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How should severity be understood in the context of reproductive genetic carrier screening?

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Abstract

Reproductive genetic carrier screening provides information about people's chance of having children with certain genetic conditions. Severity of genetic conditions is an important criterion for their inclusion in carrier screening programmes. However, the concept of severity is conceptually complex and underspecified. We analyse why severity is an important concept in carrier screening and for reproductive decision-making and show that assessments of severity can also have normative societal implications. While some genetic conditions are unambiguously associated with a high degree of suffering, there are many factors that contribute to how severe a condition is perceived to be, and perspectives will vary. Attempts to classify genetic conditions according to their severity tend to prioritise biomedical information at the expense of incorporating qualitative aspects of the impact of genetic conditions on people's lives. Further complexity arises because some genotypes can present with variable phenotypes and because some conditions are not always experienced in the same way by all people who have them. To acknowledge this complexity, we argue that an understanding of severity needs to distinguish between the severity of a genetic condition—requiring a generalised approach for purposes of policy development and programme design—and the severity of an instance of a genetic condition in a particular person. Families making reproductive decisions also require access to diverse experiences of the qualitative aspects of living with genetic conditions. As a result, reproductive carrier screening programmes must recognise and respond to the complexity inherent in determining the severity of genetic conditions.

KEYWORDS
bioethics, genetic carrier screening, reproduction, seriousness, severity

1 | INTRODUCTION

Reproductive genetic carrier screening (RGCS) offers individuals and couples information to determine their chance of having children with certain autosomal recessive or X-linked genetic conditions. It is becoming more widely available due (at least in part) to advances in DNA sequencing technologies enabling many genetic variations to be screened simultaneously at a comparably low cost. A key question in RGCS is which genes to screen. The severity of the genetic conditions to which the selected genes contribute has

become an important consideration for how RGCS programmes are designed and offered.[1] If a reproductive couple is identified through RGCS as having an increased chance of having children with a genetic condition, then their perception of the severity of that condition will almost certainly influence the reproductive choices that they go on to make.[2]

Despite the role that severity plays in RGCS programme design and implementation, this concept remains undertheorised and underspecified. It has been observed that the notion of 'serious disability' lacks clarity and specificity.[3] In this paper, we critically interrogate this gap. Although the terms 'serious' and 'severe' are distinct (severity having arguably a more negative normative valence than seriousness), we will use them interchangeably. For present purposes, both terms introduce the notion that the impact of genetic conditions can be thought of as scalar rather than binary. Furthermore, the impact will vary according to the inherent features of the condition itself as well as how the genetic condition affects the qualitative aspects of a person's health and life.

Our discussion will utilise severity in the context of population-based RGCS as a key example. In such programmes, screening is offered to people irrespective of their background chance of having a child with a genetic condition. We start by considering why severity is an important factor in health care decision-making, particularly with respect to genetic conditions and the design of genetic screening programmes. We then examine the features of severity as a concept and critically analyse various attempts to define and measure the severity of health conditions. Many of these acknowledge the complexity inherent in the concept of severity, and the fact that context and perspective influence perceptions of a condition's severity. The development of therapies for severe genetic conditions may also influence perceptions of their severity.[4] We argue that it is essential that RGCS programmes respond to these complexities, both when developing screening panels and when supporting individuals and families to make decisions based on a screening result. We conclude by considering how a more generalised understanding of a condition's severity can inform RGCS programme design, while allowing for qualitative and contextual factors to be incorporated into people's reproductive decision-making related to RGCS.

2 | WHY FOCUS ON SEVERITY?

The implications of how the concept of severity is generally determined and approached are significant in health care systems. In some jurisdictions, severity functions as a priority-setting criterion for health care resource allocation.[5] A health condition's severity can also inform decisions about patient access to services. The degree of severity attributed to a health condition is also important in legal regulation of health decisions, particularly at the start of life: withdrawing neonatal life support, access to prenatal diagnosis and termination of pregnancy.[6] Despite this important role, Savell and Karpin point out that there is no established definition to distinguish a 'serious disability'. Nor is there typically guidance as to how this concept should be operationalised. Different stakeholders will also have divergent views on severity, which will vary with context and circumstance and according to their personal values.

Whilst population-scale RGCS for large numbers of conditions is a relatively new concept, a key aspect of the sequencing method used (often whole-exome sequencing) is that the genes screened and variants identified need not be limited to a narrow set of known pathogenic variants. Of course, this does not mean that every gene should be screened and every variant *should* be reported—a screening panel also needs to satisfy relevant public health principles and be feasible and valid to offer at a population scale.[7] There is support for using severity as one criterion for determining which genes to screen in RGCS.[8] Additionally, a severity threshold will, in some circumstances, be a relevant consideration for whether a genetic variant identified in a screening test will be reported.

