confusion about the status of embryos, as well as confusion about the status of fetuses and persons. This article reviews a set of determinations about embryonic status, mostly by courts of law, since that is the setting to which disputes about embryos are often brought for resolution. In examining these decisions, it is important to note that judicial decisions about embryonic status generally reflect context (the character of the dispute itself) and the ideological perspective of particular judges—the decision makers. The phenomenon is not unfamiliar, particularly within the context of the debate about abortion in the United States. As a result of the collapse of American values that supported a host of community-based moral arbiters (from the ‘priest,’ to the school principal, to the doctor), disputants now seek alternative venues for resolving disputes. Courts of law have offered an alternative. Yet, the notion that embryonic (or fetal) status can be assessed and clarified through judicial decision-making is discomfiting. Parenthood is a deeply personal choice complicated by cultural norms and, at least in part, protected by the Fourteenth Amendment to the U.S. Constitution. The significance of that protection for progenitors of frozen embryos is less clear.

That courts of law are acting as moral arbiters in disputes about the disposition of embryos no longer wanted by the progenitors for reproduction occasions practical and theoretical consequences. A wide swath of legal decisions, aimed at resolving disputes about the disposition of frozen embryos, illustrates the apparent need to determine embryonic status in the course of settling such disputes.

This article focuses, as well, on a set of practical questions not often entertained in court. These questions follow from the continuing obligation of cryopreservation facilities to store embryos apparently no longer needed

for reproductive purposes. Such facilities face significant confusion in considering how best to handle cryopreserved embryos frozen in the context of caring for the reproductive needs of intending parents who cannot be located and who stopped paying storage fees, sometimes years earlier.

BACKGROUND

In vitro fertilization (IVF) first resulted in a successful human pregnancy and birth in 1978 [1]. Since that time, reliance on assisted reproductive technology has become increasingly common among individuals and couples facing infertility or medical conditions that make natural reproduction unlikely or impossible. Since 1978, millions of babies conceived in vitro have been born throughout the world [2]. Over 300,000 reproductive technology attempts—most of which included IVF—occurred in the United States in 2018 alone [3].

Ontological assumptions about the beginning of life are complicated by discourse about the definition of terms used in reproductive medicine. Human beings have 23 diploid (paired) sets of genetic material, commonly referred to as 46 chromosomes. A gamete is one of two paired haploid reproductive cells, male (spermatozoon) and female (oocyte), whose union is necessary to initiate the development of a new human being. When the female gamete (oocyte) is fertilized by the male (spermatozoon), cell division occurs. An embryo represents the early stage of development from the fourth day of fertilization through the eighth week when sexual organs form. Individual gametes or an embryo may be cryopreserved (frozen) and stored in liquid nitrogen at a temperature of -196 degrees Celsius [4]. Embryos are usually cryopreserved during the first week of fertilization. Cryopreserved embryos are successfully thawed 90% of the time and lead to successful implantation about as often as implantation with fresh embryos [5]. This article will focus on cryopreserved embryos within the first week of human development and on individual gametes.

The process of creating embryos through IVF has often resulted in more embryos than can reasonably be implanted in one woman during any reproductive cycle [6]. By the 1980s, it had become possible to cryopreserve embryos not used in a particular reproductive cycle [7]. Cryopreserving and storing extra embryos have eased the cost and burden of infertility treatments and limited the risk to women of undergoing multiple cycles of drug-induced superovulation and ova extraction [5]. The first successful pregnancies using embryos that had been cryopreserved and thawed occurred in the early 1980s [8]. Increasingly, fertility clinics have offered patients the opportunity to have embryos not used in a particular treatment cycle frozen for future use [5].

However, patients often do not use all of their cryopreserved embryos (frequently referred to as pre-embryos)¹ for reproductive purposes even over significant periods of time [9]. Sometimes they accomplish their reproductive goals. Sometimes they decide to refrain from further infertility treatment for other reasons. Many who defer parenthood often grapple for years with indecision regarding disposal, donation, or use of their cryopreserved embryos [10]. Intending parents with extra embryos may not be able to decide easily how to dispose of embryos no longer wanted for their own reproductive use.² This essay uses the term “intending parent(s)” to refer both to progenitors and to those intending to become parents through use of embryos produced by others. Either group may decide to store frozen embryos (whether created through their own gametes or donated gametes).

For intending parents no longer interested in becoming parents through the use of cryopreserved embryos, choices include donation to others for reproduction, donation to research (stem cell research or other sorts of research) [11],³ embryo destruction, and delaying the decision about how to dispose of extra frozen embryos through continued storage [12]. These choices, often grounded—implicitly or explicitly—on assumptions about embryonic status, can be daunting, leading to significant uncertainty. In the face of this uncertainty, the default position for people with cryopreserved embryos has often been continued storage. As a result, embryos may remain in storage long after couples have lost any interest in using them for reproductive purposes and even after couples have stopped paying storage fees for the continued cryopreservation of the embryos [9]. This presents a dilemma for cryopreservation storage facilities, especially in cases in which the facilities have lost contact with the intending parents [9]. Some directors of cryopreservation facilities have expressed uncertainty about their legal and ethical obligations regarding unclaimed embryos. Medical research has suggested including disposition options during the informed consent process. It is not clear whether or not implementation of that suggestion will be beneficial [10]. This article will proceed to examine, respectively, uncertainty among cryopreservation facilities faced with unclaimed embryos about what

¹ Language choices can play a strong part in determining visions of embryos and fetuses. A number of courts have used the term “pre-embryo” (or “preembryo”) in resolving disputes about the fate of frozen embryos. In part at least, that term suggests that the cells whose fate is at issue enjoy a status below that of “embryos.” This article, aimed at examining diverse perspectives about embryonic status, will use the term “embryos” which seems the more neutral of the two terms.

