



# Predictive genetic testing in minors for late-onset conditions: a chronological and analytical review of the ethical arguments

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## ABSTRACT

Predictive genetic testing is now routinely offered to asymptomatic adults at risk for genetic disease. However, testing of minors at risk for adult-onset conditions, where no treatment or preventive intervention exists, has evoked greater controversy and inspired a debate spanning two decades. This review aims to provide a detailed longitudinal analysis and concludes by examining the debate's current status and prospects for the future. Fifty-three relevant theoretical papers published between 1990 and December 2010 were identified, and interpretative content analysis was employed to catalogue discrete arguments within these papers. Novel conclusions were drawn from this review. While the debate's first voices were raised in opposition of testing and their arguments have retained currency over many years, arguments in favour of testing, which appeared sporadically at first, have gained momentum more recently. Most arguments on both sides are testable empirical claims, so far untested, rather than abstract ethical or philosophical positions. The dispute, therein, lies not so much in whether minors should be permitted to access predictive genetic testing but whether these empirical claims on the relative benefits or harms of testing should be assessed.

## INTRODUCTION

Predictive genetic testing, offered alongside in-depth counselling, has established itself as an accepted component of care for adults at risk of developing a late-onset genetic condition. Similarly, there is broad support for the provision of predictive testing for conditions, which manifest in childhood or adolescence, especially where there are effective interventions available during this time (eg, familial adenomatous polyposis (FAP) coli). Conversely, there is considerable controversy associated with offering these tests to minors for conditions, which rarely manifest prior to adulthood. This paper investigates this controversy.

Dispute arises when testing outcomes cannot clearly provide a benefit for the minor. Canadian investigators Bloch and Hayden, in a 1990 editorial in response to requests to perform predictive tests in minors for Huntington's disease (HD), argued that access to predictive genetic testing should be restricted to those  $\geq 18$  years of age.<sup>1</sup> The debate that ensued highlighted the need for guidelines to

assist the practice of clinicians worldwide. In the same year as Bloch and Hayden's seminal publication, the International Huntington Association together with the World Federation of Neurology entered the debate with the publication of the first policy statement addressing this newly controversial area.<sup>2</sup> Subsequent years saw the publication of several more guidelines and recommendations relating to predictive testing in minors. In 2006, a systematic review of all guidelines and policy statements concerning the predictive and pre-symptomatic testing of minors was undertaken.<sup>3</sup> Despite the subtle differences in the published statements, policies and guidelines, they agree in recommending against testing in minors where there is no medical benefit in the immediate future, as Borry *et al* discuss in their systematic review<sup>3</sup>:

'It is clear that the availability of medical benefit is the most important justification to perform predictive and presymptomatic genetic testing in minors, regardless of the onset of the disease. The absence of medical benefit is the most important justification to defer testing until the adolescent or adult is able to make a personal decision on this matter after a full discussion and exploration of the issues.'

Almost two decades since the publication of the first guidelines concerning predictive testing in minors, considerable disagreement still exists in the literature. Opponents of testing highlight potential harms, while proponents look to testing as an opportunity to promote benefit, with each side drawing upon fundamental ethical principles to support their diametrically opposed positions. The evolution of this ethical discourse over the past 20 years, with its various arguments for and against testing, has not so far been tracked and analysed. This review aims to fill that gap, by providing a detailed chronology and mapping of how the arguments entered the discourse and developed over the years. This mapping will offer an opportunity for the debate to advance by making clear where the key points of disagreement lie.

This review is not simply a catalogue of the arguments for and against testing in minors, but rather an analysis of the longitudinal evolution of the debate, highlighting the relative emphasis given to certain arguments. This review provides a new framework for understanding the debate, bringing to the surface untested claims and highlighting the opportunities for empirical research.

**METHODS****Data collection**

A comprehensive review of the literature on predictive testing in minors for late-onset conditions was performed. Bloch and Hayden's 1990 publication<sup>1</sup> is the earliest significant entry in the debate and, for the purpose of the literature search, was taken as the starting point. The search included publications up to December 2010. The search was limited to publications in English and a subset of medical databases. Searches were performed using the databases PubMed, Medline, Web of Science, PsychInfo and CINAHL. Initial keywords were: child OR childhood OR minor OR adolescen\*; predictive OR presymptomatic OR susceptibility OR predispositional; adult onset; genetic test\*; Huntington\* and BRCA\*. A secondary manual search was directed by selected citations in the published literature.

