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Navigating Unsolicited Findings in Pediatric Genomic Sequencing: Ethical Guidelines for Children with Developmental Delay

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Abstract

Massively parallel sequencing methods, including whole exome sequencing (WES) and whole genome sequencing (WGS), can uncover unsolicited findings (UFs) that are unrelated to the original diagnostic goal. These approaches are commonly applied in the diagnostic evaluation of children with developmental delay (DD). However, existing policy guidelines on informed consent and the return of UFs are not adequately prepared to handle the unique moral issues that can emerge in such pediatric cases. In the present paper, we demonstrate that the current policy tendency to downplay the importance of the child's future autonomy is mistaken, even when DD is involved. In earlier empirical research performed by our team, we observed that the future development of children with DD is often unpredictable, including uncertainty about whether they will eventually acquire the capacity for autonomous decision-making. Parents occasionally described feeling trapped in a Catch-22 situation when asked to decide about UFs before undergoing WES in a trio-analysis (where both parental and child DNA are sequenced).
A key motivation for agreeing to WES was the hope of obtaining clearer information about their child's potential development. At the same time, responsible decision-making about whether to receive or forgo information on UFs requires some understanding of the child's likely future capacity for autonomy. This problematic Catch-22 arises directly from current policy requirements that compel parents to choose UFs before sequencing takes place (trio analysis). We contend that this observation has important implications for revising existing policies on the return of UFs in WES/WGS. Accordingly, we propose new guidelines that incorporate two main elements. First, the informed consent procedure should be implemented in stages. Second, distinct criteria should be applied for withholding or disclosing a UF in DD cases, depending on the degree of certainty regarding the child's prospective development of autonomous capacities. When integrated with a dynamic consent approach, these two elements of our proposed guidelines could help resolve major moral difficulties encountered when children undergo genomic sequencing to investigate a DD.

Keywords: Unsolicited findings, Genomic sequencing, Children, Return of results, Future autonomy

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Introduction

The advent of massively parallel sequencing technologies, such as whole exome sequencing (WES) and whole genome sequencing (WGS), has sparked

extensive discussion on how to manage findings unrelated to the primary purpose of sequencing, commonly known as 'unsolicited findings' (UFs) [1]. These have also been described as 'incidental findings' or 'unanticipated findings.' They differ from 'secondary findings,' which are deliberately sought but still unrelated to the initial diagnostic question [2].

Clinically significant UFs can be medically actionable, meaning that treatment or preventive measures (e.g., regular screening) exist to reduce the risk of serious or life-threatening outcomes, either immediately or later in life. Alternatively, they can be inactionable when no such interventions are available. These findings may pertain to the child or the parents (in the case of trio analysis) and may also carry implications for additional relatives whose DNA is not sequenced. Furthermore, clinically relevant UFs may hold reproductive importance for the child, the parents, and other family members. The potential discovery of UFs may additionally create tensions between the child's best interests and the interests of the family or parents. This situation prompts the question of what constitutes morally appropriate conditions for disclosure or nondisclosure.

A range of models and policy recommendations have been formulated to address these possible conflicts. Various proposals offer differing solutions for balancing the interests of the child, parents, and other family members when making decisions about genetic testing, genomic sequencing, and the return of results [3-11]. Policy statements such as those issued by the American College of Medical Genetics and Genomics (ACMG) [6, 7] and the American Society of Human Genetics (ASHG) [4] have moved away from the earlier widespread agreement on predictive testing in minors. That earlier consensus generally recommended postponing testing for carrier status and adult-onset conditions until adulthood, primarily to respect future autonomy and welfare [12-18]. The ACMG recommends proactive screening for specific, medically actionable adult-onset conditions, such as BRCA1 or BRCA2, while allowing patients or parents of minors who lack decision-making capacity to opt out of receiving such results [6, 7]. In its 2015 statement, the ASHG maintains that there is no ethical obligation to actively look for secondary findings unrelated to the clinical reason for testing. Yet, it is ethically acceptable to do so provided there is a clear clinical benefit for the child or other family members. The ASHG further recommends offering parents the option to decline secondary findings, although this choice may be overridden when preventive interventions are available that could reduce illness or death. Notably, this position does not treat the age of onset (childhood versus adulthood) as a decisive factor, thereby allowing greater flexibility in disclosing medically actionable adult-onset conditions [4].

