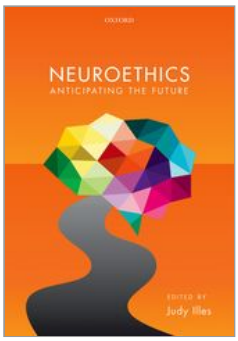

Neuroethics: Anticipating the future
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Minors and incompetent adults: A tale of two populations

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Abstract and Keywords

The participation of vulnerable populations in biomedical research—such as minors and incompetent adults—has in the past, and will continue to be a central consideration in bioethics considering they warrant special protections against potential rights violations and exposure to undue risk. These populations, however, should not be excluded from the opportunity to benefit from scientific progress through their research participation. The promises of personalized medicine for improved diagnosis and treatment of pediatric diseases further underscores this pressing need for their inclusion. This chapter provides both a retrospective and prospective analysis of research participation, with a special focus on the involvement of minors and incompetent adults in the data-intensive research typical of personalized medicine and genomic translation. The authors propose reverse vulnerability as one conceptual lens through which to examine the ethical intersectionalities associated with data-intensive research participation within both populations. The chapter includes a discussion of how situational vulnerabilities unfold for minors and incompetent adults while participating in data-intensive research, as well as how these vulnerabilities are implicated in future ethics governance in the post genomic era.

Keywords: Consent, ethical convergence, biomedical research, data sharing, minors and incompetent adults

Introduction

Biomedical research enables improvements in diagnosis and treatment of human diseases, and participation in research is the cornerstone of such medical progress. Indeed, the scholarly beginnings of the bioethics field are often attributed to human rights questions concerning the ethics of human participation in research, and which have since influenced every biomedical field from pediatrics (Diekema 2006) to aging (Kim et al. 2001), and genomics (Knoppers 2013) to neurology (Choudhury et al. 2014). The completion of the Human Genome Project in 2003 brought about paradigmatic shifts in the nature and conduct of biomedical research. This shift toward data-intensive science is evident in the ways that analysis, exchange, and reporting now occur increasingly in virtual (e.g., the cloud commons (Stein et al. 2015)) rather than physical spaces.

The participation of humans in research remains nevertheless a central consideration in bioethics, and an increasingly complex area for policy development as research becomes more data intensive and data driven. This is particularly true for the participation of categorically vulnerable populations in biomedical research—such as minors and incompetent adults—who warrant special protections against potential rights violations and exposure to undue risk or, to undue exclusion and deprivation of the benefits of research. In this chapter, we provide both a retrospective and prospective analysis of research involving these two populations with a special focus on the data-intensive sciences such as genomics and its related “omics” disciplines. In doing so, our analysis adopts what we term “reverse vulnerability” as one lens through which to examine the ethical intersectionalities between both populations in an effort to better complement governance strategies to the contemporary realities of data-intensive science and data sharing.

The first and second parts of this chapter provide a policy overview of research participation and the protection of minors and incompetent adults living with dementia. We comment on the practical and theoretical implications of reverse vulnerability to an emerging area of contemporary policy development: international data sharing. A reinvigorated (p.370) discussion of research participation involving minors and patients living with dementia necessarily precedes, in our view, policy-making for sharing research data.

Historically, the *parens patriae* doctrine was the first to legitimize the legal status of vulnerable persons and the State’s obligation to protect them. This legal doctrine stipulates that the government acts as a guardian of all persons legally incapable of acting on their own, even in the absence of specific legislation (Griffith 1991). Such State powers

are protective of both property and personal interests, and are usually exercised by the courts. Both children and incompetent adults are legally presumed to be unable to make decisions concerning their health, welfare, or involvement in research. It was not until the *Nuremberg Code* in 1947, and later the *Declaration of Helsinki* in 1964, that the interests of minors and incompetent adults were specifically addressed in medical research.

Ethical principles outlined in the *Nuremberg Code* emphasized protection through exclusion, while the *Declaration* endorsed their inclusion albeit with special protections. Most countries recognize parents or family members as primary decision-making authorities for minors and incompetent adults. Surprisingly, however, neither the 1989 United Nations (UN) Convention on the Rights of the Child, nor the 2006 UN Convention on the Rights of Persons with Disabilities (the latter encompassing incompetent adults such as “those living” with dementia) explicitly addresses their inclusion in research.

From these historically protective stances toward vulnerable populations in research, international ethics norms evolved to adopt more promotional approaches. The European Clinical Trials Directive is but one example that testifies to this evolution, which positively mandates the inclusion of children and incompetent adults in clinical trials in Europe (European Parliament & the Council of the European Union 2014, s. 32(1)).