² The word “dispose,” as used here, refers to any method of providing for the embryos’ future (e.g., use in research, donation to another party or couple; continuing storage; discard with no future use).

³ A couple of studies found that patients undergoing fertility treatment are more positive about donating extra embryos for infertility research than for stem-cell research.



e Biagio e Cesare Arrigo, Antonio/Azienda Ospedaliera SS. (2019). *Cryopreservation of stem cells in liquid nitrogen* (edited). Photograph. Retrieved from https://commons.wikimedia.org/wiki/File:Antonio_e_Biagio_e_Cesare_Arrigo_Cryopreservation.jpg.

to do with those embryos, uncertainty among intending parents about the fate and status of their stored embryos, and uncertainty among judges about how best to resolve disputes about the disposition of stored embryos. Judicial examination of the uncertainty of embryonic status reflects social perspectives of the time. In effect, court decisions provide a historical passport for an anthropological excursion.

UNCERTAINTY AMONG CRYOPRESERVATION FACILITIES

Experts have estimated that at least hundreds of thousands of embryos are cryopreserved in the United States [13]. Others estimate that the number is in the millions [5]. (These numbers include, but are not limited to, unclaimed embryos.) Potential fees owed by intending parents for storage per cryopreserved embryo cycle usually range from \$500 to \$1,000 each year but can be more than that [9]. One owner of a fertility clinic in Florida that provides patients with the opportunity to cryopreserve and store embryos reported that over one-fifth of the embryos stored at his clinic had been “abandoned”⁴ [9]. Embryos are generally not considered to be unclaimed until the intending parents fail to pay annual storage fees for several years and cannot

⁴ In general, embryos are said to be “abandoned” if storage fees have not been paid for at least five years and the patients does not respond to communication from the clinic that has stored the embryos [9]. The term in application to unclaimed embryos seems to have been used first in 1983 in reference to the embryos of Elsa and Mario Rios. The couple had had embryos cryopreserved at a medical facility in Australia before they were both killed in a plane crash. Cattapan, A. & Baylis, F. (2015). Frozen in perpetuity: ‘Abandoned embryos’ in Canada. *Reproductive Biomedicine and Society Online*, 1(2), 104-112. <https://doi.org/10.1016/j.rbms.2016.04.002>.

be reached for guidance about their preferences.

In general, the uncertainty and ambivalence of embryo storage facilities would seem to rest on concerns about legal liability (sometimes connected to unresolved questions about embryonic status) and concern for intending parents who have stopped paying for embryo storage but who may preserve an emotional connection to their frozen embryos. Fertility clinic directors have expressed concern about the moral status of unclaimed embryos in light of guidance from the American Society for Reproductive Medicine, which has asserted that embryos deserve “respect” [9]. It has not, however, been clear how that respect should be expressed.

Regulation of embryo storage, and of reproductive assistance, has been minimal in the United States. That may reflect multiple challenges inherent in the debate about abortion that make many regulatory rules controversial. In 1992, Congress enacted the Fertility Clinic Success Rate and Certification Act (FCSRCA) to mandate that fertility clinics report and publish data for all performed procedures and clinic-specific success rates to the Centers for Disease Control and Prevention (CDC). Approximately 1.7% of all infants born in the United States every year are conceived using ART. In 2017, 87,535 cryopreserved oocytes or embryos were stored with the intent of future use. In the absence of broad legal regulation, however, cryopreservation facilities are left without legal protection should they place a time limit on the storage of unclaimed embryos [14].

The Society for Assisted Reproductive Technology recommends the use of mental health counselors and support organizations to assist parents in navigating the emotions that accompany infertility treatment as well as the many decisions that arise during the process [15]. The fertility clinic is not just performing a single service but facilitating a journey that may or may not lead to parenthood. This journey reflects the inability of the fertility clinic to predict the subjective value of the emotional connection of the progenitor with a one-week-old cryopreserved embryo.



Metzler, L. (2015). *Hand in hand with dad*. Photograph. Retrieved from <https://unsplash.com/photos/B32qg6Ua34Y>.

UNCERTAINTY AMONG INTENDING PARENTS

The uncertainty of intending parents about the status of their embryos reflects the complicated strands of an encompassing social debate. It also reflects changes in perspective as intending parents’ plans for the use of frozen embryos shift over time. For many intending parents beset by conflicting views of how best to dispose of embryos no longer wanted for reproductive purposes, perspectives about embryonic status can become murky. This reflects shifting desires for parenthood and often confusion about their relationship to these embryos.