WES/WGS is often carried out in children diagnosed with developmental delay (DD). In two prior empirical investigations by our research group, we performed semi-structured interviews with parents of children receiving clinical WES to clarify a DD. Interviews took place both before and after the return of individual results, focusing on parents' reasons for wanting or not wanting different categories of UFs as well as their actual experiences after receiving WES outcomes. Our findings indicate that the developmental trajectory of these children, including their potential to gain autonomous decision-making abilities, frequently remains uncertain [19]. Consequently, and perhaps counter to common assumptions in DD cases, safeguarding the child's best interests may require protecting their future autonomy.

In the present paper, we demonstrate that the current policy tendency to downplay the importance of the child's future autonomy is mistaken, even when DD is involved. We defend an alternative ethical perspective on the child's best interests that gives appropriate weight to preserving future autonomy in relation to the interests of parents and family. Drawing on this view of interests together with the results of our empirical work on parents' experiences with WES for DD, we put forward revised guidelines for informed consent and the return of UFs. These guidelines are grounded in the concept of dynamic consent as a standard element of clinical practice. Dynamic consent uses information technology systems that enable individuals to update their preferences for receiving results over time [20]. While our recommendations adopt the core idea of dynamic consent, they also call for restricting the range of choices available in pediatric cases. Current recommendations from the European Society of Human Genetics support further research "to help inform the development of a responsible re-contacting process and develop tools to support dynamic consent procedures" [21].

Results and Discussion

Qualitative findings: the undesirability of decisional Catch-22s and the desirability of default opt-ins and opt-outs

In our earlier investigations, we observed that the specific policy framework presented to parents posed decision-making challenges akin to a Catch-22, especially when decisions involved UFs related to adult-onset conditions and carrier status. **Table 1** presents the different categories of UFs along with the corresponding policy positions applied at University Medical Center Utrecht during the period when the interviews took place. In some instances, it remained unclear whether a young child currently experiencing DD would later acquire the abilities required for autonomous decision-making. One primary motivation for parents' consent to WES was the desire to obtain greater clarity about their child's developmental prospects [19]. Nevertheless, the center's policy mandated that parents decide on UFs before sequencing began. Certain parents indicated that they required at least a preliminary sense of their child's potential to develop autonomous decision-making capacity to make well-considered choices about UFs in the present. They perceived this requirement as a contradictory, paradoxical predicament, akin to a Catch-22.

Table 1. UMCU's return of UFs policy for WES in parent–child trio-analysis. From: Uncertain futures and unsolicited findings in pediatric genomic sequencing: guidelines for return of results in cases of developmental delay

Child: UF categories	Policy perspective	Parents: UF categories	Policy perspective
Severe disorders that are medically actionable during childhood [a]	Disclose	Severe disorders that are medically actionable† during childhood	Not relevant
Severe disorders that are only medically actionable in adulthood	Advise disclosure, with the option to opt out	Severe disorders that are only medically actionable in adulthood	Advise disclosure, with the option to opt out
Severe conditions lacking medical actionability	Do not disclose	Severe, non-actionable conditions medically	Advise non-disclosure, with the option to opt in
Carrier status for serious conditions following X-linked or autosomal recessive inheritance	Do not disclose	Carrier status for serious conditions following X-linked or autosomal recessive inheritance	Advise non-disclosure, with the option to opt in

1. a: 'Medically actionable' means that there is treatment or prevention (e.g., in the form of controls) to limit the chances of a serious or fatal outcome. For inactionable conditions, such interventions/preventive measures are lacking

Another outcome of our prior research was that some parents of young children did not raise the issue of uncertainty about their child's potential for autonomous development [19]. These parents appeared to ground their preferences for accepting or declining UFs on the presumption that their child would ultimately become autonomous, despite this assumption being doubtful given the child's existing DD and/or accompanying medical conditions. Overlooking the uncertainty concerning the child's developmental trajectory may likewise impair parents' ability to engage in truly responsible decision-making. Such complexities need to be taken into consideration when formulating informed consent procedures and policies for WES.

An additional insight from our previous study was that parents regarded the use of defaults ('disclose, but allow opt-out,' 'withhold, but allow an opt-in') across various UF categories as beneficial. Parents believed that a rigid policy offering no options whatsoever regarding which UFs to receive would fail to accommodate the unique contextual elements of their individual circumstances. Furthermore, the availability of choices was appreciated because it supported more informed decision-making by encouraging parents to thoughtfully weigh both the potential drawbacks and benefits of receiving or declining particular types of UFs in light of their own specific situation. Combining choice with defaults **(Table 1)** was considered advantageous. Parents explained that this approach was helpful because healthcare professionals presumably had sound rationales for recommending disclosure or withholding certain information, which, in turn, prompted parents to consider new factors when deciding whether to accept or decline that information.