Table 19.1 summarizes the Directive, as well as other international ethics guidelines with specific mention of research involving vulnerable persons.

Table 19.1 International ethics guidelines on the participation of vulnerable persons in medical research

International convention/ guidelines/policy	Participation of legally incompetent persons in research	Ethical rationale
World Medical Association (WMA) Declaration of Helsinki (2013) Ethical Principles for Medical Research Involving Human Subjects	**Article 13:** All vulnerable groups should receive specifically considered protection **Article 28:** For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.	**Article 20:** Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.
Council for International Organizations of Medical	**Guideline 15:** Research involving vulnerable persons	**Commentary on Guideline 15:**

International convention/ guidelines/policy	Participation of legally incompetent persons in research	Ethical rationale
Sciences (CIOMS) (2016) International Ethical Guidelines for Health-related Research Involving Humans	When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups in the conduct of the research.	… It is important to recognize that vulnerability involves not only the ability to provide initial consent to participate in research, but also aspects of the ongoing participation in research studies. In some cases, persons are vulnerable because they are relatively (or absolutely) incapable of protecting their own interests. This may occur when persons have relative or absolute impairments in decisional capacity, education, resources, strength, or other attributes needed to protect their own interests. In other cases, persons can also be vulnerable because some feature of the circumstances (temporary or permanent) in which they live

International convention/ guidelines/policy	Participation of legally incompetent persons in research	Ethical rationale
		makes it less likely that others will be vigilant about, or sensitive to, their interests.
United Nations Declaration on Bioethics and Human Rights (2005) **[Articles 7–8]**	**Article 7:** Persons without the capacity to consent	**Article 8: Respect for human vulnerability and personal integrity** In applying and advancing scientific knowledge, medical practice and associated technologies, human vulnerability should be taken into account. Individuals and groups of special vulnerability should be protected and the personal integrity of such individuals respected.

International convention/ guidelines/policy	Participation of legally incompetent persons in research	Ethical rationale
	In accordance with domestic law, special protection is to be given to persons who do not have the capacity to consent: (a) authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned and in accordance with domestic law. However, the person concerned should be involved to the greatest extent possible in the decision-making process of consent, as well as that of withdrawing consent; (b) research should only be carried out for his or her direct health benefit, subject to the authorization and the protective conditions prescribed by law, and if there is no research alternative of comparable effectiveness with research participants able to consent. Research which does not have potential direct health benefit	

International convention/ guidelines/policy	Participation of legally incompetent persons in research	Ethical rationale
	should only be undertaken by way of exception, with the utmost restraint, exposing the person only to a minimal risk and minimal burden and, if the research is expected to contribute to the health benefit of other persons in the same category, subject to the conditions prescribed by law and compatible with the protection of the individual's human rights. Refusal of such persons to take part in research should be respected.	

International ethics guidelines promote the inclusion of incompetent adults in research as for minors, provided certain special protections. The benefits, either direct or indirect, as a result of their participation justify such inclusion in part, to say nothing of the fact that certain diseases belong to these groups exclusively. Furthermore, improved standards of care for conditions earlier or later in life may not otherwise emerge without the participation of these populations. Data-intensive research involving vulnerable groups, we argue, must reconcile protective and promotional stances to make way for realistic and proportional risk analysis and governance. Only then can we facilitate, rather than obstruct, a future of open science required to advance (personalized) medicine for minors and patients living with dementia, among others.

Children and minors

The history of children in biomedical research has been (paradoxically) marked by both grave human rights abuses as well as groundbreaking clinical progress. Their participation in research has, in turn, long raised ethical concerns. An era of over-protectionism ensued in the wake of research abuses involving children such as those at the Willowbrook State (p.372) (p.371) (p.373) School, Staten Island, New York City, between the late 1950s and early 1970s (Diekema 2006). While the motivation for a protectionist approach was well intentioned, such policies resulted in children's near exclusion from biomedical research generally. The consequences of which resulted in a dearth of pediatric-specific therapies (Fernandez et al. 2003), felt even today as standards of care derived from clinical trial findings are often extrapolated from studies in adults.

Children and adolescents are not miniature adults, but differ both physiologically and psychologically. Thus, pediatric research is essential to developing treatments that are safe and effective for children and adolescents, specifically. Advances in pediatric health research improve the way we understand child and adolescent health, disease, and development, and how these are influenced by factors such as genetics and the environment. Classical tensions related to the involvement of children as vulnerable participants in research are synthesized in Table 19.2, and include how researchers determine the appropriate level of protection, the extent of parental authority and surrogate decision-making, and gauge the developing autonomy of minors. Transformative biotechnologies such as next-generation sequencing instantiate these classic tensions, but also shape new challenges around their responsible deployment and applications in the clinic.