2.1 | Considering the degree of severity in RGCS

The degree of severity of conditions associated with genes screened in RGCS has at least three implications:

(i) Utility for reproductive decision-making: Offering RGCS for severe conditions aims to enable people to make informed reproductive decisions either to avoid or to prepare for the birth of a child with the condition. Evidence suggests that offering screening for conditions that have significant physical and/or

[1]Henneman, L., Borry, P., Chokoshvili, D., Cornel, M. C., van El, C. G., Forzano, F., Hall, A., Howard, H. C., Janssens, S., Kayserili, H., Lakeman, P., Lucassen, A., Metcalfe, S. A., Vidmar, L., de Wert, G., Dondorp, W. J., & Peterlin, B. (2016). Responsible implementation of expanded carrier screening. *European Journal of Human Genetics*, *24*(6), e1–e12; Kirk, E. P., Ong, R., Boggs, K., Hardy, T., Righetti, S., Kamien, B., Roscioli, T., Amor, D. J., Bakshi, M., Chung, C. W. T., Colley, A., Jamieson, R. V., Liebelt, J., Ma, A., Pachter, N., Rajagopalan, S., Ravine, A., Wilson, M., Caruana, J., & Delatycki, M. B. (2021). Gene selection for the Australian Reproductive Genetic Carrier Screening Project ("Mackenzie's Mission"). *European Journal of Human Genetics*, *29*(1), 79–87.

[2]Ghiossi, C. E., Goldberg, J. D., Haque, I. S., Lazarin, G. A., & Wong, K. K. (2018). Clinical utility of expanded carrier screening: Reproductive behaviors of at-risk couples. *Journal of Genetic Counseling*, 27(3), 616–625.

[3]Savell, K., & Karpin, I. (2008). The meaning of "serious disability" in the legal regulation of prenatal and neonatal decision-making. *Journal of Law and Medicine*, *16*(2), 233–245.

[4]Newson, A. J., Dive, L., Cini, J., Hurley, E., & Farrar, M. A. (2022). Ethical aspects of the changing landscape for spinal muscular atrophy management in Australia. *Australian Journal of General Practice*, *51*(3), 131–135.

[5]Barra, M., Broqvist, M., Gustavsson, E., Henriksson, M., Juth, N., Sandman, L., & Solberg, C. T. (2020). Severity as a priority setting criterion: Setting a challenging research agenda. *Health Care Analysis: HCA. Journal of Health Philosophy and Policy*, *28*(1), 25–44. https://doi.org/10.1007/s10728-019-00371-z

[6]Savell & Karpin, op. cit. note 3.

[7]Dive, L., & Newson, A. J. (2021). Ethics of reproductive genetic carrier screening: From the clinic to the population. *Public Health Ethics*, *14*(2), 202–217; Dive, L., Archibald, A. D., & Newson, A. J. (2021). Ethical considerations in gene selection for reproductive carrier screening. *Human Genetics*, *141*, 1003–1012.

[8]Delatycki, M. B., Alkuraya, F., Archibald, A., Castellani, C., Cornel, M., Grody, W. W., Henneman, L., Ioannides, A. S., Kirk, E., Laing, N., Lucassen, A., Massie, J., Schuurmans, J., Thong, M. K., van Langen, I., & Zlotogora, J. (2020). International perspectives on the implementation of reproductive carrier screening. *Prenatal Diagnosis*, *40*(3), 301–310; Henneman, L., et al., op. cit. note 1; Kirk, E. P., et al., op. cit. note 1.

intellectual impacts is generally supported by all stakeholders.[9] However, the inclusion of mild and/or variable conditions is more contentious: this information may be difficult to incorporate into reproductive decision-making and there tends to be wider variation in how reproductive couples use this information.