Several studies have explored responses of intending parents to cryopreserved embryos created for reproductive purposes, including intending parents who no longer want to use their frozen embryos for reproductive purposes but who are conflicted about what should be done with those embryos. On the whole, the relationship of intending parents to their frozen embryos, including those no longer needed or wanted for reproduction, is personal and may be shaped by a series of familial emotions, including expectation, anxiety, lost promise, and commitment.

Intending parents with cryopreserved embryos in the United States often have significant difficulty determining how to deal with extra embryos (the so-called “disposition decision”) [16]. Some couples feel uncomfortable affecting any disposition option.

[C]ouples are initially focused on the immediate goal of achieving a pregnancy... and do not anticipate that having the ability to store surplus embryos will present a challenge in the future. During this initial reassurance stage, the ability to store surplus embryos is viewed as a bonus because at this point the couples do not know how many attempts they will need to achieve their first (and subsequent) pregnancies. Yet, once pregnancy had been successfully achieved and their childbearing completed, the second-stage reaction of most couples was characterized by avoidance of the issue, most commonly by just keeping the embryos frozen, often with the implied assumption that the decision could be postponed, perhaps indefinitely. [16]

In short, initial determinations by intending parents about how to dispose of their cryopreserved embryos may be re-shaped as they experience changes in their responses to the frozen embryos. Research conducted by Susan Klock et al. supports this suggestion. Klock et al. reported that over one-quarter of couples who stored frozen embryos at Klock’s U.S. fertility clinic had embryos still in storage at the end of the facility’s initial three-year storage limitation period. Researchers surveyed 41 couples about disposition choices both at the beginning of treatment and after a period of embryo storage. Significantly, a large majority (71%) of these couples expressed dif-

ferent choices at the start of treatment and at the end of the initial three-year storage period [17].⁵

Lyerly et al. reported that intending parents reject most disposition options made available to them. In a mixed method study of 1,020 fertility couples with cryopreserved embryos from nine geographically diverse clinics, the authors reported that reasoning regarding embryo disposition evolves with reproductive intent. Reluctance among intending parents to select among disposition options was high regardless of desire for future pregnancy. The authors suggested that intending parents who ascribed personhood or high importance to the embryo, fetus, or future child were more likely to make a disposition decision than others. Yet, generally, intending parents included in the study found that the options offered for disposing of cryopreserved embryos no longer wanted for reproductive purposes were unattractive [10].

Still other studies echo similar findings and suggest that intending parents' disposal determinations about cryopreserved embryos are difficult at all stages of reproductive treatment, both in the United States and in other countries. A U.S. study involving 58 couples who had successfully relied on a donor egg to conceive and who had one or more additional embryos cryopreserved in storage found that almost three-quarters of those interviewed (58 women and 37 men) had difficulty deciding what to do with their cryopreserved embryos [16].⁶ On average, this group of intending parents had had embryos in storage for more than four years. The struggles faced by intending parents with stored cryopreserved embryos in the U.S. about embryo disposition seem to track "the complex nature of the couples' conceptualization of their embryos." This may reflect some sense—even among pro-choice intending parents—that embryos are "virtual' children" [16].

⁵ On this, the authors explain:

"Thirteen of 22 couples who had initially opted for disposal now wanted either to use or to donate the embryos. Nine of 11 couples who had initially opted for donation to an infertile couple no longer chose that option: 2 couples now decided to use the embryos, 2 chose to thaw them, 3 continued storage, and 2 donated the embryos to research. Seven of eight couples who had initially planned to donate the embryos to research now chose either to use the embryos or to dispose of them." [17]

⁶ Nachtigall et al. found that the "disposition decision process" involved four states: 1. reassurance (provided by having excess embryos during the period of IVF care); 2. avoidance (after a couple's "childbearing [was] completed"); 3. confrontation (facing "discomfort and uncertainty when actually confront[ing] the disposition decision"); and 4. resolution (experienced by only some of the couples and leading to a "sense of completeness and resolution"). Conceptualizations of these embryos included viewing them as children, as members of the parent or parents' family, as a "kind of genetic or psychological insurance policy," and as providing future medical benefit to existing children. More confounding still, couples sometimes view cryopreserved embryos as "symbols of the infertility" they endured [16].

This is important and suggests that ideological positions in the debate about abortion may not always harmonize with personal decisions about one's embryos or one's fetus.

Intending parents who imagined their cryopreserved embryos as open to suffering were less likely than others to decide to have their embryos destroyed [16]. And those who thought of the embryos as "virtual' children" worried about losing any control over the embryos' welfare. The researchers concluded that this concern explained the reluctance of these intending parents to donate extra embryos to others for reproductive purposes [16]. This supports the researchers' findings that these intending parents were more comfortable with the destruction of their embryos than with a decision that would hand those embryos over to others' control (whether in reproductive or research settings).