Table 19.2 International guidelines for the participation of minors in biomedical research

Guideline	Relevant clause
Council for International Organizations of Medical Sciences (CIOMS) (2016) International Ethical Guidelines for Health-related Research Involving Humans	**Guideline 17** Children and adolescents must be included in health-related research unless a good scientific reason justifies their exclusion. [T]heir distinctive physiologies and emotional development may also place children and adolescents at increased risk of being harmed in the conduct of research. Moreover, without appropriate support, they may not be able to protect their own interests due to their evolving capacity to give informed consent. Specific protections to safeguard children's rights and welfare in the research are therefore necessary. ◆ Before undertaking research involving children and adolescents, the researcher and the research ethics committee must ensure: • A parent or a legally authorized representative of the child or adolescent has given permission; and • The agreement (assent) of the child or adolescent has been obtained in keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity. ◆ If children reach the legal age of maturity during the research, their consent to continued participation should be obtained. ◆ In general, the refusal of a child or adolescent to participate or continue in the research must be respected, unless, in exceptional circumstances, research

Guideline	Relevant clause
	participation is considered the best medical option for a child or adolescent. ◆ For research interventions or procedures that have the potential to benefit children or adolescents, the risks must be minimized and outweighed by the prospect of potential individual benefit. ◆ For research interventions or procedures that have no potential individual benefits for participants, two conditions apply: • The interventions and procedures should be studied in adults first, when these interventions and procedures target conditions that affect adults as well as children and adolescents, unless the necessary data cannot be obtained without participation of children or adolescents; and • The risks must be minimized and no more than minimal. ◆ When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in adults, a research ethics committee may permit a minor increase above minimal risk.
United Nations Human Rights Office of the High Commissioner (1989) United Nations Convention on the	**Article 12** 1. State Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.

Guideline	Relevant clause
Rights of the Child	2. For this purpose, the child shall in particular be provided the opportunity to be heard in any judicial and administrative proceedings affecting the child, either directly, or through a representative or an appropriate body, in a manner consistent with the procedural rules of national law.

Inclusion

Today, the need to include children and adolescents in research is recognized by international guidelines such as the United Nations Educational, Scientific and Cultural Organisation (UNESCO) *Declaration on the Human Genome and Human Rights* published in 1997 (s. 5(e)) and 2005 (s. 7), the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-Related Research Involving Humans* (2016, s. 3, 17), and the Council of Europe *Convention on Human Rights and Biomedicine* (1997, s. 17(1)(ii)(iii)) and its *Additional Protocol* (2005, s. 15(1)(i)(ii)). Indeed, such guidelines generally indicate that vulnerable persons, such as minors, should be included in research when it is justifiable, when their rights are protected, and when their safety and well-being have been considered.

Overall, minors can be involved in pediatric research when the research cannot be carried out on adults (World Medical Association (WMA) 2013, s. 20); parental consent, as well as the minor's assent (when possible) has been obtained; and the research involves minimal risk. There is a stronger justification for their inclusion when direct clinical benefit is anticipated (World Medical Association (WMA) 1964, s. 17; Council of Europe 1997, s. 17(1)(ii)(2), 2005, s. 15(2); UNESCO 1997, s. 5(e), 2005, s. 7(b); CIOMS 2002, s. 8–9; CIOMS 2016, s. 17). Other guidelines formulate differently their position that "the interventions and procedures should be studied in adults first [. . .], unless the necessary data cannot be obtained without participation of children or adolescents; and the risks must be minimized and no more than minimal." However, "when the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in adults, a research ethics committee may permit a minor increase above minimal risk" (CIOMS, 2016, s. 17). (p.374)

(p.375) ### Consent

As children do not have the legal capacity to consent to their own participation in research, international norms generally state that parental consent or permission of the authorized legal representative is required (WMA 2013, s. 28; Council of Europe 1997, s. 6.2, 17(1)(iv), 2005, s. 15(1)(ii); CIOMS 2016, s. 17; UNESCO 2005, s. 7), and that the best interests of the child should be considered in this decision (UNESCO 2003, 2005). They furthermore stipulate what information should appear in the consent form so as to ensure parental consent is fully informed (e.g., the goal and nature of the research, the potential risks and benefits, the right to withdraw, the protection of privacy and confidentiality, the compensation for participation) (Council of Europe 1997, s. 5, 2005, s. 13(2); UNESCO 2005, s. 6(2)). Some guidelines also set more technical requirements, such as adapting consent language in line with the capacity of parents (Council of Europe 2005, s. 13(1); UNESCO 2005, s. 6(2)). Although required, the scope of parental consent can be controversial in particular research contexts. Longitudinal cohort studies or pediatric biobanking testify to this, where consent to research participation is a continuous process that may span a lifetime.