Inclusion criteria were articles published in peer-reviewed journals and concerned primarily with the predictive genetic testing of minors (under the age of 18 years) for adult-onset conditions for which testing provides no immediate medical benefit (eg, HD and familial cancers associated with BRCA mutations). Only articles that substantively addressed this issue were included. Exclusion criteria included articles that were predominantly concerned with carrier testing in minors (eg, gene testing to identify Tay Sachs disease heterozygotes) or testing of conditions for which medical intervention commences prior to adulthood (eg, FAP). Guidelines and policy statements were also excluded, as there is already published work summarising these recommendations.<sup>3</sup> Empirical studies, including systematic reviews, were also excluded on the basis that this review aimed to survey the normative opinion-driven contributions, which make claims regarding ethically best practice. A total of 53 papers satisfied the inclusion criteria and were included in this review.

**Data analysis**

Interpretative content analysis<sup>4</sup> was used to identify and catalogue discrete arguments presented for and against predictive testing of minors for late-onset conditions. Arguments were catalogued, regardless of whether the authors were putting forward their own personal views or were citing other authors' arguments to review past literature. Papers were also included if they referred to the relevant argument, regardless of the author's judgement on the worth of that argument. In this way, a true chronology of the arguments was developed, documenting new arguments as they arose and the way in which existing arguments gained strength in the literature through multiple further citations. These arguments were then grouped according to whether they supported or opposed predictive genetic testing in minors and then subgrouped according to the content of the argument. The process of coding and allocating arguments to appropriate groups was performed by all authors and discussed within the team until consensus was achieved. This data is presented in box 1, linking each argument with the paper(s) in which it was referenced, with the total number of times each argument has arisen in the literature recorded. Beside the description for each argument is a label listing the year the argument first appeared in the literature, the year it was most recently mentioned and the cumulative number of times the argument has appeared during that period. For example, an argument labelled '1990–2008:26' appeared first in 1990, was last referred to in 2008 and has appeared in a total of 26 papers. Figure 1 presents this information visually.

**RESULTS**

Of the 33 discrete arguments identified, 16 opposed and 17 supported predictive genetic testing in minors. The arguments were subsequently grouped according to 10 thematic categories, four against (1A–1D) and five in favour (2A–2E) of testing. The arguments and categories are presented in box 1 and the following discussion uses this framework.

**DISCUSSION**

The battlefield was set in the period 1990–1994, with eight separate publications regarding predictive genetic testing in minors. At the beginning of the ethical debate, authors promoted a conservative approach, arguing against testing for minors. Eight distinct arguments against predictive testing came to light in the very first year. Indeed, the case against testing was largely established by 1994, and these initial arguments against testing appeared repeatedly in the following years. By contrast, momentum in favour of testing evolved more slowly, with most arguments beginning to surface in the mid-to-late 1990s. Beyond this broad commentary on the 'shape' of the discourse thus far, there is no obvious pattern.

Certain arguments are more frequently cited in the literature than others (1A.1, 1B.1, 1C.1–1C.3, 1D.1, 1D.2, 2A.1 and 2C.1). There are a number of considerations that come to bear in examining the relative frequency of each of the arguments. The prominence of an argument, in terms of the number of times it appears, provides an element of insight into the level of importance attributed to it by commentators. Repetition in these terms, though, does not necessarily connote a strong or even sound argument. Clarke<sup>47</sup> points to this trap in noting that it is insufficient to, 'look at the length of the two, rather arbitrary, lists of arguments and then come to the unwarranted conclusion that the two opposed sets are of equal force'. An argument is not intrinsically significant simply because it has appeared in the literature. It must be tested against opposing positions. That said, there is some value in a tally, to understand what authors to date have considered important.