Difficulty determining the fate of extra cryopreserved embryos is not a challenge unique to infertility patients in the United States, although decisions about embryo disposition sometimes differ from one geographic setting to another. In a number of European countries, a significant majority of people with cryopreserved embryos no longer wanted for reproductive purposes agreed to donate the embryos for research. Seventy-three percent of patients treated with IVF in Switzerland have made that choice, as have between 57 and 60% in Denmark [18]. This pattern differs from that in the United States.

In some European countries, the law limits options. In Poland, for instance, couples cryopreserving embryos have very limited options regarding the disposition of stored embryos. Polish law precludes both destroying surplus embryos and donating them for research [19, 20]. As a practical matter, those with stored embryos in Poland must use them for reproductive purposes or the embryos will remain in storage indefinitely [19].

A prospective study of patients in France who relied on both IVF and intracytoplasmic sperm injection (ICSI) (direct injection of spermatozoon into the oocyte) examined the relevance of "specific pre-embryo representations" to couples' decisions about how to dispose of extra cryopreserved embryos [6]. In Bruno et al., couples were asked to select among six representations of embryos: "a mere thing, a potential person, a child, a project, a cluster of cells or life itself." Two of these representations may be confusing: "project" implies a "parental project" aimed at reproducing, and "life itself" suggests that the embryos are alive but do not enjoy personhood. Furthermore, there is some overlap among many of these representations. Very few (1.2% of the respondents) described embryos as mere things. Among those who did not view the embryo as a "child," the majority decided to donate extra embryos to research. Those viewing extra embryos as potential people or as human life were more likely than others to want their embryos donat-



Machnitzki, T. R. (2013). *Tennessee Supreme Court building in Nashville, Tennessee*. Photograph. Retrieved from https://commons.wikimedia.org/wiki/File:Tennessee_Supreme_Court_building_Nashville_TN_2013-07-20_004.jpg

ed to an infertile couple for reproductive purposes. But surprisingly, this group was also more likely than other groups of patients to “stop cryopreservation.” In contrast, Nachtigall et al. reported that intending parents who believed their pre-embryos could suffer generally opted against destruction of the pre-embryos [16]. Bruno et al. explain this decision by referring to “the commitment and emotional investment of these persons to their ‘children-embryos’ as probably too strong to accept donating them. They prefer discontinuing the storage of their embryos rather than abandoning them to another future that they will not witness.” That intending parents with frozen embryos created from donated gametes (ova or sperm) rather than from their own gametes were ten times more likely to provide for embryo donation than other intending parents [6], suggests that people attributed significance to a genetic link between themselves and their cryopreserved embryos.

The same French study further suggests that about a quarter of patients with cryopreserved embryos viewed those embryos as having more than one status [6]. A secondary analysis, which contained only four of the six possible embryo representations (“potential person, cluster of cells, project, or child”), revealed that about three-quarters of the respondents selected one description of their frozen embryos, 17.7% selected two, 4.5% selected three, and 0.9% selected all four [6]. This is an important finding because it suggests that people may simultaneously hold diverse—sometimes even conflicting—images of their frozen pre-embryos. Legal cases brought by intending parents alleging harm due to the loss of or damage to their embryos

often reflect similarly inconsistent representations of embryos.⁷ A case of this sort is considered below.

UNCERTAINTY AMONG JUDGES

Courts have entertained questions about embryonic status within the context of particular disputes. To some extent, judicial conclusions about embryonic status reflect the specific issues at stake in individual cases. In addition, judicial conclusions sometimes reflect judges’ own perspectives and beliefs about the status of embryos. One legal case, entertained by three Tennessee courts—a trial court (1989), an intermediate appellate court (1990), and the state’s highest court (1993)—encompasses a broad panoply of judicial responses and suggests three discrete visions of embryonic status [22]. The case, *Davis v. Davis* (“*Davis*”), was occasioned by a dispute between Junior and Mary Sue Davis, a divorcing couple, about the fate of seven cryopreserved embryos. Further, the decision of Tennessee’s highest court in *Davis v. Davis* [23] created a framework for responding to such disputes that has often been applied by courts throughout the United States as they have faced disputes between intending parents about the fate of frozen embryos.

Davis is worth considering in some detail, particularly because each of the three state courts that rendered decisions in the case relied on a different understanding of embryonic status than that assumed by the other two. However, each court’s vision of embryos did not necessarily harmonize with its determination regarding the fate of the couple’s embryos. This is especially true of the decision of Tennessee’s highest court in *Davis*.

In short, a continuum of views about the ontological status of embryos is reflected in the three Tennessee court decisions in this case. The dispute involved a divorced couple named Mary Sue and Junior Davis. Each party’s specific preferences regarding seven cryopreserved embryos, created for reproductive purposes from Mary Sue’s ova and Junior’s sperm, shifted over time. However, Junior Davis consistently contended that parenthood should not be forced on him, moving over time from a preference for continued cryopreservation to one for embryo destruction. Mary Sue, in contrast, wanted to use the embryos for reproductive purposes—at first, for herself,

⁷ As a general matter, state laws that characterize embryonic or fetal status are not always consistent with other laws—for instance, those involving wrongful life claims or homicide. Those inconsistencies are rarely justified or even discussed. Roxland and Caplan note that a state “legislature [may] believe[] that there are sufficient deterrent effects of allowing a prosecution for wrongful death of a fetus in order to protect the life and safety of pregnant women, but does not believe that a pre-implantation embryo should be accorded all of the rights of a person” [21].