Not only should consent be ongoing throughout the research project, but it should be renewed if significant changes are made to the research protocol (Council of Europe 2005, s. 24(2)). In addition, the CIOMS also states that, “if children reach the legal age of maturity during the research, their consent to continued participation should be obtained” (CIOMS 2016, s. 17). The likelihood requiring reconsent are perhaps greatest for longitudinal studies, where child participants eventually reach the age of majority while still enrolled in the study. A minor’s capacity to consent can thus evolve over time, and during the course of the research. As a result, this may necessitate the re-contact of minors once they reach the age of majority, or once they become legally capable of deciding for themselves (Knoppers et al. 2016).

Assent of the child

In addition to parental or legal representative consent, applicable norms and policies surrounding the involvement of children in research consider the emerging maturity of a child, even if children do not have the legal capacity to consent. The 1998 international *Convention on the Rights of the Child* recognizes a child's right to be heard in decision-making despite their inability to consent. Specifically, "[a] child who is capable of forming his or her own views [has] the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child" (United Nations General Assembly 1989, s. 12(1)). Thus, it is equally important for the researcher to obtain the assent of a child who has the capacity to participate at this level prior to inclusion in research (WMA 2013, s. 28–29; Council of Europe 1997, s. 6(2), 2005, s. 15(1)(iv); CIOMS 2016, s. 17, 2008, s. 13–14; UNESCO 2003, s. 8(b)(c), 2005, s. 7(a)). Since 1964, the WMA has adopted this position in the *Declaration of Helsinki* (2013, s. 29), as well as the CIOMS (2016, s. 17), (p.376) the Council of Europe in the *Convention on Biomedicine* (1997, s. 6(2)) and its *Additional Protocol* (2005).

Despite recognizing the child's assent dependent on age and maturity, this concept is not uniformly defined or determined across clinical contexts. The UNESCO *Universal Declaration on Bioethics and Human Rights* defines assent as the duty to involve a person who is unable to express consent "[…] to the greatest extent possible in the decision-making process of consent, as well as that of withdrawing consent" (2005, s. 7(a)). The International Bioethics Committee of UNESCO identifies the circumstances in which this involvement should occur in their *Report on Consent*: individuals unable to consent "[…] should be involved in the decision-making process according to their age, maturity, and/or degree of capacity to consent" (2008, s. 164).

In addition to the absence of strict criteria, determining a child's capacity can also vary according to the quality or quantity of information given, the research environment, or the relationship with the researcher or the research team. A change in any of these contextual factors could have a significant effect on the child's capacity as a result, which may occur at any point throughout the course of a research project. As with consent, assent is a continuous process that may need to be reconfirmed throughout the duration of the research, especially in the case of longitudinal studies and, more increasingly with genomic data sharing that spans years or decades.

Dissent of the child

All norms governing pediatric research state that the opposition of a child to participate in research (dissent of the child) should be respected (WMA 2013, s. 29; Council of Europe 1997, s. 6(2), 2005, s. 15(1)(iv); CIOMS 2016, s. 17, 2008, s. 13–14; UNESCO 2003, s. 8(b)(c)), even if parental consent has been obtained. Most international norms, however, do not provide further guidance on how to formally acknowledge the child's dissent. Dissent typically requires a minor to possess the same level of capacity that is needed for assent. Thus, if the child is too young, too immature, or unable to understand the nature of the research, his or her dissent may be overridden. The CIOMS (2002), for example, outlines that the dissent of a minor must be respected, unless, in exceptional circumstances, research participation is considered the best medical option for a child or adolescent (s. 17). The return of genetic/genomic results and incidental findings with next-generation sequencing puts these issues of consent/assent and dissent into sharp relief, and will be discussed in depth in the following section ("Return of results and incidental findings").

Return of results and incidental findings

The focus on the return of results and incidental findings in the pediatric context dovetail on the increasing use of next-generation sequencing in the clinic. At the international level, the 2014 P^3G (Public Population Project in Genomics and Society) international *Statement on the Return of Whole-Genome Sequencing Results in Paediatric Research*, (p.377) in consideration of the child's best interests, holds that the potential to return incidental findings should be addressed at the time that informed consent is obtained (i.e., the decision to return results or not should be agreed upon in advance) (Knoppers et al. 2014a). Incidental findings that are "scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered" (Knoppers et al. 2014a, p.5), while those that relate to an adult-onset disorder should not be returned, so as to preserve the child's future autonomy and decision-making ability. The *Statement* also confirms that the views of the child or adolescent should be considered at the time of consent/assent based on his or her age and maturity (Knoppers et al. 2014a), reinforcing the need to respect the child's evolving decision-making capacities.

