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Navigating Uncertain Outcomes: Returning Genomic Results in Children with Developmental Delays

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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 primary diagnostic objective. These methods are commonly applied in pediatric cases of developmental delay (DD). However, current guidelines for informed consent and the return of UFs are not fully equipped to address the unique ethical challenges that arise in these cases. Previous empirical research by our group indicates that the future development of children with DD—and whether they may eventually achieve capacities for autonomous decision-making—can be uncertain. Parents sometimes experience a Catch-22 when deciding on UFs prior to WES in trio-analysis (sequencing of both parents' and child's DNA). A key motivation for consenting to WES is often to gain insights into the child's potential developmental trajectory. Responsible decision-making regarding the receipt or refusal of UF information requires some understanding of the child's likely future autonomy. This dilemma is largely due to policies that require parents to make decisions about UFs before sequencing. We argue that this insight should inform revisions to existing policies on the return of UFs in WES/WGS. We propose guidelines featuring two key elements: first, a staged informed consent process; and second, differential rules for disclosing or withholding UFs in children with DD, based on the degree of confidence in their prospective autonomous capacities. When implemented alongside a dynamic consent approach, these guidelines could help address significant ethical challenges encountered in genomic sequencing for children with developmental delays.

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

Background

The use of high-throughput sequencing techniques, such as whole exome sequencing (WES) and whole genome sequencing (WGS), has raised important questions about how to handle unexpected results that are unrelated to the original reason for testing, often called unsolicited findings (UFs) [1]. These are sometimes labeled "incidental" or "unanticipated" findings, and are different from secondary findings, which are deliberately sought even though they are not linked to the initial diagnostic goal [2].

Clinically relevant UFs may be actionable—meaning medical or preventive interventions exist to reduce the risk of serious outcomes—or non-actionable, meaning no effective intervention is available. UFs can appear in the child, the parents (during trio-analysis), or even have implications for other family members. Some findings may also carry reproductive significance. The presence of UFs can create tension between the child's best interests and family interests, raising ethical questions about if, when, and how such results should be shared.

Several ethical models and policy guidelines exist to address these tensions, offering different approaches to balancing the interests of children, parents, and relatives in genetic testing and result disclosure [3–11]. For example, the American College of Medical Genetics and Genomics (ACMG) [6, 7] and the American Society of

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Human Genetics (ASHG) [4] have updated prior positions that generally recommended postponing predictive testing for minors. These older guidelines focused on protecting a child's future autonomy and welfare by delaying tests for adult-onset or carrier conditions [12–18]. The ACMG now supports actively searching for certain actionable adult-onset conditions, like BRCA1/BRCA2, while allowing parents of children who cannot consent to opt out [6, 7]. The ASHG emphasizes that actively searching for secondary findings is optional, but permitted if results have clear clinical benefit for the child or family. Parents may opt out, although this can be overridden when interventions exist to reduce harm. The child's age or timing of onset is not central in these recommendations, which can allow disclosure of adult-onset findings [4].

WES/WGS is commonly used in children with developmental delay (DD). In previous studies, we interviewed parents before and after receiving WES results to explore their experiences and decisions about UFs. These studies showed uncertainty about whether children with DD would eventually develop the capacity to make autonomous decisions [19]. Protecting these children's best interests may therefore include safeguarding their future autonomy, contrary to what policy debates often assume.

This paper argues that current guidelines underestimate the importance of considering a child's future autonomy, even in DD cases. We propose an ethical framework that balances children's future autonomy with parental and family interests. Based on our findings, we suggest new guidelines for informed consent and returning UFs. These guidelines incorporate a dynamic consent approach, allowing preferences about results to be updated over time [20]. Our framework adapts dynamic consent for children, limiting certain choices when necessary. Similarly, the European Society of Human Genetics (2019) calls for research to support responsible re-contact processes and tools for dynamic consent [21].

Qualitative findings: the challenges of Catch-22 decisions and the value of default opt-ins/opt-outs

Our research revealed that policies requiring parents to decide about UFs before sequencing can create a Catch-22 situation, particularly for adult-onset conditions and carrier-status findings. **Table 1** shows UF categories and policies at the University Medical Center Utrecht during the interviews. For some children with DD, it is unclear whether they will develop future decision-making capacity. Parents often consent to WES to understand their child's developmental potential [19], but mandatory pre-sequencing UF choices forced parents to decide without sufficient knowledge of their child's future autonomy, producing a paradoxical dilemma.