For example, in sex chromosome aneuploidy detected via a noninvasive prenatal screening (NIPS) test, some parents reflect that they would have preferred not to have known about it.[10] Other forms of ambiguous or uncertain information, such as variants that have incomplete penetrance or variable expressivity, can also be perceived as unhelpful by reproductive couples and may cause distress.[11]

(ii) Impact of reproductive interventions: Reproductive interventions available to reproductive couples who are identified through RGCS as having an increased chance of having children with a severe genetic condition include prenatal genetic testing and possible termination of pregnancy (if already pregnant), in vitro fertilisation with preimplantation genetic testing, using donor embryos or gametes, or choosing not to have children. There are also additional interventions such as cascade testing of family members. These options can come with significant physical and psychological impacts as well as financial burdens for the couple and/or the health system. It can be important to weigh the impact of the condition with the impacts of the interventions. Where the condition is severe, the impacts to the individual, family and healthcare system are likely to be significant and the reproductive intervention may be more easily justified, whereas when the condition is milder and possibly manageable, the reproductive intervention may be highly burdensome and more difficult to justify in relation to the possible impact of the condition. It is important that the services that follow from RGCS are targeted appropriately to severe conditions for which their impact is warranted.[12]

(iii) Societal implications of screening for the condition: At the policy or societal level, offering screening for a genetic condition suggests that avoiding having a child with the condition is acceptable. Concerns about the potential for RGCS to 'shape society' have been expressed by healthcare providers and those offered population-based carrier screening.[13] As such, programmes that screen for genetic conditions with a wider range of severity in their presentation have been subject to criticism as they can be perceived as expressing a discriminatory view of those who live with the condition screened for.[14] As evidenced by the wide acceptance of other types of reproductive screening programmes like NIPS, once a condition is included on an RGCS panel, it may become perceived as the social norm to screen for that condition and expected that couples will take steps to avoid having a child with the condition.

These implications suggest that careful consideration and consultation is needed to understand the role of severity in shaping individual and societal understandings of genetic conditions and the interventions available to predict, treat or avoid them. However, the pre-existing focus on and use of severity are also subject to critique due to the aforementioned lack of specificity of this concept.[15]

2.2 | Severity, health behaviour and the responsibilisation of choice

The notion of severity also features in models explaining health behaviour. 'Perceived severity' is a key domain in the Health Belief Model, which proposes factors that contribute to whether an individual enacts a health behaviour.[16] In this model, perceived severity sits alongside perceived susceptibility, perceived benefits and perceived barriers, to suggest that if a person perceives the consequences of the condition to be severe, they will be more likely to undertake the health behaviour to avoid it. However, whilst carrier screening research suggests that all four Health Belief Model domains influence decision-making, findings around the role of perceived severity in decision-making are mixed.[17] This may be

[9]Boardman, F. K., Young, P. J., Warren, O., & Griffiths, F. E. (2018). The role of experiential knowledge within attitudes towards genetic carrier screening: A comparison of people with and without experience of spinal muscular atrophy. *Health Expectations*, *21*(1), 201–211; Ong, R., Howting, D., Rea, A., Christian, H., Charman, P., Molster, C., Ravenscroft, G., & Laing, N. G. (2018). Measuring the impact of genetic knowledge on intentions and attitudes of the community towards expanded preconception carrier screening. *Journal of Medical Genetics*, *55*(11), 744–752; Plantinga, M., Birnie, E., Abbott, K. M., Sinke, R. J., Lucassen, A. M., Schuurmans, J., Kaplan, S., Verkerk, M. A., Ranchor, A. V., & van Langen, I. M. (2016). Population-based preconception carrier screening: How potential users from the general population view a test for 50 serious diseases. *European Journal of Human Genetics*, *24*(10), 1417–1423; Thomas, L. A., Lewis, S., Massie, J., Kirk, E. P., Archibald, A. D., Barlow-Stewart, K., Boardman, F. K., Halliday, J., McClaren, B., & Delatycki, M. B. (2020). Which types of conditions should be included in reproductive genetic carrier screening? Views of parents of children with a genetic condition. *European Journal of Medical Genetics*, *63*(12), 104075.

[10]Reiss, R. E., Discenza, M., Foster, J., Dobson, L., & Wilkins-Haug, L. (2017). Sex chromosome aneuploidy detection by noninvasive prenatal testing: Helpful or hazardous? *Prenatal Diagnosis*, *37*(5), 515–520.

[11]Watts, G., & Newson, A. J. (2021). To offer or request? Disclosing variants of uncertain significance in prenatal testing. *Bioethics*, *35*(9), 900–909; Werner-Lin, A., Walser, S., Barg, F. K., & Bernhardt, B. A. (2017). "They Can't Find Anything Wrong with Him, Yet": Mothers' experiences of parenting an infant with a prenatally diagnosed copy number variant (CNV). *American Journal of Medical Genetics. Part A*, *173*(2), 444–451.

[12]Individuals may differ in their views on the conditions for which various reproductive interventions are warranted; furthermore, severity is not the only criterion to determine the appropriateness of reproductive interventions. However, a discussion of the criteria for use of various reproductive interventions is beyond the scope of this paper.