In sum, a framework addressing pediatric research exists at the international level. The principles and guidance, however, typically stem from research ethics norms applicable in the clinical setting, and which are not always applicable in the data-intensive research context typified by genomics. The norms included here underscore the need to include children in research, but do not provide specific guidance on

how to manage the evolving maturity of children and their capacity to consent to research. While it has been established that the pediatric population should neither be excluded from medical research nor considered therapeutic orphans (Shirkey 1968, 1999; Rieder & Hazardous Substances Committee 2011), amending these international norms to address contemporary ethical uncertainties, namely in the data-intensive sciences and genomics, is warranted.

Guidance is furthermore lacking with respect to how these uncertainties in the data-intensive sciences relate to incompetent adults living with dementia. Such persons' inability to consent to research participation is an ethical intersectionality they share with children and minors. We explore this intersectionality, which we define as "reverse vulnerability" in further depth in the next section ("Incompetent adults").

Incompetent adults

As the global population ages, so too has there been a steady increase in dementia and dementia-related diseases across high-, middle-, and low-income countries (Brookmeyer et al. 2007). With nearly 7.7 million new cases per year (World Health Organization 2012, 2016), there is considerable clinical demand (Fox & Petersen 2013; Ngandu et al. 2015) and political pressure for innovative research with curative goals (Department of Health & Prime Minister's Office 2013; Canadian Institutes of Health Research 2014). Timely diagnosis, health-related quality of life, and innovation in new therapies for patients living with dementia, however, are markedly lacking. Advances in genomics hold great promise toward improving patient outcomes through drug discovery, elucidating risk reduction strategies, and slowing disease progression. To realize this promise, research priorities, data governance mechanisms, and alternative frameworks for consent are needed. In particular, collaboration between dementia research and care, and improvement in the accessibility of genomic and health data should be promoted (p.378) across borders. Respect for persons and data protections for patients living with dementia have both emerged as ethical priorities in turn. Perhaps more acute than in the pediatric context, the scope of decision-making authority among legally authorized representatives is increasingly becoming a barrier to the sharing of incompetent adults' research data.

Inclusion

Similar to minors, the inclusion of incompetent adults living with dementia in research is protected under international conventions and guidelines summarized in Table 19.3. While these conventions and guidelines acknowledge that incompetent adults warrant special protections in research—and some explicitly identify living with dementia as a hallmark scenario of vulnerability in adults—the guidelines differ in their management of vulnerability and types of research permissible as determined by level of risk. For example, the *Declaration of Helsinki* stipulates that research with vulnerable populations is "only justified if the research is responsive to the health needs or priorities of this group" (WMA 2013, s. 20) while the CIOMS guidelines outline a set of criteria for determining ethically appropriate participation (2016, s. 17). The UNESCO *Declaration on Bioethics and Human Rights* (2005) is unique in this regard in two ways. First, it invokes concepts of both minimal risk as well as minimal burden in rationalizing the participation of vulnerable groups. Second, the human rights orientation of these guidelines marry the concepts of personal integrity and best interests standards upon which the decision to participate in research should be based for groups such as incompetent adults. Legally authorized representatives (LARs) are the primary shareholders of these best interests on behalf of incompetent adults, as well as for minors.

Legally authorized representatives

One emerging area of comparative policy interest relates to the scope of substitute decision-making authority to share research data derived from research with incompetent adults living with dementia. Markedly lacking in the consensus guidelines compared here is which individuals are eligible to serve as appropriate substitute decision-makers for incompetent adults in the research context. The limited guidance available has drawn primarily from the clinical context to date. For the purposes of care decisions, the substitute is often legally determined through the appointment of a LAR in most jurisdictions. One study found, however, that court-recognized LARs may in fact impede participation in dementia research in some European countries (Galeotti et al. 2012). Similar debates as to who may serve as LARs and the extent of their authority are underway in the United States (Derse & Spellecy 2015; Yarborough 2015) and Canada (Wildeman et al. 2013), where scholars are interrogating whether policies should "expand the concept of durable power of attorney for health care to include research participation to facilitate substituted judgments" (Taylor et al. 2015, p.64). **(p.379)** **(p.380)**

Table 19.3 International guidelines for the participation of incompetent adults living with dementia in biomedical research