In the last 5 years all but one (1A.6) argument has continued to appear, highlighting that the debate is ongoing, with little resolution. The debate, such as it is, has adopted a to-and-fro pattern defined by parallel lines of argument, rarely intersecting and relying heavily on fundamentally opposed positions on core principles of bioethics with no reconciliation in sight. That no arguments have 'dropped off' the list testifies to a prevailing inertia. No argument has gained supremacy over others. The same core arguments are cited repeatedly, with only subtle variations, suggesting that a different approach may now be required. Clinical practice has forged on ahead of the discourse and predictive genetic testing in minors has become a reality.<sup>57</sup> Formal guidelines have evolved to admit some flexibility into considering requests for predictive testing in minors, although they do not provide a framework or criteria to guide this process.

In reviewing the arguments listed in this review, two groups of claims can be identified. A minority are value claims supported by a preordained broader ethical stance, where there is no possibility of empirical investigation. Three (of 33) arguments clearly fit into this category ('testing minors fails to respect their future autonomy', 'testing minors breaches their confidentiality when their results are disclosed to their parents' and 'it is important to avoid professional paternalism'). Of greater interest is the second group of arguments, which are all testable empirical claims that have not yet been tested. Examples of such testable, but so far untested, claims include: 'A positive test result may lead to depression' (1A.5); 'Testing can

## Box 1 A chronology of arguments for and against predictive testing of minors, 1990–2010

**Arguments against testing minors**

## 1A. Psychological harm for the individual

- 1A.1 A positive test result may have a negative impact upon self-image and esteem (1990–2010:29)<sup>1 5–32</sup>
- 1A.2 Testing may induce feelings of guilt and/or blame by an individual and/or family (1994–2010:22)<sup>5–11 13 14 18 20 21 23 24–26 32–39</sup>
- 1A.3 An individual testing positive risks stigmatisation by immediate and extended family members (1994–2010:20)<sup>5 6 11 13 14 16 19–21 23–26 28 30 32 33 35 40 41</sup>
- 1A.4 A positive test result may increase an individual's anxiety (1994–2010:15)<sup>6 10 13 14 18 21 23 24 26 30–33 38 42</sup>
- 1A.5 A positive test result may lead to the development of depression (2001–2010:7)<sup>6 8 13 20 26 31 36</sup>
- 1A.6 It is possible that symptoms not due to the condition may be misattributed to early manifestation of the disorder (1990–2001:4)<sup>1 20 27 43</sup>

## 1B. Negative effect on family

- 1B.1 Testing can have a negative effect on family relationships (1990–2010:32)<sup>1 5–7 9–11 13–20 22–27 30–34 36 42 44–47</sup>
- 1B.2 A positive result may lead to modification of parental expectations (vulnerable child syndrome) (1994–2010:14)<sup>5 6 11 12 18 20 23 24 26 32 35 38 45 47</sup>

## 1C. Social discrimination and restrictions

- 1C.1 Discrimination related to insurance (1994–2010:30)<sup>1 5 7 10 12–15 17 19–24 26–28 31–37 39 41 45 46 48</sup>
- 1C.2 Social discrimination by peers (1990–2008:29)<sup>1 5–7 10 11 13–16 18–21 23–27 32–36 40 41 44 45 49</sup>
- 1C.3 Discrimination related to employment (1994–2008:27)<sup>5 7 10–15 17 19–21 23 24 26 28 32 33–37 41 45 46 48</sup>
- 1C.4 Discrimination related to education (1990–2008:13)<sup>1 16 17 19 23 24 26–28 32 35 36 48</sup>
- 1C.5 A positive result may restrict an individual's life choices in ways that are out of their control (1990–2010:7)<sup>5 18 24 26 34 38 45</sup>

## 1D. Autonomy

- 1D.1 Testing minors fails to respect their future autonomy (1990–2010:37)<sup>1 5–9 12–17 19–23 26–36 38 40–43 47 48 50 51</sup>
- 1D.2 Testing minors breaches their confidentiality when their results are disclosed to their parents (1990–2010:29)<sup>1 5–7 9 12–17 19 20 23 24 26 27 29 30 32–34 36 38 40 41 47 50 51</sup>
- 1D.3 When testing minors, the risk of information being misunderstood is high (1994–2006:9)<sup>5 14 23 24 32–34 40 41</sup>