[13]Archibald, A. D., Hickerton, C. L., Jaques, A. M., Wake, S., Cohen, J., & Metcalfe, S. A. (2013). 'It's about having the choice': Stakeholder perceptions of population-based genetic carrier screening for fragile X syndrome. *American Journal of Medical Genetics. Part A*, *161A*(1), 48–58.

[14]De Wert, G. M., Dondorp, W. J., & Knoppers, B. M. (2012). Preconception care and genetic risk: Ethical issues. *Journal of Community Genetics*, *3*(3), 221–228; Parens, E., & Asch, A. (2003). Disability rights critique of prenatal genetic testing: Reflections and recommendations. *Mental Retardation and Developmental Disabilities Research Reviews*, *9*(1), 40–47; Scully, J. L. (2008). Disability and genetics in the era of genomic medicine. *Nature Reviews Genetics*, *9*(10), 797–802.

[15]Boardman, F. K., & Clark, C. C. (2022). What is a 'serious' genetic condition? The perceptions of people living with genetic conditions. *European Journal of Human Genetics*, *30*, 160–169.

[16]Janz, N. K., & Becker, M. H. (1984). The Health Belief Model: A decade later. *Health Education Quarterly*, *11*(1), 1–47.

[17]Chen, L.-S., & Goodson, P. (2007). Factors affecting decisions to accept or decline cystic fibrosis carrier testing/screening: A theory-guided systematic review. *Genetics in Medicine*, *9*(7), 442–450.

because, without personal experience of the condition/s, they can be difficult for people to conceptualise.[18]

The lack of lived experience and the limited role of severity in people's decisions to undergo RGCS mean that particular care should be taken with respect to severity in programme design. Including a condition in a screening programme is not a neutral decision: it sends a message to participants (who place trust in those who developed the programme) about the condition's severity. Additionally, care should be taken in offering 'bespoke' RGCS options, where those undertaking a screening test can select which conditions to screen for. The epistemic barrier to fully conceive of what life with a particular condition will be like means that caution should be exercised with respect to deferring the responsibility for this choice to those having screening. Participants rely on those who choose which conditions are included in RGCS panels to select appropriately, which means that severity must be taken seriously, especially at the stage of programme design.

2.3 | Incorporating severity into RGCS

It is important to interrogate the prominent role that severity plays both in selecting which conditions to screen for in RGCS and also in the subsequent choices of prospective parents. The severity of the genetic condition is not the only criterion for choosing which conditions to screen for in RGCS.[19] Some conditions are included because of the clinical utility of knowing about the condition in advance. For example, milder bleeding disorders such as Factor V deficiency or milder haemophilia might not be considered severe genetic conditions. However, if they are detected prenatally, the information is valuable since it can inform the clinical management of birth and neonatal care. Reflecting this, Korngiebel et al.'s taxonomy[20] to categorise conditions that parents might choose to screen for includes severity, but also captures other factors such as whether medical intervention is required over the lifespan.

In sum, the severity of conditions screened in RGCS is important because it impacts reproductive decision-making of prospective parents, societal perspectives on the condition, health behaviour and how people engage with the notion of screening, as well as decisions and policy around health service development. We acknowledge that there is more work to do regarding the *justification* for severity being among a prominent criterion for inclusion in RGCS and how severity is incorporated into decisions around development of RGCS programmes. However, that analysis is beyond the scope of this paper and cannot proceed until we are clearer about what severity is and why it is important. Here, we acknowledge that avoiding the suffering associated with having a child born with a severe genetic condition is *among* the goals of RGCS programmes. Accordingly, severity is among the central considerations to determine whether a condition is included in RGCS and also plays a significant role in families' decision-making and uptake of various reproductive options following a screening test. In the following section, we critically review how the concept of severity has been conceptualised in the bioethics literature and consider some attempts to classify the severity of genetic conditions, reflecting on the inadequacy of algorithmic attempts to determine severity and the challenge of categorising genetic conditions according to their severity.

3 | DEFINING AND UNDERSTANDING SEVERITY

Severity has many different dimensions and the way it is conceptualised often depends on the context or purpose for which it is being defined. In some countries, for example, Norway and Sweden, severity has been used as a criterion in setting priorities for health care resource allocation. In this context, severity is poorly understood, but is acknowledged to be fundamentally multidimensional.[21] Barra et al. make observations about the application of severity in the health care priority setting and identify several avenues for further exploration that may aid in clarifying the concept. Their analysis shows that severity is often understood in relation to needs and desires, suffering, social context and temporality—notions that are inherently normative. They suggest that it may be useful to theorise severity as an 'essentially contested concept' in the sense that it is appraisive or evaluative and internally complex, and admits of modification as circumstances change. But at the same time, modification will occur in ways that cannot always be predicted.[22] Examples of essentially contested concepts related to health and genomics include 'harm' and 'disease'.[23] Such concepts involve an evaluative component and a value judgement, and as the circumstances change—around the person, or our understanding of the science, and so forth—the way we understand the concept is subject to modification in unpredictable ways. Severity also overlaps and intersects in various ways with a range of related concepts such as urgency, need, well-being and harm. It has been argued that prioritising severity is unjustified, in part due to the difficulty of