Parental autonomy and the best interests of the child

For this discussion, autonomous action refers to self-directed behavior. Such actions are deliberate, voluntary, and unconstrained. Individuals ought to be free to reach their own decisions, provided they do not infringe upon the rights of others.

As caregivers, parents should be granted substantial latitude to make decisions on behalf of their child; parental autonomy generally merits respect. However, parents also bear responsibilities toward their child that stem from the child's best interests, which limit the extent

to which parental autonomy may be exercised. When there is a reasonable expectation that a child will develop autonomous capacities, parents are obligated to create and maintain the conditions necessary for the growth and exercise of those capacities. Consequently, parents must nurture their child's (emerging) autonomy. Numerous ethical frameworks strongly endorse the value of respecting individual autonomy and, by extension, protecting children's future autonomy. A critical aspect of safeguarding future autonomy involves refraining from making irreversible decisions on matters that could reasonably be deferred until the child is capable of making independent decisions [22]. This principle applies to certain choices concerning the acquisition of knowledge about their genetic profile. Safeguarding future autonomy serves the child's best interests when the child has the potential to achieve autonomy.

In many cases, however, children who presently have DD will not ultimately develop autonomous capacities. Yet, as our empirical findings demonstrate, the extent of this uncertainty varies. These epistemological scenarios can be understood as lying along a continuum. At one end are situations supported by substantial evidence that the child will be unable to develop autonomous capacities (high confidence). At the opposite end are cases marked by insufficient evidence to determine whether the child can develop such capacities (low confidence). For children for whom there is high confidence that autonomous capacities will not emerge, future autonomy cannot serve as a basis for restricting parental authority over the return of UFs. In these instances, serving the child's best interests entails focusing on their present and future welfare.

When the available evidence is ambiguous or absent concerning the child's inability to develop autonomous capacities, moral responsibility requires proceeding under the assumption that such development remains possible. Therefore, the lower the confidence that a child cannot develop autonomous capacities, the greater the weight that must be given to considerations of future autonomy when determining the child's best interests. As previously noted, incorporating future autonomy considerations imposes boundaries on which UFs may be disclosed or withheld.

In clinical settings, both the promotion of children's best interests and the respect for parental autonomy create ethical obligations for healthcare professionals. Professionals are required to honor parents' medical decisions for their child, as parents are typically best positioned to understand their child's specific needs and interests. Nonetheless, this obligation to respect parental choices is limited by the professional's duty to safeguard the child's best interests. When a healthcare provider has compelling reasons to believe that a parental decision conflicts with the child's best interests, they are ethically required to intervene to protect the child under their care.

Guidelines for informed consent and return of results

To better align informed consent procedures and the management of UFs with the particular challenges faced by children receiving WES through trio analysis (in which DNA from both parents and the child is sequenced and evaluated) to investigate developmental delay (DD), our proposed guidelines incorporate two core components. The first component replaces the conventional single-moment approach to consent with a multi-stage process. This phased method offers the key advantage of reducing the kinds of decision-making traps, such as Catch-22 scenarios, that arise for parents when their child's prospects for developing autonomous capacities remain uncertain. The second component introduces differentiated rules for deciding whether to withhold or disclose UFs at the current time; these rules are calibrated according to the level of confidence—higher or lower—that the child will be unable to acquire autonomous decision-making abilities in the future. Given the inherent unpredictability of developmental forecasts, the intricate and evolving character of genetic data, and the possibility of conflicting family interests, we recommend that parents be given what we call 'provisional choices' for selected UF categories. These choices would be supported by established default positions (opt-in or opt-out) to facilitate more thoughtful and informed choices. Because these selections are provisional, they remain open to review and possible reversal by a multidisciplinary team. The team would base its evaluation on three considerations: first, an assessment of the child's best interests, including whether future autonomy should play a role in that assessment; second, the rationale parents offered for their provisional decisions about UFs during the consent discussion, particularly when those decisions deviate from the default recommendation (such as requesting information when withholding is advised, or declining information when disclosure is advised); and third, the likely interests of other relatives whose DNA is not part of the sequencing. **Figure 1** presents an overview of the

guidelines. The sections that follow provide a more detailed explanation of these two features.