**Arguments in favour of testing minors**

## 2A. Psychological benefit for the individual

- 2A.1 Testing may decrease uncertainty for the individual (1990–2010:30)<sup>1 5–7 9 11 13 15 17–23 25 26 29 30 32 34 35 39 40–42 45 52–54</sup>
- 2A.2 Testing may decrease anxiety for the individual (1990–2010:17)<sup>1 5–7 13 16 17 20 24 25 29 34 39 40 44 45 51</sup>
- 2A.3 Testing can have a positive effect on an individual's identity, self-image and self-esteem (2005–2010:14)<sup>5 6 8 9 11 13 16 18 19 22 26 29 36 52</sup>
- 2A.4 Testing allows an individual to psychologically prepare for the future (1997–2010:11)<sup>5 10 16 26 27 29 39 42 45 51 52</sup>
- 2A.5 There is no evidence of negative psychological consequences of testing (1995–2010:10)<sup>6 9 15 17–20 22 29 42</sup>
- 2A.6 Testing may decrease depression for the individual (1993–2006:5)<sup>5 17 9 27 53</sup>

## 2B. Positive effect on family

- 2B.1 Testing may decrease anxiety for the parents (1990–2010:23)<sup>1 5–7 13 15–17 20 24–27 29 30 34 38–40 42 44 45 51</sup>
- 2B.2 Testing may have a positive effect on family relationships (1995–2008:14)<sup>5 9 11 15 16 18 20 23 26 27 34 36 47 54</sup>
- 2B.3 Testing may promote realistic parental expectations of their child (1998–2008:4)<sup>11 18 23 36</sup>

## 2C. Planning for the future

- 2C.1 Testing may enable a family to realistically plan for the future (1990–2010:30)<sup>1 5–11 13–20 23–29 32 36 42 45 51 52 54</sup>
- 2C.2 Testing may inform reproductive decisions for the individual (1997–2006:14)<sup>5 7 10 13 14 16 17 19 22 39 45 51 52 55</sup>

## 2D. Avoiding/preventing harm

- 2D.1 Harm could result from not testing (2001–2010:8)<sup>5 6 9 17 20 26 30 56</sup>