[18]Archibald, A. D., Jaques, A. M., Wake, S., Collins, V. R., Cohen, J., & Metcalfe, S. A. (2009). "It's something I need to consider": Decisions about carrier screening for fragile X syndrome in a population of non-pregnant women. *American Journal of Medical Genetics Part A, 149A* (12), 2731–2738; Metcalfe, S., Jacques, A., Archibald, A., Burgess, T., Collins, V., Henry, A., McNamee, L., Sheffield, L., Slater, H., Wake, S., & Cohen, J. (2008). A model for offering carrier screening for fragile X syndrome to nonpregnant women: results from a pilot study. *Genetics in Medicine, 10*(7), 525–535.

[19]Kirk, E. P., et al., op. cit. note 1.

[20]Korngiebel, D. M., McMullen, C. K., Amendola, L. M., Berg, J. S., Davis, J. V., Gilmore, M. J., Harding, C. O., Himes, P., Jarvik, G. P., Kauffman, T. L., Kennedy, K. A., Simpson, D. K., Leo, M. C., Lynch, F. L., Quigley, D. I., Reiss J. A., Richards, C. S., Rope, A. F., Schneider, J. L., … Wilfond, B. S. (2016). Generating a taxonomy for genetic conditions relevant to reproductive planning. *American Journal of Medical Genetics, Part A, 170*(3), 565–573.

[21]Barra, M., et al., op. cit. note 5.

[22]Gallie, W. B. (1955). Essentially contested concepts. *Proceedings of the Aristotelian Society, 56*, 167–198.

[23]Examples that Gallie offers of essentially contested concepts are those that describe domains that intersect with human activity and whose interpretation varies according to context, such as 'work of art' or 'democracy'.

defining the concept.[24] However, the fact that the concept of severity or seriousness is explicitly referenced in many facets of health policy and programme design makes it important to have some understanding of how to assess severity in relation to health conditions.

Severity plays a significant role in genetics and genomics. As mentioned earlier, if a genetic condition is considered severe, that determination can trigger a range of occurrences including reporting a result from RGCS or offering a termination of pregnancy. The significance of such decisions makes it important to clarify how to determine whether a genetic condition is a severe one. It has been demonstrated that genetics professionals do not always concur about the seriousness of genetic conditions and that factors such as social and economic circumstances can affect perceptions of severity.[25] While lived experience or other nonclinical factors contribute to perceptions of severity, until recently, attempts to categorise genetic conditions according to their severity have been largely informed by clinical voices.[26]

There are different ways to approach assessing the severity of a genetic condition. One U.S. group, for example, has developed a severity index informed by an algorithm that assesses various clinical aspects of a condition. By stratifying disease characteristics into tiers, the algorithm integrates different clinical features of conditions to classify them according to severity. Characteristics of genetic conditions that contribute to determinations of severity include reduced lifespan, intellectual or physical disability, impaired mobility and vision, hearing or other sensory impairment[27] (including persistent pain).[28] Empirical studies have shown that severity as determined by this algorithm generally aligns with the choices that couples make following a carrier screening result[29] as well as the criteria set out by the American College of Obstetricians and Gynaecologists.[30] This approach represents an attempt to quantify or standardise assessments of severity.

Despite the advances in understanding severity that such classification systems have brought, a problem with algorithmic approaches to standardising severity is that they rely on clinical features of genetic conditions and thus privilege biomedical information. They do not factor in other aspects such as suffering (incorporating impacts on affected individuals and on their families), social context, lived experience, self-rating of quality of life and health and temporality[31] or factors like phenotypic variability or uncertainty of presentation.[32] A person's perspective and their experience of genetic conditions significantly impact how they assess the severity of genetic conditions.[33] Moreover, people who live with genetic conditions and their families often have differing views on the severity of their condition compared to those who lack relevant lived experience.[34] The range of experiences and perceptions of genetic conditions also highlights the importance of ensuring that a range of perspectives are incorporated into determinations of severity and the shortcomings of attempts to categorise genetic conditions on a unidimensional—that is, mild to severe—continuum.[35]