and later, through embryo donation to others.⁸

A state trial court concluded that the frozen embryos were “human beings, *in vitro*, to be known as the Davises’ child or children” [22]. That court’s summary of the essential issue at stake in the Davises’ dispute directed its conclusion: “What then is the legal status to be accorded a human being existing as an embryo, *in vitro*, in a divorce case in the state of Tennessee?” [22]. The trial court’s decision reflected what would seem to have been the only reasonable response in light of that court’s understanding of the central issue to be decided—the fate of seven “human beings.” The court wrote:

[I]t is to the manifest best interest of the children, *in vitro*, that they be made available for implantation to assure their opportunity for live birth; implantation is their sole and only hope for survival. The Court respectfully finds and concludes that it further serves the best interest of these children for Mrs. Davis to be permitted the opportunity to bring these children to term through implantation. [24]

Further, the trial court concluded that “temporary custody” of the “human embryos” should be “vested in Mrs. Davis... and that all matters concerning support, visitation, final custody and related issues be reserved to the Court for further consideration and disposition at such time as one or more of the seven cryogenically preserved human embryos are the product of life birth” [22]. The trial court’s vision of embryonic status as that of personhood harmonized with its holding in the case. In effect, the court conceptualized the dispute as a custody dispute between divorcing parents.

In sharp contrast to the trial court’s vision of embryonic status as full personhood, a Tennessee intermediate appellate court seemed to view the Davises’ embryos as property. In 1990, this court sent the case back to the trial court, directing the trial court to “vest[] Mary Sue and Junior with joint control of the fertilized ova and with equal voice over their disposition” [24]. This conclusion followed the court’s summary of “scientific distinctions between fertilized ova that have not been implanted and an embryo in the mother’s womb” [24]. The court stressed that the Davises’ embryos had not yet begun to develop nervous, circulatory, or pulmonary systems and that, as a general matter, “*in vitro* fertilization results in a low success rate” [24]. In effect, the court dismissed any claim that the embryos enjoyed personhood, treating them far more like property than children or potential children.

Finally, Tennessee’s supreme court, the state’s highest court, heard the case. That court interpreted the decision of the intermediate appellate court

⁸ Over time, the parties’ preferences changed. Later, Mary Sue, who had remarried, sought the right to donate the embryos to a couple without children. Junior opposed donation but asked that the embryos be discarded [23].

to suggest that the “interest” of Mary Sue and Junior in the frozen embryos was “in the nature of a property interest” [24]. The state supreme court expressly considered the status of the embryos, referring to the subject of that inquiry as “the ‘person’ vs. ‘property’ dichotomy” [24]. However, the court did not accept the trial court’s understanding of the embryos as children or the intermediate appellate court’s suggestion that they should be treated as property.

The state supreme court looked to the ethical guidelines of The American Fertility Society (“Society”) for direction [24]. The Society’s Ethics Committee opined:

[T]he preembryo deserves respect greater than that accorded to human tissue but not the respect accorded to actual persons. The preembryo is due greater respect than other human tissue because of its potential to become a person and because of its symbolic meaning for many people. Yet, it should not be treated as a person, because it has not yet developed the features of personhood, is not yet established as developmentally individual, and may never realize its biologic potential. [25]

Following the Society’s guidance, the *Davis* court concluded that “pre-embryos are not, strictly speaking, either ‘persons’ or ‘property,’ but occupy an interim category that entitles them to special respect because of their potential for human life” [24]. Yet, the court also declared its readiness in future cases⁹ to look to a contract entered into by intending parents and fertility clinics to resolve disputes such as that between Mary Sue and Junior Davis [24]. It is hard to discern how the special respect extended to embryos would necessarily be actualized through such contractual agreements. Contractual arrangements might be expected to safeguard the autonomous choices of the intending parents but would be far less likely to ensure protection for their embryos or affect the “special respect” presumptively owed to them.

Even more, the court explained that “[i]n the absence of... agreed modification,” the progenitors’ “prior agreements should be considered binding” [24]. In fact, the court resolved the dispute about the Davises’ embryos by weighing “the relative interests” of Mary Sue and Junior [23]. This involved assessing Mary Sue’s “right to procreate” against Junior’s “right to avoid procreation” [23, 26]. The embryos were eventually thawed and given to Junior Davis for disposition. This resolution would seem to have accorded respect to the progenitors’ balanced interests but not, in particular, to the embryos. In effect, the decision appropriated a frame that focused on one type of familial relationship—that between divorcing spouses. That frame displaced

⁹ The Davises had not entered into agreements with each other or with the fertility clinic where they received care.

and substituted for concern with embryonic status and the “special respect” the court had accorded embryos. The court seemed not to notice the shift from its apparent focus on embryonic status to a determination that took account of the intending parents’ preferences and that submerged concern for any “respect” that—according to the court’s own vision—might be owed to the embryos.