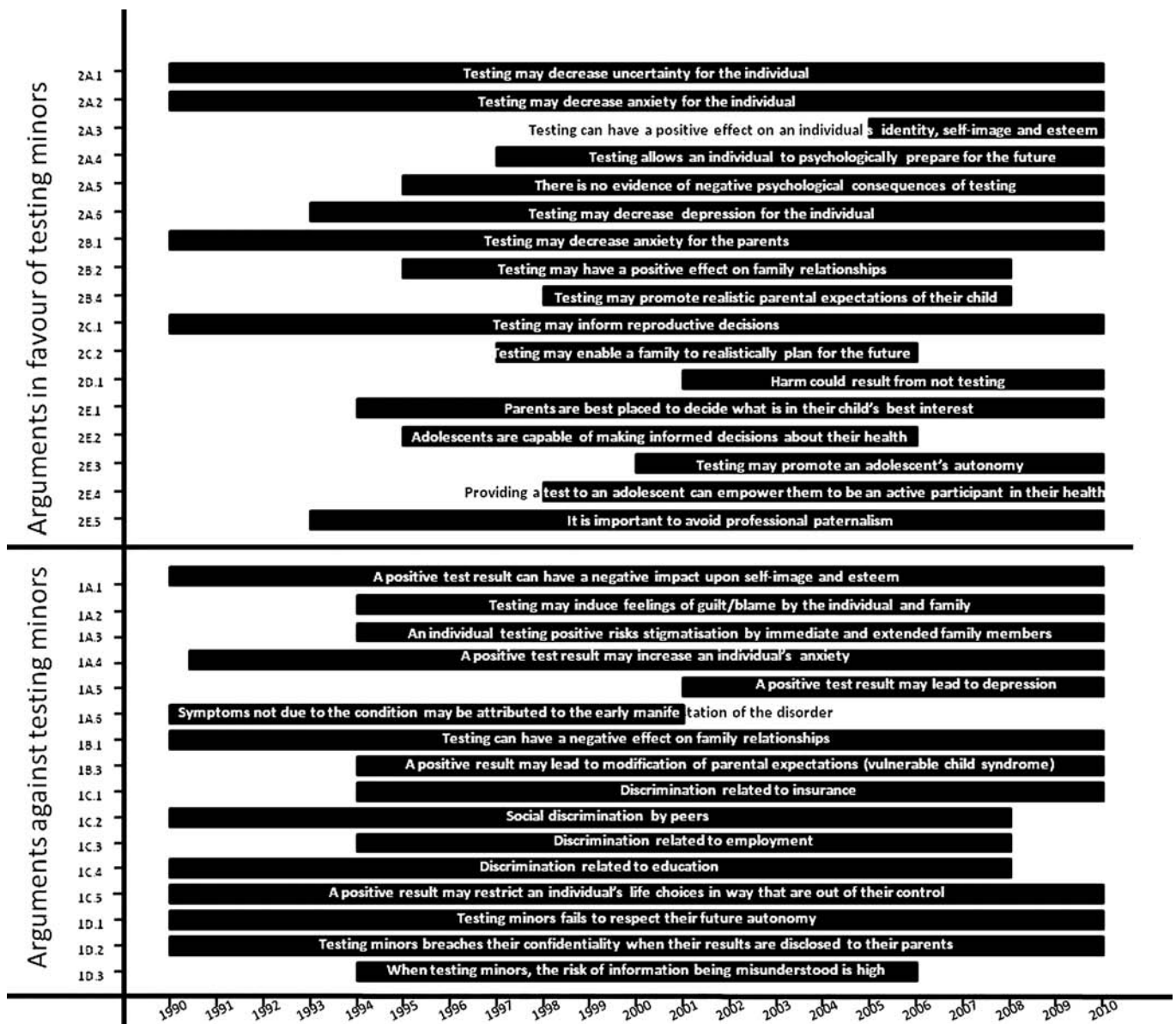
## 2E. Autonomy

- 2E.1 Parents are best placed to decide what is in their child's best interest (1994–2010:19)<sup>5 6–10 13 18 20 24 26 29 31 34 36 39 42 47 51 53</sup>
- 2E.2 Adolescents are often capable of making informed decisions about their health (1995–2006:13)<sup>5 6 13 19 22 23 28 34 35 39 46 49 54</sup>
- 2E.3 Testing may promote an adolescent's autonomy (2000–2010:10)<sup>5 13 16 19 20 29 36 40 47 52</sup>
- 2E.4 Providing a test when the request comes directly from the adolescent can empower that individual to be an active participant in their health (1998–2010:7)<sup>5 13 19 22 29 39 47</sup>
- 2E.5 It is important to avoid professional paternalism (1993–2010:6)<sup>5 13 35 42 53 54</sup>

have a negative effect on family relationships' (1B.1); 'Testing can decrease uncertainty' (2A.1) and 'Harm could result from not testing' (2D.1). This group of untested claims forms the ethical subtext of the debate over predictive genetic testing in minors. This subtext concerns the ethics of collecting the evidence to settle the question. If most arguments are empirical claims, eminently testable, the matter at hand is whether to test

these claims or if the potential outcomes of this research are too harmful to even attempt. Some argue that the harms and benefits of testing should be assessed in empirical research,<sup>5</sup> while others argue that the potential for harm is too great to ethically conduct this research.<sup>46</sup>

Many of the arguments for and against testing are mirror images of one another. Some authors highlight particular



**Figure 1** A visual representation of how the debate has evolved over the past two decades. Each black bar represents a discrete argument, indicating the year the argument first appeared in the literature, and the year it was most recently mentioned.

outcomes as net negatives, whereas others look to the benefits associated with these same outcomes. For example, the new knowledge represented by a test result is viewed in negative terms as burdensome or else, more positively, as empowering knowledge enabling future decision-making, thereby promoting autonomy.<sup>20</sup> There are underlying, mostly unacknowledged, values working to direct the commentators to one or the other interpretation. Working from the same set of ethical principles and concerns (eg, harm, benefit and autonomy), the commentators on either side of the debate have reached opposing conclusions and this sticking point is the position we remain in.