It is increasingly clear that algorithmic attempts to classify genetic conditions' severity according to their 'objective' features are inherently limited and do not accurately reflect the experience of people who live with genetic conditions.[36] It has been argued that the 'objectivist' (biologically oriented) approach is insufficient, and an adequate account of the severity or seriousness of genetic conditions must also integrate 'constructivist' approaches to health and disease, namely, those that are normatively oriented, based on social constructs and human values.[37] While Boorse's bio-statistical (nonnormative) theory of health has been prominent for decades,[38] the difficulty of characterising disease without any reference to normative features is increasingly recognised.[39] This means that rather than being purely quantifiable as deviation from some kind of statistically 'normal' functioning, disease involves an element of being undesirable or harmful.[40]

Assessments of the severity of genetic conditions cannot, therefore, make reference solely to the objective biological features associated with the condition. This is not only because some genotypes can present with a wide range of variable phenotypes but also because a disease or genetic condition is not always experienced in the same way by all people who have it. Rogers and

[24]Hausman, D. (2019). The significance of 'severity'. *Journal of Medical Ethics*, *45*(8), 545–551.

[25]Wertz, D. C., & Knoppers, B. M. (2002). Serious genetic disorders: can or should they be defined? *American Journal of Medical Genetics*, *108*(1), 29–35.

[26]Boardman & Clark, op. cit. note 15.

[27]We note that there is significant variability in the impact of different kinds of sensory impairments; however, debating the classifications in this algorithm is beyond the scope of the current discussion.

[28]Lazarin, G. A., Hawthorne, F., Collins, N. S., Platt, E. A., Evans, E. A., & Haque, I. S. (2014). Systematic classification of disease severity for evaluation of expanded carrier screening panels. *PLoS One*, *9*(12), e114391.

[29]Ghiossi, C. E., et al., op. cit. note 2.

[30]Arjunan, A., Bellerose, H., Torres, R., Ben-Shachar, R., Hoffman, J. D., Angle, B., Slotnick, R. N., Simpson, B. N., Lewis, A. M., Magoulas, P. L., Bontempo, K., Schulze, J., Tarpinian, J., Bucher, J. A., Dineen, R., Goetsch, A., Lazarin, G. A., & Johansen Taber, K. (2020). Evaluation and classification of severity for 176 genes on an expanded carrier screening panel. *Prenatal Diagnosis*, *40*(10), 1246–1257; The American College of Obstetricians and Gynecologists. (2017). Carrier screening in the age of genomic medicine. Committee Opinion No. 690. *Obstetrics and Gynecology*, *129*, 35–40.

[31]Barra, M., et al., op. cit. note 5; Boardman & Clark, op. cit. note 15.

[32]Korngiebel, D. M., et al., op. cit. note 20.

[33]Boardman, F. K. (2017). Experience as knowledge: Disability, distillation and (reprogenetic) decision-making. *Social Science & Medicine*, *191*, 186–193; Thomas, L. A., et al., op. cit. note 9.

[34]Boardman, F. K., et al., op. cit. note 9.

[35]Newson, A. J., & Dive, L. (2021). Taking seriousness seriously in genomic health. *European Journal of Human Genetics*, *30*, 140–141.

[36]Boardman, op. cit. note 33; Kleiderman, E., Rahimzadeh, V., Knoppers, B., Roy, M.-C., Laberge, A.-M., & Ravitsky, V. (2022). The serious factor in expanded prenatal genetic testing. *The American Journal of Bioethics*, *22*(2) 23–25.

[37]Kleiderman, E., Ravitsky, V., & Knoppers, B. M. (2019). The 'serious' factor in germline modification. *Journal of Medical Ethics*, *45*(8), 508–513.

[38]Boorse, C. (1975). On the distinction between disease and illness. *Philosophy & Public Affairs*, *5*(1), 49–68; Boorse, C. (1977). Health as a theoretical concept. *Philosophy of Science*, *44*(4), 542–573.

[39]See, for example, Kingma, E. (2010). Paracetamol, poison, and polio: Why Boorse's account of function fails to distinguish health and disease. *The British Journal for the Philosophy of Science*, *61*(2), 241–264.

[40]Harm is another contested bioethical concept that pertains to understandings of health and disease; however, an exploration of the overlap and relation between the concepts of severity and harm is beyond the scope of this paper. For more on harm and disease, see, for example, McGivern, P., & Sorial, S. (2017). Harm and the boundaries of disease. *The Journal of Medicine and Philosophy*, *42*(4), 467–484; Wilkinson, S. (2010). *Choosing tomorrow's children: The ethics of selective reproduction*. Oxford University Press.