Even more, only one of the three *Davis* courts’ presumptions about embryonic status—that embryos enjoy personhood (the presumption of the trial court)—would seem to place strict limits on the terms of their disposition. As in any custody case, the trial court’s specific holding depended on its analysis of the embryos’ “best interests.” It would have been almost impossible for the trial court, having characterized the embryos as children, to have ordered their disposal as waste. The other courts that rendered decisions in *Davis* variously characterized the embryos as something like property (the intermediate appellate court) and as neither property nor persons but owed special respect because of their potential for personhood (the state supreme court). The intermediate appellate court’s decision harmonized with its characterization of the embryos, but that decision did not resolve the dispute between Junior and Mary Sue.¹⁰ The decision of the state supreme court did not reflect its presumptions about embryonic status.

As noted, the state’s highest court granted Junior Davis the right to dispose of the embryos [23]—a decision which would not seem to have paid deference to its own conclusion that cryopreserved embryos enjoy an intermediate status between persons and property and, as such, are owed special respect. In short, courts have felt compelled to characterize cryopreserved embryos in responding to disputes about their disposition but have not always harmonized their holdings with those characterizations. This suggests a need to discern what embryos “are” along with minimal commitment to various formations of embryonic status. There is, in short, a noteworthy disconnect between presumptions about embryonic status and determinations about the disposition of cryopreserved embryos. That disconnect suggests that assertions about the status of embryos are often not grounded in deeply embedded assumptions and, as a result, often do not affect rulings.

Despite the disconnect between the Tennessee Supreme Court’s characterization of the embryos’ status and its disposition of the case, the deliberations of the state’s supreme court in *Davis* about embryonic status have been invoked often in subsequent cases involving disputes about cryopreserved embryos. The court’s view of embryos as intermediate between people

¹⁰ The intermediate appellate court granted “joint custody” of the embryos to Junior and Mary Sue, explaining that they “share[d] an interest in the seven fertilized ova” [23]. This decision may have rested on the presumption—correct, as it turned out—that the court’s decision would be appealed to the state’s highest court.



Bolovtsova, E. (2020). *Man and woman holding hands figurine*. Photograph. Retrieved from <https://www.pexels.com/photo/man-people-woman-adult-6077476>.

and property has been echoed by other courts in their attempts to resolve disputes between intending parents about the disposition of frozen embryos [27].

The narrative attending disputes about cryopreserved embryos also seems to affect judges’ presumptions about embryonic status. Although not a definitive pattern, there is a tendency for courts to view embryos as property in cases occasioned by non-familial disputes more often than they do in the context of familial disputes, such as that between the Davises.

The *Davis v. Davis* Tennessee supreme court ruling cited a bailment contract case decided in an earlier Virginia case, *York v. Jones* (“York”). *York* was decided by a federal district court in Virginia in 1989 (four years before the Tennessee supreme court’s ruling in *Davis*) and is illustrative of a dispute involving frozen embryos that was not grounded on a dispute between the intending parents. The case was initiated by a couple, the intending parents and progenitors of the embryo at issue against a fertility clinic at which they had received reproductive treatment. The court in this case presumed that embryos should be categorized as property. On that presumption, it ruled in favor of the intending parents against the fertility clinic that stored the couple’s cryopreserved embryo [28].

Steven York and Risa Adler-York had been treated for infertility at the Jones Institute for Reproductive Medicine (“Jones Institute”) in Norfolk, Virginia. Six embryos had been created from the couple’s gametes. Five were inserted in Risa’s uterus, but a pregnancy did not follow [29]. A sixth embryo was frozen for future reproductive use. A year later, the couple asked the Jones Institute to transfer that embryo to the Institute for Reproductive Research, a hospital in Los Angeles. After the Jones Institute refused the request, the couple sued. Judge Clarke, writing for the federal court in Vir-

ginia, largely side-stepped considerations of familial relationships and presumptions common to the resolution of familial disputes and concluded that the cryopreservation agreement between the couple and the Jones Institute had created a bailor-bailee relationship.¹¹ (Said simply, a bailment involves one party, the bailee, holding and promising to safeguard for the duration of the bailment, property owned by another party, the bailor). In the context of the York case, the court's invocation of the bailor-bailee relationship suggested that the intending parents (the bailors) had given their embryos to the fertility clinic (the bailee) for safe-keeping and that the embryos, because they were owned by the couple, could be retrieved by them at a future point in time.