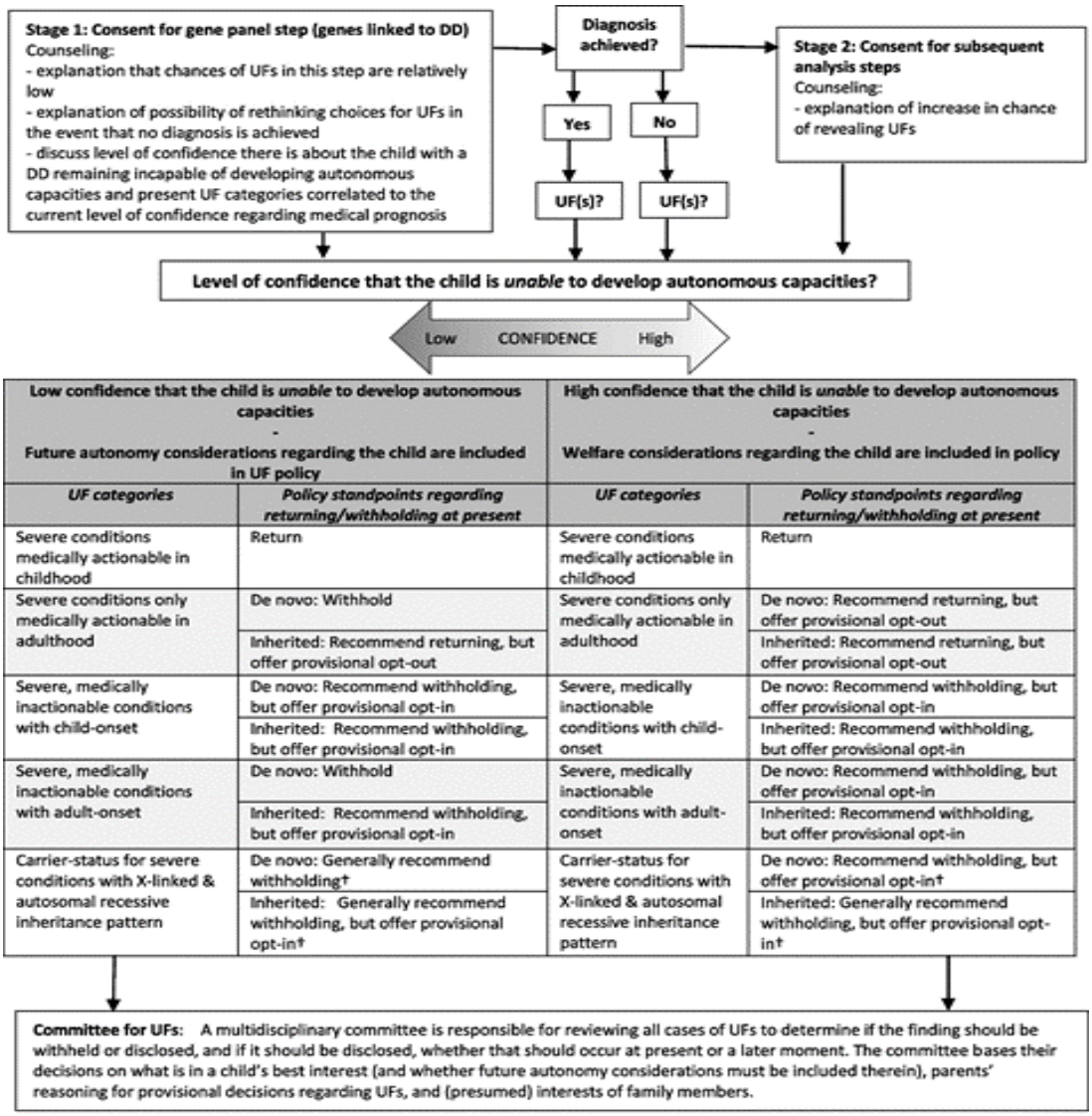

Figure 1. WES (trio-analysis) in pediatric cases of DD: consent and return of UFs guidelines. From: Uncertain futures and unsolicited findings in pediatric genomic sequencing: guidelines for return of results in cases of developmental delay

Staging informed consent

The initial component of our guidelines builds on the notion that consent for WES should be divided into successive phases that correspond to the progressive stages of trio-analysis. Implementing consent in this stepwise fashion helps prevent parents from encountering Catch-22-like dilemmas. A further benefit is that it reframes consent as an extended, deliberative process rather than a brief, one-off event. People generally need adequate time to evaluate different options and reach thoughtful conclusions, and a staged procedure supports this requirement [23, 24].