Whereas arguments in favour of predictive genetic testing of minors highlight consequences of receiving both gene-positive and gene-negative results, the arguments against predictive testing have focused heavily on the scenario in which a minor receives a gene-positive test result, largely excluding any serious analysis of potential outcomes. Of the arguments listed above, 11 of 16 assume an unfavourable test result (1A.1, 1A.3–1A.6, 1B.2 and 1C.1–1C.5). Authors appear to believe that

the negative ramifications associated with this 50% probability (a gene-positive test result) are so profound that they outweigh any potential positive impact derived from a gene-negative result. Completely missed from this binary analysis is the possibility that there may be positive ramifications from a gene-positive result, or negative impacts from a gene-negative result and, importantly, the potential adverse effects of *not* testing.

In keeping with the overall lack of systematic work in the area, commentators have rarely discussed which of their arguments specifically apply to infants and younger children, older children or adolescents. A developmental perspective is indispensable, considering each argument as it applies along the trajectory of child and adolescent development. For this review, the authors attempted to categorise each argument by the age group most affected, specifically 'older' minors, 'younger' minors and arguments applicable to all minors. Here, 'younger' minors are 'young people who do not possess the cognitive capacities that allow them to appreciate the implications of predictive testing'.<sup>5</sup> 'Older' minors are considered to have

developed the capacity to discuss and comprehend, to some meaningful extent, the testing process and potential long-term repercussions associated with testing. Some arguments clearly applied to one developmental stage; however, in most cases, making this distinction was challenging and made it more complicated when the original work of other authors were referred. For example, we felt that argument 1D.2 ('testing minors breaches their confidentiality when their results are disclosed to their parents') related more to younger minors where the request for a test comes from a third party (typically parents) but also acknowledge that some commentators argue that this applies equally for older minors. Ultimately, a developmental stratification was omitted from this review, because there was insufficient raw data, in that the literature to date has not adopted a developmental perspective, generalising, for the most part, across the entire child and adolescent developmental trajectory. Ethical issues vary significantly along the developmental pathway and it is recommended that future work make specific reference to the developmental context for their argument(s) in favour or opposed to predictive testing in minors.

## CONCLUSION

Some novel conclusions can be drawn from this review of the two-decade-long discourse surrounding predictive genetic testing in minors for late-onset conditions where no effective pre-adulthood preventive medical intervention exists. The discourse remains stalled, arguing in theoretical terms over whether the testing is right or wrong, without a clear in principal resolution. One explanation may be that this state of affairs is the consequence of significant and strong moral arguments on both sides of the debate. However, we suggest that the problem arises from the lack of empirical evidence to substantiate either side of the debate. Meanwhile, clinical practice and guidance have evolved to adopt a more flexible patient-centred approach. To date, published work has provided little guidance towards defining an ethical framework for applying this new flexibility. Instead, the opposing positions roll along parallel lines, moving no closer to a critical analysis of the quality of each argument and relying on the same ethical principles of harm, benefit and autonomy to justify their opposing positions.

It is clear that the earliest arguments were opposed to testing and have retained currency, while arguments in favour were initially seen more sporadically and have only gained momentum in recent years. Many of the arguments are mirror images of one another, drawing on core ethical principles but arriving at diametrically opposed positions. Authors arguing against testing have focused heavily on the negative implications of a gene-positive test result and have failed to fully canvass the broad potential benefits and harms of gene-negative or gene-positive results, or the potential benefits and harms of not permitting testing. Most of the arguments forming the debate are in fact testable empirical claims, which have not been tested to date. Only a minority are value claims where an ethics discourse is the only means of further exploration. The dispute, therein, lies not so much in whether minors should be permitted to participate in predictive genetic testing but whether these empirical claims on the relative benefits or harms of testing should be assessed. Some authors argue that empirical evidence is required, while others point to a list of potential harms as sufficient to settle the debate and avoid both testing and research into its implications.

There remains an impasse, with little empirical evidence to guide an analysis of the assumptions and values, which underlie

many of the arguments made thus far. Many of the arguments against testing highlight potential negative outcomes of testing. There are three possible responses to this situation. The first is to consider the possible negative outcomes of testing to be so onerous that we should remove the possibility of these negative outcomes by completely ceasing the practice of predictive genetic testing in minors. The second is to develop guidelines that allow clinicians to go ahead and make their own clinical and moral decisions based on their judgement in individual cases, and the third possibility is to systematically collect empirical evidence to test the claims regarding negative consequences and reform guidelines based on this evidence. We advocate the latter, which would allow the systematic collection of evidence in controlled and clearly defined settings.

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