[T]he Cryopreservation Agreement created a bailor-bailee relationship between the plaintiffs and the defendants. While the parties in this case expressed no intent to create bailment, under Virginia law, no formal contract or actual meeting of the minds is necessary. Rather, all that is needed "is the element of lawful possession however created, and duty to account for the thing as the property of another that creates the bailment." The essential nature of a bailment relationship imposes on the bailee, when the purpose of the bailment has terminated, an absolute obligation to return the subject matter of the bailment to the bailor. The obligation to return the property is implied from the fact of lawful possession of the personal property of another. [28]

In designating the relationship between the progenitors and the reproductive technology clinic as a bailment, the court in *York* presumed—apparently without pondering the matter—that the couple's frozen embryo (referred to as a "pre-zygote" by the court) was property and that it belonged to the progenitors. Thus, in the court's view, the Yorks were presumed to be the bailors in the arrangement between the parties; The Jones Institute was the bailee. The court's description of the Cryopreservation Agreement between the

¹¹At the start of its rendition of the "facts" of the case, the court did note that the Yorks sought fertility care with the hope that they would "become the parents of their own genetic child" [28]. That is virtually the only language referring to family relationships in the opinion. Further the court considered the defendants' motion to discuss plaintiff's count IV which alleged that defendant's control over the embryos interfered with plaintiff's "constitutional right to reproductive privacy in violation of the first, fourth, ninth and fourteenth amendments." The court did not consider the substance of the allegation. It denied the defendant's motion to discuss this count, countering the defendant's Eleventh Amendment claim with the conclusion that the clinic was "deemed a governmental and public instrumentality" but that it had "a high degree of autonomy over both its internal operations and in the discharge of the statutory powers and duties conferred upon it. The Court is satisfied that the plaintiffs' judgment, if any, will not be paid from the state treasury" [28].

Yorks and the Institute buttressed the court's conclusion that the embryo was property. That contract provided that the fate of the York's frozen embryo, should the couple separate and disagree about its use, would be decided in a property settlement.¹²

Other courts facing disputes between intending parents and third parties (usually fertility clinics and physicians providing reproductive care) have viewed embryos through two or more discrete lenses [30]. This readiness resembles that of some intending parents with frozen embryos (as indicated by the study in France, noted above) to view their frozen embryos through discrete lenses—a small number even claiming to see their embryos, at once, as potential people, cells, part of a project, and as a child.

A case brought by Belinda and William Jeter against the Mayo Clinic Arizona ("Mayo") illustrates this possibility. The couple sued the Clinic after they learned that Mayo had lost or misplaced five of their cryopreserved embryos [30]. The couple, largely following the demands of the law with regard to various claims against the clinic, asserted—inconsistently, it would seem—that their embryos were potential children (to support a wrongful death claim), that they were "potentially viable human beings" (in support of a "breach of fiduciary claim"), and that, implicitly, they were property (to support a claim for "loss of irreplaceable property" and in support of a claim that Mayo Clinic Arizona had breached a bailment agreement with the couple). The inconsistency may appear to be paradoxical—allowing claims based on different assumptions of the embryos' status—but is permitted by the law.

A state appellate court declined to opine regarding the Jeters' assertion that the embryos were people—a claim needed to succeed on a wrongful death claim. The court found the question best left to the state legislature. The court then concluded that the Jeters had a potential ground for moving forward with their case pursuant to an Arizona law that someone who agrees to serve another with regard to the protection of "the other's person or things" can be liable if harm befalls that person or thing [30]. Here, the court agreed expressly to presume the embryos "things" for which the Mayo

¹² The court quoted part of a consent form signed by the Yorks:

We may withdraw our consent and discontinue participation at any time without prejudice and we understand our pre-zygotes will be stores only as long as we are active IVF patients at The Howard and Georgeanna Jones Institute for Reproductive Medicine or until the end of our normal reproductive years. We have the principle [sic] responsibility to decide the disposition of our pre-zygotes. Our frozen pre-zygotes will not be released from storage for the purpose of intrauterine transfer without the written consents of us both. In the event of divorce, we understand legal ownership of any stored pre-zygotes must be determined in a property settlement and will be released as directed by the order of a court of competent jurisdiction. ... [28]

Clinic Arizona had accepted responsibility. At the same time, the court accepted the possibility that the Jetters might succeed on the basis of a “claim for breach of fiduciary duty,” which presumed the couples’ embryos to be potential human beings. Finally, the appellate court concluded that the Jetters could move forward with their claim that the Clinic had breached a bailment agreement with them. That agreement rested on the premise that the Jetters’ lost embryos were property.

BEYOND FAMILIAL OR CONTRACT METAPHORS

So far, this paper has focused on disputes about embryos between divorcing spouses and on non-familial disputes between intending parents and third parties. There are a set of challenging issues about embryonic status and disposition that comprise a third domain. This domain is distinct from the other two, although it often involves family relationships. Each of the examples considered in earlier sections of this essay depended for resolution on the presumptions of autonomous individuality by relevant decision makers. Cases in this third domain do not and, indeed, cannot depend on that presumption.

This third domain involves decisions about embryos or gametes that cannot be resolved through recourse to the decisions of autonomous individuals because the presumptive decision maker does not enjoy capacity or is deceased and left no relevant instructions. Decisions about the preservation of posthumously donated sperm, or even ova, fall into this category as do cases about cryopreserved embryos or gametes created for reproductive use by intending parents who die, often accidentally, before their embryos or gametes have been used for the intended purpose.

The *Estate of Desta* raised this issue in a probate court in Texas [31]. In the course of fertility treatment, Yenenesh Desta and her husband, Yeyehyirad Lemma, had eleven embryos cryopreserved. The couple (referred to by the Texas probate court as the Lemma-Destas) were killed by a gunman in the summer of 2012. They died without wills. Further, their agreements with the facility that was storing their frozen embryos did not provide for the situation that had arisen—the death of both intending parents. The couple had one intestate heir, a two-year old child named Kedus Desta.