Guideline	Relevant clause
Council for International Organizations of Medical Sciences (CIOMS) (2016) International Ethical Guidelines for Health-related Research Involving Humans	**Guideline 16: Research involving adults incapable of giving informed consent** Adults who are not capable of giving informed consent must be included in health-related research unless a good scientific reason justifies their exclusion. As adults who are not capable of giving informed consent have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. At the same time, they may not be able to protect their own interests due to their lack of capacity to provide informed consent. Specific protections to safeguard the rights and welfare of these persons in research are therefore necessary. Before undertaking research with adults who are not capable of giving informed consent, the researcher and the research ethics committee must ensure that: ◆ A legally authorized representative of the person who is incapable of giving informed consent has given permission and this permission takes account of the participant's previously formed preferences and values (if any); and ◆ Assent of the subject has been obtained to the extent of that person's capacity, after having been provided with adequate information about the research at the level of the subject's capacity for understanding this information. If participants become capable of giving informed consent during the research, their consent to continued participation must be obtained.

Guideline	Relevant clause
	In general, a potential participant's refusal to enrol in the research must be respected, unless, in exceptional circumstances, research participation is considered the best available medical option for an individual who is incapable of giving informed consent. If participants have made advance directives for participation in research while fully capable of giving informed consent, the directives should be respected. For research interventions or procedures that have the potential to benefit adults who are incapable of giving informed consent, the risks must be minimized and outweighed by the prospect of potential individual benefit. For research interventions or procedures that have no potential individual benefits for participants, two conditions apply: ◆ The interventions and procedures should be studied first in persons who can give consent when these interventions and procedures target conditions that affect persons who are not capable of giving informed consent as well as those who are capable, unless the necessary data cannot be obtained without participation of persons who are incapable of giving informed consent; and ◆ The risks must be minimized and no more than minimal When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in persons who can give informed consent, a research ethics committee may permit a minor increase above minimal risk.
	Commentary on Guideline 16 […]A person may be incapable to give informed consent for a variety of reasons (for example, dementia, some psychiatric conditions and accidents). Persons can

Guideline	Relevant clause
	become capable of giving informed consent after a certain period, or they can be incapable to decide whether they should be treated for a certain disease but capable to decide whether they want to enjoy a meal. This illustrates that a lack of decisional capacity is time-, task- and context-specific
Political Declaration and Madrid International Plan of Action on Ageing (United Nations Second World Assembly on Ageing 2002)	12(j) Harnessing of scientific research and expertise and realizing the potential of technology to focus on, inter alia, the individual, social and health implications of ageing, in particular in developing countries; 75(e) Encourage, at all levels, arrangements and incentives to mobilize commercial enterprises, especially pharmaceutical enterprises, to invest in research aimed at finding remedies that can be provided at affordable prices for diseases that particularly afflict older persons in developing countries and invite the World Health Organization to consider improving partnerships between the public and private sectors in the area of health research 86(b) Develop, where appropriate, effective strategies to increase the level of quality assessment and diagnosis of Alzheimer's and related disorders at an early stage. Research on these disorders should be undertaken on a multidisciplinary basis that meets the needs of the patient, health professionals and carers;
United Nations Principles for Older Persons (United	**Article 7** Older persons should remain integrated in society, participate actively in the

Guideline	Relevant clause
Nations General Assembly 1991)	formulation and implementation of policies that directly affect their well-being and share their knowledge and skills with younger generations. **Article 8** Older persons should be able to seek and develop opportunities for service to the community and to serve as volunteers in positions appropriate to their interests and capabilities.

Consent, assent, and dissent

The ethical significance of assent is, as in the case of children, transferable to research with incompetent adults (Black et al. 2010). Mild to moderate cognitive and memory-impaired adults have been shown to meaningfully engage in discussions of research participation with researchers and their substitute decision-makers (Kim et al. 2004, 2011; Karlawish 2008). These studies importantly substantiate the involvement of such persons in research participation decisions as their abilities will allow. In incompetent adults living with dementia, their cognitive decline can be gradual, sudden, or episodic in accordance with (p.381) the severity of their disease. Decision-making capacity may therefore be task, time, and context dependent.

Taken together, these decisional capacities should be evaluated on a continuous basis, and a LAR identified early in the dementia trajectory. According to the conventions and guidelines outlined in Table 19.3, adults living with dementia who are deemed incompetent should be granted the opportunity to assent or dissent to participation in research before becoming incompetent. A LAR may override a decision in cases where the participant has not stated an express wish to be involved in research, or when their participation would constitute greater than minimal risk. Like for children, the best interests standard varies considerably by jurisdiction and in how it is invoked to justify one’s inclusion or exclusion from research, particularly if no direct clinical benefit is anticipated. *The United Nations Convention on the Rights of Persons with Disabilities* (2008) safeguards the right to engage in political, social, and cultural life, which could be interpreted to include participation in research as an exercise of civic engagement. The *Convention* protects the rights to dignity, autonomy, independence, and participation in society. We argue that decision-making associated with

the type(s) of research participation, as well as the sharing of research data should be considered extensions of the latter participatory right protected under the *Convention*.