Walker[41] characterise the concept of disease as having a multi-dimensional kind of vagueness. One aspect is the difficulty that many features of diseases (such as undesirability, harm and we could include severity) come in degrees, but for decisions based on how harmful a condition is, a line must be drawn—this is known as 'threshold vagueness'. The other is that diseases have many different features. Similarly, with severity, features like dysfunction, impairment, deviation from a statistical norm or undesirability can contribute to a health condition being considered a disease (or a severe condition). However, it is difficult to compare different conditions and make generalised decisions since many conditions will show some, but not all, criteria—this is called 'criterial vagueness'. In the context of determining the severity of genetic conditions, as with many other diseases, there will always be vagueness or variability in how severe a condition is thought to be, due to the differing features of conditions and the varying perspectives on how they affect the lives of people who have them.

Some algorithmic approaches have developed classifications that go beyond a unidimensional spectrum of clinical severity to incorporate qualitative aspects reflecting the impact of genetic conditions on people's lives. Korngiebel et al.[42] have developed one such multi-dimensional approach to classification. Their approach attempts to reflect more closely the experience of living with genetic conditions and what prospective parents need to know in order to make decisions about participating in a screening programme. Their taxonomy goes beyond classifying conditions according to *clinical* severity—although there are categories of serious and moderate/mild—and additionally reflects other aspects such as the requirement for regular medical intervention and the degree of uncertainty in how a condition might present. The aim is to group conditions into categories that will be useful to support decision-making for prospective parents considering RGCS.[43] As such, it focuses on the impact of the condition, considering factors such as the extent of medical intervention required for people who have the condition, and classifies conditions according to the unpredictability of outcomes. This taxonomy, and subsequent efforts to apply it to categorise hundreds of gene–condition pairs,[44] goes beyond merely classifying the severity of genetic conditions solely by their objective or clinical features. It attempts to integrate the more normative or evaluative aspects of genetic conditions and their impact on people's lives into assessments of severity. This is an important aspect of responding to the complexity of severity; however, as we argue below, different evaluations of severity should play a role in both developing RGCS programmes and in individual (and family) decision-making based on a screening test result. The inherent variability in determinations of severity, along with the importance of diverse perspectives for understanding the impact of a condition, highlights a significant conceptual challenge in determinations of severity—one that is particularly salient in relation to genomics and reproductive decision-making. There is a distinction between severity as a *property* of a particular genetic condition and the severity of an *instance* of that condition in a particular person. The second of these—the severity of an instance of a genetic condition—can be understood as a personalised interpretation of the extent to which a person is impacted by a condition. This is influenced by the circumstances of the person and family, contextualised within their community and society. However, as we will now discuss, more generalised understandings of a genetic condition's severity—severity as a property of the condition—remain important for purposes of policy and programme design.[45]

4 | WORKING WITH SEVERITY TO IMPLEMENT ETHICALLY ROBUST RGCS

Severity will always play an important role in RGCS. Ethically robust RGCS must therefore respond to the complexity in how severity of genetic conditions is understood. We must acknowledge the multiple dimensions inherent in the concept and pay attention to epistemic factors that contribute to the determination of whether a condition is severe.

The severity of genetic conditions is relevant both at the programme level and for individual decision-making following RGCS. It plays a role at various points of RGCS programme design, implementation and policy development. Severity is an important consideration—although not the only criterion—for selecting which genes to include in an offer of RGCS. Offering screening for a genetic condition sends an implicit message that there are valid reasons for avoiding the birth of a child with that condition or that knowing about the condition prenatally can be beneficial for clinical management. Developing a screening panel will, by necessity, rely on generalised understandings of a condition's severity. However, the selection of genes to include needs to be undertaken via a transparent process that incorporates a diverse range of perspectives, including those of multiple affected individuals and carers, and evidence from these groups. As discussed earlier, since severity tends to be less influential in people's decisions to participate in a screening programme, potential participants place trust in those who design the programme to select conditions appropriately. It is therefore crucial to take severity seriously when selecting genes/conditions to include.

[41]Rogers, W. A., & Walker, M. J. (2018). Précising definitions as a way to combat overdiagnosis. *Journal of Evaluation in Clinical Practice, 24*(5), 1019–1025.

[42]Korngiebel, D. M., et al., op. cit. note 20.

[43]This paper examines prospective parents' choices between categories of results that they can elect to receive: Serious, moderate/mild, unpredictable, late onset. As we have noted above, there are some concerns about making parents responsible for choosing the conditions to screen for, given their lack of epistemic access to what life might be like with each specific condition. A comparison between RGCS that offers such choices to parents, as opposed to a 'one size fits all' model, is beyond the scope of this paper.