A Texas probate was asked to determine what should be done with the deceased couple’s frozen embryos in light of the absence of directions from them and the absence of defined law regarding disposal. The court looked to *Davis v. Davis* [22, 24], decided in Tennessee over a decade earlier, and to two California cases involving the disposition of frozen sperm that had been cryopreserved by men who died before disposition of the sperm [32, 33]. Each of the latter two cases included statements of intention from the men about their preferences regarding disposition of their frozen sperm. In the

Desta case, no relevant intentions had been voiced by either gamete donor.

While echoing the conclusion of Tennessee’s highest court in *Davis* that embryos are owed “special respect” [24, 31], the Texas court treated the embryos as property to be distributed as part of the Lemma-Desta estate. The court noted that the embryos had “a value under Texas law,” a conclusion suggested by the readiness of Texas law to allow frozen embryos to be “the subject of an enforceable contract” (a conclusion the court identified on the basis of Texas precedent—a decision reached by a Texas court in 2006 in a case involving a dispute about frozen embryos) [31]. The court opined that the absence of a relevant agreement indicating the Lemma-Destas’ intentions regarding the embryos precluded the court from authorizing their implantation, donation or destruction. Accordingly, the court characterized the eleven frozen embryos as part of the property that would pass to the Lemma-Destas’ toddler son. The court ordered that the embryos remain cryopreserved until that child reaches majority.

In short, the *Lemma-Desta* court was ready to treat the embryos as property. Yet, as if to hedge society’s moral bets, it followed the *Davis* court in presuming to owe a “special respect” to the Lemma-Destas’ frozen embryos. But it responded to the absence of any statement about the intending parents’ preferences should they both die before disposing of the embryos by treating those embryos as part of the couple’s property, to be inherited by their only intestate heir.

CONCLUSION

The several cases reviewed here show that courts (in all likelihood reflecting the society within which they function) are able to reach a *modus vivendi* in cases occasioned by disputes between divorcing parents about the fate of cryopreserved embryos. In such cases, courts often presume cryopreserved embryos to have an intermediate status between property and persons—thereby suggesting their potential personhood—but then allow agreements between intending parents to govern the disposition of their embryos. In effect, these courts displace concern for the embryos with a more familiar challenge—respecting the various interests and needs of each party to a divorce.

In disputes occasioned by the loss of or harm to embryos, courts are often stymied because they are generally reluctant to categorize embryos as property—a characterization required for the success of available legal claims through which intending parents can seek redress. Even more, in these cases, judicial determinations of embryonic status seem to be incidental as often as they are intentional. More specifically—and more disconcerting—courts seem ready to allow embryonic status to be defined almost arbitrarily. Differing decisions can perhaps be viewed through the lens of the

parties bringing the case versus the court arbitrating the case.

Finally, particular conundrums face courts asked to determine the fate of embryos in cases in which the progenitors have died without leaving instructions regarding their intentions for the embryos. Such cases are important because they show that the firm regard for the decisions of autonomous individuals that guides most court decisions about the fate of cryopreserved embryos can be displaced and replaced by other presumptions.

Many of the concerns considered here attach as well to discussions of gamete or fetal status. Yet, there are differences that render gametes, embryos, and fetuses distinct, each from the other two. Gametes (sperm and ova) do not carry the full complement of human chromosomes, and have thus often been viewed as enjoying a lesser ontological status than embryos, even by people ready to attach personhood to embryos. Fetuses, on the other hand—the central subject of abortion discourse—cannot be safeguarded through cryopreservation. In effect, options for fetal survival are fewer than those providing for embryonic survival. Still, it remains difficult, if not impossible, to definitively identify the moment at which a gamete, an embryo, or a fetus becomes a person.

Facilities storing cryopreserved embryos generally assume that intending parents commit themselves through consent agreements to lifelong reproductive decisions regarding their cryopreserved embryos. In contrast, the law more readily recognizes that parental intentions change over time, and autonomous individuals can choose to govern their own genetic material. The law's readiness in certain cases to treat embryos as akin to property can result in disposition decisions that may belie the intentions of the intending parents. This is particularly clear in *Estate of Desta*, discussed above. By including the Lemma-Desta embryos in the couple's estate, a disposition decision was left (years hence) to the couple's toddler son. There was no evidence that this option harmonized with the couple's preferences.

Continued uncertainty and debate, sometimes acrimonious, surround understandings of embryonic status. The debate is less vituperative than that surrounding abortion. Still, decisions about the disposition of frozen embryos no longer wanted for reproduction by the intending parents are often fraught with anxiety for fertility clinics and other embryo storage facilities, for intending parents, and even, from time to time, for judges faced with resolving disputes about the disposition of embryos. Those anxieties are unlikely to be assuaged soon and require a practical legal and moral solution. As long as the debate about abortion continues to play a prominent, often divisive, role in American social discourse, a less contentious debate about embryonic status and the disposition of cryopreserved embryos will survive at its margins.

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