Table 1. UMCU's Policy on Reporting Unsolicited Findings (UFs) for Whole Exome Sequencing (WES) in Parent–Child Trio Analysis

Child: UF Categories	Policy Position	Parents: UF Categories	Policy Position
Serious conditions treatable or preventable in childhood[a]	Disclose	Serious conditions treatable or preventable in childhood	Not applicable
Serious conditions treatable or preventable only in adulthood	Disclosure recommended, opt-out available	Serious conditions treatable or preventable only in adulthood	Disclosure recommended, opt-out available
Serious conditions without treatment or prevention options	Do not disclose	Serious conditions without treatment or prevention options	Withholding recommended, opt-in available
Carrier status for severe conditions with X-linked or autosomal recessive inheritance	Do not disclose	Carrier status for severe conditions with X-linked or autosomal recessive inheritance	Withholding recommended, opt-in available

Parental perspectives and decision-making

In our previous research, we found that some parents of young children did not mention uncertainty regarding their child's potential for developing autonomy [19]. These parents often assumed their child would eventually become autonomous, despite the child's current developmental delay (DD) or co-existing health conditions. Overlooking this uncertainty can undermine parents' ability to make well-informed, responsible decisions about unsolicited findings (UFs). Recognizing these complexities is important when designing policies and informed consent processes for WES.

Another finding was that parents valued the use of default options—such as "disclose with the possibility to opt out" or "withhold with the option to opt in"—for different categories of UFs. Parents indicated that having no choice at all would fail to account for the specific circumstances of their family. Offering choices supports thoughtful decision-making by encouraging reflection on the potential benefits and harms of receiving or declining different UFs. Defaults were seen as helpful because they provided professional guidance, prompting parents to consider new aspects of their decision and the implications of accepting or declining specific results **(Table 1)**.

Parental autonomy and children's best interests

For our purposes, autonomous action is defined as self-directed, intentional, and uncoerced decision-making, where the individual's choices do not infringe on the rights of others. Parents are entrusted with considerable decision-making authority on behalf of their children, and this parental autonomy generally warrants respect. However, this authority is constrained by duties to act in the child's best interests. If a child is reasonably expected to develop autonomous capacities, parents have a responsibility to foster these capacities by creating conditions that allow the child to make their own decisions. Protecting future autonomy is considered a core aspect of acting in a child's best interest, particularly regarding decisions that could be postponed until the child is capable of self-determination, such as learning about their genetic information [22].

In children with current DD, it may be uncertain whether they will develop autonomous capacities. Our research suggests this uncertainty exists on a spectrum. On one end, there may be strong evidence that a child is unlikely to develop autonomy (high confidence). In such cases, future autonomy cannot justify restricting parental decisions about UFs; the focus should instead be on the child's current and future welfare. On the other end, there may be little or no evidence about a child's potential for autonomy (low confidence). In these situations, it is morally appropriate to assume that the child could develop autonomous capacities. The greater the uncertainty regarding future autonomy, the more it must factor into determining the child's best interests, which in turn sets limits on what UFs may ethically be disclosed or withheld.

Healthcare professionals' responsibilities

In clinical practice, considerations of children's best interests and respect for parental autonomy create ethical duties for healthcare providers. Professionals should generally respect parental decisions, as parents are often best positioned to understand their child's needs. Nevertheless, this duty is limited by the obligation to protect the child's welfare. When a parental decision appears likely to conflict with the child's best interests, healthcare providers must intervene to safeguard the child's well-being.

Discussion

Guidelines for informed consent and return of results

To better align informed consent and the return of unsolicited findings (UFs) with the needs of children undergoing WES in trio-analysis (where both parents' and the child's DNA are sequenced) for developmental delay (DD), we propose guidelines with two key elements.

First, informed consent should not be treated as a single, static event. Instead, a staged consent process is recommended. This approach helps reduce the decisional dilemmas resembling Catch-22 situations that parents face when the child's future autonomy cannot be reliably predicted.