At UMCU, the standard steps for analyzing WES data in children with DD are as follows. The process begins with

a focused gene panel that screens roughly 1000 genes known to be associated with developmental delay. Should this initial screen fail to produce a diagnosis, the next phase examines all variants present in the child but absent in the parents—referred to as 'de novo' variants—along with any inherited variants for which the child is homozygous, compound heterozygous, or carried on the X chromosome. These analytical layers serve as deliberate filters to identify a diagnosis as efficiently as possible while minimizing the emergence of UFs, consistent with strong recommendations in European guidelines [11]. The probability of discovering UFs increases noticeably from the first to the second step. During our interviews at UMCU, parents were expected to approve every stage of analysis and accept the possibility of any UFs before sequencing could begin.

Under our proposed staged model, consent is initially sought only for the targeted gene panel. If that step does not yield a diagnosis, consent for the subsequent analysis of de novo and specified inherited variants is requested separately. Throughout the counseling sessions, parents would be clearly informed of the rising likelihood of UFs as testing progresses and encouraged to carefully consider their preferences should an UF appear, even in the first stage. They would also be reminded that they remain free to revise their UF preferences as they advance to the next phase and that they may choose to stop further WES testing after completing the initial stage.

The first analytical step of WES yields a diagnostic success rate of approximately 25%–50% [25]. Consequently, many children can receive a diagnosis without proceeding beyond this early phase. This arrangement allows parents to agree, at a minimum, to the initial stage and still maintain a realistic prospect of obtaining diagnostic clarity, while minimizing exposure to UFs. By doing so, the approach eases a significant part of the decision-making paralysis parents often face and helps ensure smoother access to necessary clinical care for their children. In addition, even when parents are not caught in a Catch-22, the staged consent model can still enhance decision-making quality. It gives individuals time to reflect on their UF choices again. It organizes decisions around explicit risk–benefit evaluations—balancing the value of achieving a timely diagnosis against the potential downsides of learning an unsolicited finding [26].

Return of UFs appropriate to the level of confidence regarding the child's development of autonomous capacities

A second core element of our guidelines links the decision to disclose or withhold specific categories of UFs to the degree of confidence clinicians have that a child with developmental delay (DD) will be unable to develop autonomous capacities in the future. In applying this principle, clinicians must form an informed prediction about the likelihood that the child will eventually acquire the decision-making abilities needed to handle information about UFs. These predictions can draw on various factors, including the child's current medical conditions that WES might help explain, the expected prognosis associated with those conditions, the child's observed developmental trajectory so far, and the child's age.

In situations where there is low or no confidence that the child will be unable to develop autonomous capacities—meaning it remains possible that such capacities could emerge—a cautious strategy should be adopted when considering the return of UFs related to carrier status, conditions that become medically actionable only in adulthood, and adult-onset conditions that lack any medical actionability. By contrast, when there is high confidence that the child will not develop autonomous capacities, supported by substantial evidence, the child's best interests should be interpreted primarily through the lens of current and future welfare. In these cases, parents would be granted greater latitude in their decision-making.

Granting parents this broader decision-making authority is ethically necessary to respect their autonomy. As parents in our study noted, a uniform policy applied to all cases fails to account for the wide variety of individual family circumstances, and the availability of at least some choices supports genuinely informed consent. In addition, our empirical data show that providing options encourages parents to engage in deeper reflection on the potential outcomes—such as effects on insurance, emotional consequences, or family dynamics—of learning or not learning certain genetic information. This reflective process is a vital part of informed consent.

Whenever parents are given choices regarding UFs, our guidelines require the inclusion of default policy positions ('recommend disclosure, but allow opt-out' and 'recommend withholding, but allow opt-in'). These defaults are intended to guide and support parents in making more thoughtful, informed decisions. Our

findings suggest that framing UF policies in this way can prompt parents to consider new perspectives on whether to return or withhold particular findings, thereby strengthening the quality of informed consent.