[44]Himes, P., Kauffman, T. L., Muessig, K. R., Amendola, L. M., Berg, J. S., Dorschner, M. O., Gilmore, M., Nickerson, D. A., Reiss, J. A., Richards, C. S., Rope, A. F., Simpson, D. K., Wilfond, B. S., Jarvik, G. P., & Goddard, K. A. B. (2017). Genome sequencing and carrier testing: Decisions on categorization and whether to disclose results of carrier testing. *Genetics in Medicine, 19*(7), 803–808.

[45]Kleiderman, E., Roy, M.-C., Knoppers, B., & Ravitsky, V. (2021, November 15). *A 'serious' threshold for genomic technologies—Context counts!* https://www.bionews.org.uk/page_160504

Ethical programme design can become complex and difficult when making decisions about conditions that have variable presentation: that is, they can present as either mild or severe. There are some conditions that are highly variable, such as *CFTR*-related conditions. These include cystic fibrosis (CF) as well as arguably less severe conditions such as congenital bilateral absence of the vas deferens. CF is, appropriately, one of the most common conditions to include in carrier screening because of the severity of so-called classic CF. However, not all forms of CF are as severe, and in some cases, the genotype does not accurately predict the severity of the condition in a particular person. This is just one example of a condition that poses a challenge for RGCS programme design.[46] While the severe form of the condition is generally considered relevant to include in a screening programme, milder forms may be less appropriate. There might be ways to design a programme so that the focus is on the severe forms of the condition, for example, reporting only certain variants as has been done in the Australian Reproductive Genetic Carrier Screening Program (Mackenzie's Mission).[47] However, in some instances, it may not be possible to avoid identifying the chance that a person or couple could have a child with a mild form of the condition. Therefore, RGCS programme design must consider a trade-off: is it acceptable to detect a small proportion of people who will only ever have a chance of having children with a mild form of the condition if this enables greater identification of those with an increased chance of having children with a severe form of the condition? Further conceptual and empirical research is required to help address these liminal questions.

In addition to being relevant for programme design, the severity of genetic conditions included in RGCS is among the relevant considerations in prospective parents' decision-making.[48] The severity of genetic conditions included in RGCS will influence the choices that individuals and families make about participating in a screening programme as well as the decisions that they make if they are found to have an increased chance of having a child with a genetic condition. Since RGCS can now be performed for a wide range of conditions, decisions about whether to participate in RGCS are made without specific information about each condition. Some conditions included in screening programmes might range from mild to severe in ways that cannot be predicted. Incorporating such information in pre-screen information to support couples in their decisions about participation can be challenging. Further, as discussed above, detecting a serious genetic condition might not be the only reason for deciding to screen.

If a reproductive couple are found to have an increased chance of having children with a genetic condition, then information about the condition, including its severity, is likely to influence the reproductive options that they choose. While the variability of genetic conditions in diverse individuals cannot adequately be captured at the level of programme design, it is highly relevant in the context of individual and family decision-making. Families should have access to diverse perspectives on the qualitative factors that comprise the lived experience of a genetic condition.[49] Designing RGCS that responds appropriately to diverse experiences of genetic conditions is a significant challenge that must be taken seriously.

5 | CONCLUSION

The severity of genetic conditions will always be among the important factors to consider in the context of RGCS. Severity as a concept is fundamentally complex and multidimensional. Views about the severity of genetic conditions will always vary to some extent based on context and perspective. RGCS programmes must be cognisant of and respond to this complexity. Different approaches to determining the severity of genetic conditions may be required both at the policy and programme level—which will necessitate a more generalised approach—and at the level of individual or family decision-making, where contextual and qualitative aspects of living with a genetic condition are paramount. Variability within specific genetic conditions presents an additional challenge. Wherever possible, diverse perspectives on the lived experience of genetic conditions that go beyond the biomedical aspects should be incorporated into RGCS programmes and decision supports.

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CONFLICT OF INTEREST STATEMENT

Dr Alison Archibald is employed by Victorian Clinical Genetics Services, a not-for-profit provider of reproductive genetic carrier screening. The remaining authors declare no conflict of interest.

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[46]Dive, L., et al. op. cit. note 7.
[47]Kirk, E. P., et al., op. cit. note 1.
[48]Ong, R., et al., op. cit. note 9; Plantinga, M., et al., op. cit. note 9.
[49]Korngiebel, D. M., et al., op. cit. note 20.

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