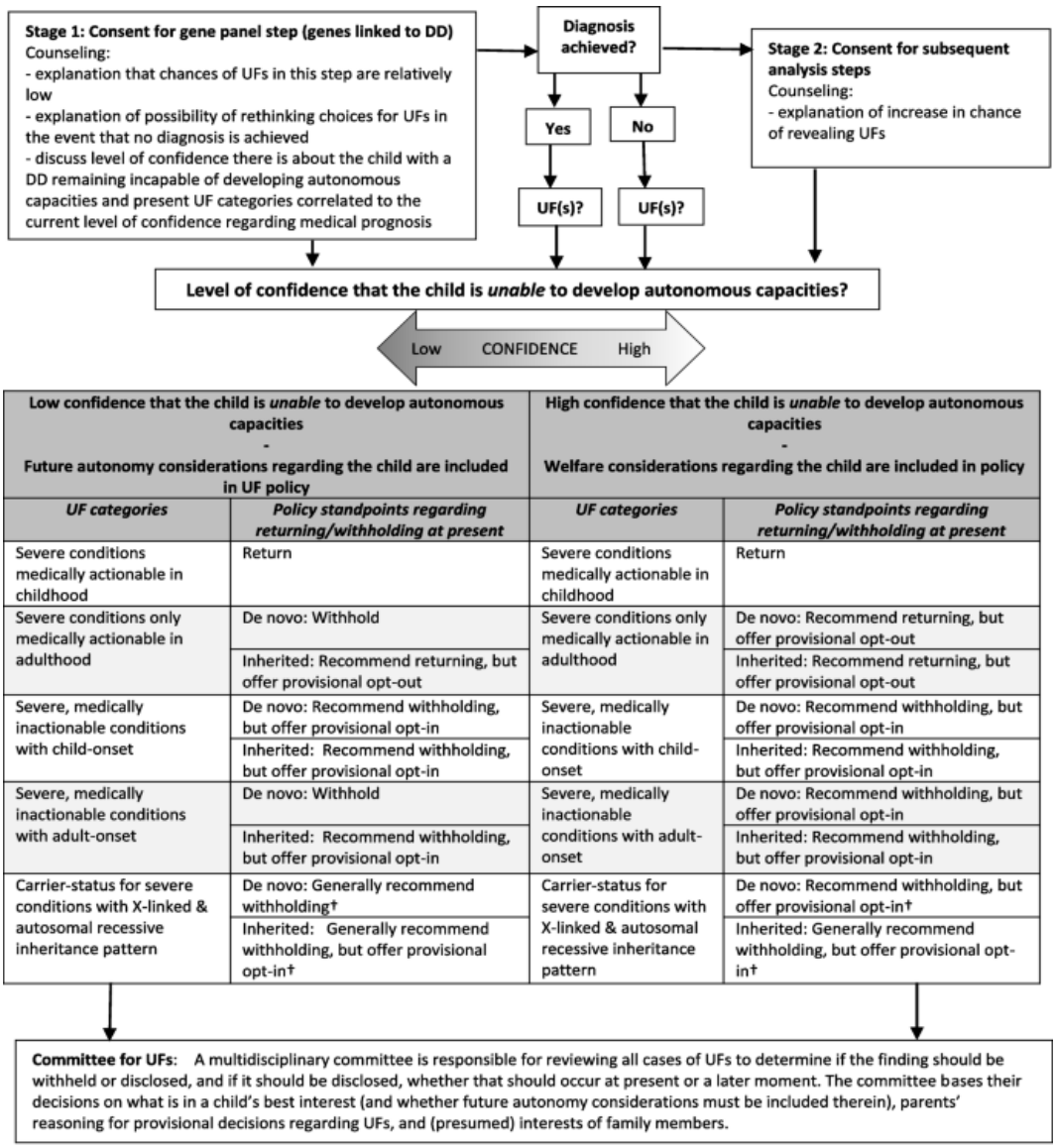
Second, the approach to disclosing or withholding UFs should vary depending on the level of confidence regarding a child's potential to develop autonomous decision-making capacities. Because predicting future autonomy is often uncertain, genetic information is complex and evolving, and family interests may differ, we suggest that parents be given "provisional choices" for certain UF categories. These choices are supported by default policies (opt-in/opt-out options) to encourage informed decision-making.