An additional layer of complexity in trio analysis arises from the fact that it is technically impossible to reveal an inherited UF affecting a parent while simultaneously withholding the same finding in the child. This occurs because sequencing data analysis works such that any inherited UF identified in the parent necessarily originates from a corresponding UF in the child. As a result, our guidelines draw a clear distinction between inherited UFs and de novo UFs identified in the child. When confidence is low that a child with current DD will be unable to develop autonomous capacities, parents receive only limited decision-making authority over de novo UFs to better protect the child's future autonomy.

Furthermore, all choices parents make about UFs under these guidelines are considered 'provisional.' In certain situations, overriding a parental choice may be ethically necessary when other competing interests are involved. Following the position outlined by Holm *et al*., and given the intricate nature of genetic information, we recommend that every case involving UFs be reviewed by a multidisciplinary committee. This committee would then decide whether to uphold or override the parents' provisional choices [8].

When the committee determines that a UF should be withheld for the time being, well-defined procedures must be established for the secure storage of information and for possible future recontact and disclosure. The committee would hold responsibility for reviewing and providing guidance on any future disclosure plans. We acknowledge that significant legal and practical obstacles currently exist regarding the long-term storage of UFs for potential later disclosure, and that suitable information technology systems are not yet widely available. The guidelines presented here implicitly highlight the ethical responsibility to actively explore and develop the necessary systems to make such recontact feasible. In this respect, our recommendations are grounded in an ideal framework rather than in the limitations of present-day practice. Ongoing efforts in biobanking research are already exploring dynamic consent models that leverage information technology systems to enable individuals to update their preferences for receiving results over time [20]. While our guidelines draw on the concept of dynamic consent, they also advocate restricting the range of available choices in pediatric cases.

Return of UFs appropriate to the level of confidence regarding the child's development of autonomous capacities

The following section outlines the recommended rules for disclosing or withholding UFs when there is only low confidence that the child will never acquire the skills needed for independent decision-making. In these situations, the guiding principle is to adopt protective steps that preserve the child's opportunity to make autonomous choices later in life:

a) Severe conditions that are medically actionable during childhood. Revealing these UFs is invariably viewed as serving the child's best interests. Survival itself is essential for any future autonomy, and maintaining strong health in childhood actively supports the growth of self-determination. This recommendation matches widely accepted pediatric policy frameworks and models [3-11]. Typical illustrations include childhood-onset cancers or congenital heart disorders.

b) Severe conditions that become medically actionable only in adulthood. Mutations in genes such as BRCA1 or BRCA2 fall into this group. Decisions about disclosure or nondisclosure in these cases hinge on whether the variant is inherited or occurred de novo. For de novo mutations, the information should be securely stored for possible future release, since it remains uncertain whether the child might eventually gain the capacity to make a personal decision. If evidence later emerges that the child will require lifelong parental supervision, parents could then be informed at that stage. When the mutation is inherited, it carries immediate medical significance and actionability for the parents and broader family. Still, postponing revelation may sometimes be warranted—for instance, to prevent complications such as denial of mortgage applications. Beyond these factors, the multidisciplinary committee must also consider the child's stake in having healthy caregivers and the potential hazards to relatives who would otherwise stay uninformed.

c) Severe, medically inactionable conditions that appear in childhood. In the case of severe childhood-onset conditions without available medical interventions, parents may provisionally decide to learn this information for both de novo and inherited variants. This is especially true when the condition is expected to produce profound cognitive disability or prove fatal early in life; here, concerns about future autonomy provide no grounds for concealment. Instead, the rationale for sharing the finding rests on a welfare-centered view of

the child's best interests. Additionally, returning such results can prevent families from enduring further prolonged searches for a diagnosis, while inherited findings may profoundly influence the reproductive planning of parents and other relatives.

d) Severe, medically inactionable conditions that manifest in adulthood. When UFs concern severe adult-onset conditions lacking medical treatments, de novo variants should ordinarily remain undisclosed at present to protect the child's potential for later autonomous decision-making. Inherited variants in this group should follow the same general rule of nondisclosure. However, limited exceptions could be made if the information holds major consequences for the reproductive choices of parents or other adult family members — for example, when there exists a substantial chance that a future child would be affected. In such circumstances, parents may provisionally elect to receive the information. Common examples in this category include adult-onset neurodegenerative diseases like ALS.

e) Carrier status for severe conditions with X-linked and autosomal recessive inheritance.