Examining ethical intersectionality in practice: Return of results and incidental findings in Canada

The Canadian College of Medical Genetics (CCMG) implicitly adopted the ethical intersectionalities of context, time, and task described herein between minors and incompetent adults in its position on the return of results (Boycott et al. 2015). Although the CCMG guidelines were drafted for application in clinical settings, they are useful for consideration in the research context as well. This is increasingly true as genomics/genetic research informs evidence-based practices, for example, and more firmly integrates into routine clinical care, diagnostics, and personalized therapies.

The CCMG *Professional and Ethical Guidelines* (Boycott et al. 2015) establish two responsibilities for the return of actionable results when they involve incompetent adults:

- ◆ Ensure the patient's best interest and appropriate level of understanding when conveying information to patients.
- ◆ Disclose all clinically relevant information to patients unless specifically instructed not to do so by the patient.

The decision to return results and incidental findings is often tailored to one of five circumstances that typify the involvement of vulnerable persons in genetic research. Figure 19.1 provides an overview of these five circumstances, and the corresponding guideline concerning the return of results. Based on the CCMG guidelines, results should be returned when incompetent adults have expressed wishes to this effect, or if the results are medically actionable for the patient in line with their best interest as is the case with children and minors. **(p.382)**

Researchers are also implicated in the fulfillment of a participant's best interest, particularly when they express prior wishes related to the return of results/ incidental findings or participation in research generally. As Figure 19.1 illustrates, participants' wishes may be unknown. In this case, researchers along with substitute decision-makers are charged with determining the appropriateness of returning results based on the clinical actionability of the result and the participant's best interest(s).

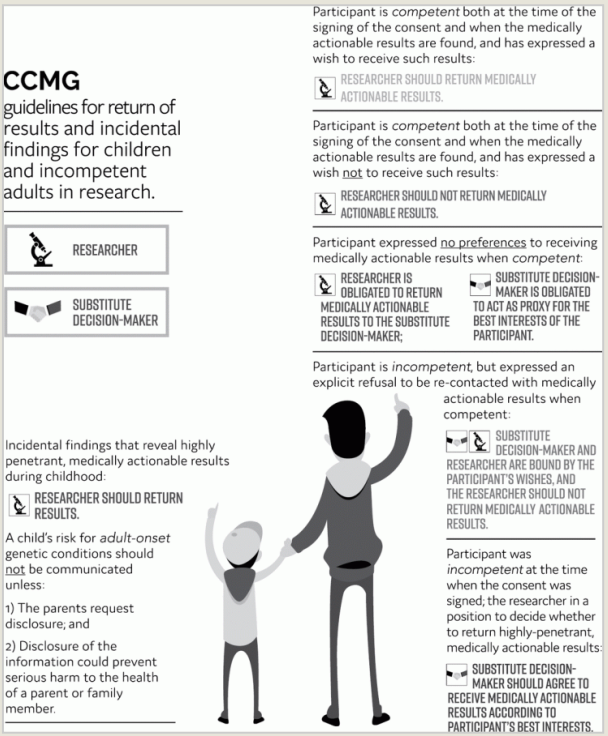

Figure 19.1 CCMG guidelines for return of results and incidental findings for children and incompetent adults in research.

(p.383) Challenges related to feasibility of re-contact for the disclosure of medically actionable incidental findings remain a challenge, as is true for disclosure to child participants and their parents, yet for different reasons. Incompetent adults lose "task" capacity that prevents them from altering previously stated preferences. In contrast, the feasibility challenges associated with re-contacting minors centers on the fact that minors *gain* task capacity to make decisions to participate in research, which may be considerably different from their parents' original consent. In addition to the familiar (or sometimes legal) challenges associated with identifying a LAR, Canadian guidelines are furthermore complicated by provincial differences in LAR policies (see, for example, Thorogood et al. 2016).

Summary
As illustrated in this chapter, minors and incompetent adults are considered situationally vulnerable within a research context. It is as a result of this vulnerability that special protections in research are justified. The nuances of such vulnerability, however, have important implications for laying a responsible governance framework for sharing research data involving both minors and incompetent adults living with dementia. Lange and colleagues have introduced the “situationality concept” for nuancing the typology of vulnerability that patients with dementia, and other vulnerable groups with limited cognitive capacity may experience (Lange et al. 2013). It aligns furthermore with the framing of vulnerability in the CIOMS (2016) guidelines: “[o]ne widely accepted criterion of vulnerability is limited capacity to consent or decline to consent to research participation” (commentary, s. 15). The limitations to capacity can be task, time, or context specific. In this way, the situational vulnerability that emerges from an inability to consent to research is a useful ethical intersectionality upon which a policy for genomic data sharing involving minors and incompetent adults living with dementia can build. Both populations share task-oriented deficiencies in their capacity to make research participation decisions, but differ in time- and context-oriented capacities. The decisional capacities of these two populations and their substitute decision-makers, as well as the special ethical protections the research community affords them, differ in their temporal and contextual specificities. Each component of capacity—time, task, and context—will be next compared for minors and incompetent adults living with dementia, respectively.