Results indicating carrier status for serious conditions with X-linked or autosomal recessive inheritance should be assigned to a dedicated category. This distinction reminds parents that the main value of these findings typically relates to possible effects on future family planning. For the majority of female carriers of X-linked disorders, the associated risks often never materialize, and even when symptoms appear, they tend to be less severe than in males. Depending on the precise risk level for an affected female, the committee may occasionally reclassify the UF into one of the other categories outlined above. Nevertheless, every future carrier's son faces a 50% chance of being affected. Parents may provisionally choose to learn about inherited UFs showing female carrier status for X-linked conditions when reproductive considerations are relevant. Yet, we advise caution when contemplating disclosure of de novo variants in situations of low confidence regarding the child's future autonomy. Unlike X-linked carrier status, autosomal recessive carrier status poses no health threat to the carrier and becomes significant only for reproduction if both parents carry the same variant. Because of the technical process of analyzing sequencing data, dual carrier status can be identified only when a UF in the child signals predisposition to the relevant condition. Should such a predisposition arise from both parents being carriers, the choice to disclose or withhold must follow the guidelines of the matching category. Our framework permits parents to provisionally select receipt of inherited UFs that carry significant reproductive weight. This approach typically precludes disclosing autosomal recessive carrier UFs when only the child and one parent are carriers. Even so, we recognize that some parents might still prefer to remain unaware of their own carrier status despite wanting (or being required) to know about the child's predisposition, which would be managed under the appropriate category above. Such a preference may arise because the information does not affect their reproductive decisions. When reviewing whether to withhold or release these UFs, the committee must also assess whether any other children of the parents could face risk of a severe, medically actionable disorder, a factor that might justify setting aside the parents' expressed wish not to receive the information.

High confidence that the child is unable to develop autonomous decision-making capacities and return of UFs

For certain children with developmental delay (DD), substantial evidence may already exist that they will never acquire the abilities required for autonomous decision-making, allowing us to express greater confidence in this outcome. In such situations, parents should be granted wider provisional decision-making authority across a larger set of UF categories, provided that doing so remains consistent with the child's overall welfare. Nevertheless, UFs involving severe conditions that are medically actionable during childhood must always be disclosed to safeguard the child's immediate health needs.

For UFs concerning severe conditions that become medically actionable only in adulthood, disclosure is generally appropriate for both the child and the parents. As noted in the low-confidence scenarios, every child benefits from having healthy parents. At the same time, we acknowledge that some parents — particularly those raising very young children — may prefer to postpone learning about de novo UFs until the point when medical interventions could realistically begin. Our guidelines, therefore, permit parents to provisionally decline receipt of both de novo and inherited variants at present, on the condition that explicit arrangements are established for future disclosure of the finding related to the child. Should parents request such a delay, the multidisciplinary committee must also evaluate any potential risks to other family members.

Regarding both de novo and inherited UFs that involve severe, medically inactionable conditions (whether with childhood or adult onset), as well as carrier-status findings for X-linked and autosomal recessive conditions, our guidelines grant parents considerably broader provisional authority. They may choose to receive this information now based on non-medical benefits or, in the case of inherited variants, on reproductive considerations, as long as the choice aligns with the child's welfare.

Conclusion

A distinctive aspect of our proposed guidelines — one that has not yet been incorporated into existing models or policy statements on informed consent and return of results for massively parallel sequencing technologies such as WES and WGS — is the requirement for disclosure rules that vary according to the level of confidence concerning the child's inability to develop autonomous decision-making capacities. This approach explicitly recognizes the uncertainty that frequently surrounds developmental outcomes, particularly among young children with DD. In developing these guidelines, we have also incorporated insights from other scholars who advocate dividing the consent process into stages and employing defaults in the shape of provisional opt-ins or opt-outs to promote more thoughtful parental decision-making [24, 27]. While the use of defaults is already widespread in clinical genetics, our empirical findings underscore their specific value in helping parents make genuinely well-informed choices. Collectively, the elements in these guidelines address major ethical challenges that arise when children undergo trio analysis to clarify a diagnosis of DD.

Future studies should prioritize resolving practical implementation issues related to secure information storage, re-contact protocols, and the standardization of multidisciplinary committee review procedures. It would also be valuable to investigate whether a staged consent process for WES is suitable across every clinical context involving minors. This includes closer scrutiny of settings where a rapid diagnosis is critical, because a two-step staged procedure inevitably delays results. One clear example is a newborn with a life-threatening condition admitted to the neonatal intensive care unit. Ongoing refinement of the guidelines should be viewed as an iterative process: they must be regularly evaluated and revised in light of emerging developments and new scholarly understanding.

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