First, the situational vulnerability of minors with respect to decision-making in research is inversely related to their burgeoning autonomy. The convergence point heralding the end of minors’ situational vulnerability and societal recognition of their decision-making ability is legally benchmarked upon reaching the age of majority. Whereas minors mature *out of* their situational vulnerability that arises from a temporary inability to consent to research (and in many cases clinical care), incompetent adults living with dementia can regress *into* situational vulnerability commensurate with their cognitive decline. The authors define this phenomenon “reverse vulnerability,” a compelling ethical consideration when charting the ethics of responsible genomic and health-related data sharing.

(p.384) Second, in the case of minors, parents are charged with deciding whether, and to what extent, to share their child’s genomic

data. Research suggests parents make this decision in line with their understanding of informational risks that data sharing poses for their children today, as they mature into adults, as well as their altruistic intentions to support further research through secondary data use.

Third, the ethical significance of task-related capacity can be directly compared between persons living with dementia and minors. That is, the cognitive tasks associated with providing informed consent to research require the same facilities and reasoning regardless of whether an incompetent adult person with dementia or a minor makes this decision. To make a decision to participate in research, a number of task-specific capacities are required. These include that prospective participants understand the nature and purpose of the investigation, they acknowledge the roles and activities necessary to participate, and they appreciate the immediate and future implications of their participation. Singh (2007), however, proposes a shift in the ethical weight researchers should attribute the task-specific capacities of vulnerable groups such as children and incompetent adults. She emphasizes the communicative process, rather than a strictly comprehension-oriented definition of task-specific capacity is relevant both to clinical and research decision-making:

> Children’s task-specific capacities defy their characterization as vulnerable, incapacitated patients who are fully dependent on surrogate decision-makers … children must have the capacity to discuss their understanding of diagnosis and treatment. This understanding need not be correct to be interesting and informative; therefore the capacity is specific to the task of communication, as opposed to understanding. (Singh 2007, p.S36)

Finally, surrogate decision-makers charged with ensuring the best interests of minors and incompetent adults are motivated by different decisional outcomes. These differences can provide some clarity to the contextual distinction in decision-making capacities between the two populations. Parents make decisions on behalf of their child temporarily, and with an overarching motivation to protect as a means of fostering independency in the future. Care providers or other legally authorized representatives also make decisions with a chiefly protective aim, yet do so as an exercise of managing the incompetent adult’s gradual dependency on others.

Sharing research data: A dual imperative framework

Ethics governance of sharing research data involving minors and incompetent adults can draw from the ethical intersectionalities that arise from their shared sources of vulnerability to fulfill dual imperatives in the biomedical research endeavor. The first imperative is a scientific one, in which the sharing of research data is required to adequately power statistical associations between genetics and human etiologies of disease, and to provide care for particular health needs at all stages of life. The second imperative is an ethical one, in which only through sharing research data can the benefits of new scientific knowledge offset the anticipated risks. Knoppers and others have written (p.385) elsewhere extensively on the human rights underpinnings of this second ethical imperative (Knoppers et al. 2014b). International support for data sharing resulted in the founding of which the Global Alliance for Genomics and Health, and adoption of its *Framework for the Responsible Sharing of Genomic and Health-Related Data* (Knoppers 2014). Founded on the right of all citizens to benefit from scientific progress (General Assembly of the United Nations 1948, s. 47), the *Framework* promotes a positive obligation on governments to act in respect of this right. For minors and incompetent adults who require LARs to act on their behalf, data sharing for research that is in their interest should be encouraged in light of their specific needs. A proportionate risk analysis that is based on the possible occurrence of real risks and the actual probability of their occurrence argues in favor of their inclusion in international data sharing initiatives. In line with the human rights foundations upon which the Global Alliance was founded, this chapter contends that the ethical intersectionalities between children and incompetent adults helps orient research and data governance that is better tailored to the contemporary challenges facing them in the post-genomic era. Policy collaboration and empirical policy research are needed if vulnerable populations are to continue benefiting from the fruits of scientific progress made possible through concerted data sharing efforts.

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