The provisional nature of these choices means they can be reviewed and, if necessary, modified by a multidisciplinary committee. This committee evaluates decisions based on three considerations:

1. The child's best interests, including whether future autonomy needs to be factored in.
2. Parents' reasoning behind their provisional choices, especially if they deviate from the default policy (e.g., opting in when disclosure is usually withheld, or opting out when disclosure is recommended).

3. The interests of other family members whose DNA was not sequenced but may be affected by the WES results.

Figure 1 illustrates the proposed guidelines. The following sections provide a detailed explanation of each of these components.



Low confidence that the child is *unable* to develop autonomous capacities - Future autonomy considerations regarding the child are included in UF policy		High confidence that the child is *unable* to develop autonomous capacities - Welfare considerations regarding the child are included in policy	
UF categories	***Policy standpoints regarding returning/withholding at present***	***UF categories***	***Policy standpoints regarding returning/withholding at present***
Severe conditions medically actionable in childhood	Return	Severe conditions medically actionable in childhood	Return
Severe conditions only medically actionable in adulthood	De novo: Withhold	Severe conditions only medically actionable in adulthood	De novo: Recommend returning, but offer provisional opt-out
	Inherited: Recommend returning, but offer provisional opt-out		Inherited: Recommend returning, but offer provisional opt-out
Severe, medically inactionable conditions with child-onset	De novo: Recommend withholding, but offer provisional opt-in	Severe, medically inactionable conditions with child-onset	De novo: Recommend withholding, but offer provisional opt-in
	Inherited: Recommend withholding, but offer provisional opt-in		Inherited: Recommend withholding, but offer provisional opt-in
Severe, medically inactionable conditions with adult-onset	De novo: Withhold	Severe, medically inactionable conditions with adult-onset	De novo: Recommend withholding, but offer provisional opt-in
	Inherited: Recommend withholding, but offer provisional opt-in		Inherited: Recommend withholding, but offer provisional opt-in
Carrier-status for severe conditions with X-linked & autosomal recessive inheritance pattern	De novo: Generally recommend withholding†	Carrier-status for severe conditions with X-linked & autosomal recessive inheritance pattern	De novo: Recommend withholding, but offer provisional opt-in†
	Inherited: Generally recommend withholding, but offer provisional opt-in†		Inherited: Generally recommend withholding, but offer provisional opt-in†

Committee for UFs: A multidisciplinary committee is responsible for reviewing all cases of UFs to determine if the finding should be withheld or disclosed, and if it should be disclosed, whether that should occur at present or a later moment. The committee bases their decisions on what is in a child's best interest (and whether future autonomy considerations must be included therein), parents' reasoning for provisional decisions regarding UFs, and (presumed) interests of family members.

†Carrier status for X-linked conditions in females and situations in which both parents are carriers of an autosomal recessive condition are sometimes better treated according to the dictates of the other categories.

Figure 1. WES (trio-analysis) in pediatric cases of DD: consent and return of UFs guidelines

Staging informed consent

The first component of our proposed guidelines is that informed consent for WES should be organized in stages, aligned with the steps of trio-analysis. This staged approach helps prevent the Catch-22 dilemmas that parents of children with uncertain future autonomy often face. It also frames consent as an ongoing process rather than a single moment, giving parents time to consider their options thoughtfully [23, 24].

At UMCU, trio-analysis for clarifying a developmental delay typically follows these steps. Initially, a targeted gene panel is used to examine roughly 1,000 genes linked to DD. If no diagnosis is achieved, the analysis expands to include all de novo variants in the child and inherited variants where the child is homozygous, compound

heterozygous, or variants on the X-chromosome. These steps function as diagnostic "filters," aiming to maximize efficiency while minimizing the likelihood of uncovering UFs, in line with European guidelines [11]. The probability of detecting UFs increases from the first to the second step. Previously, parents were required to consent to all analysis steps and potential UFs before sequencing began.

In contrast, our staged consent model separates these steps. Parents first consent to the targeted gene panel. If no diagnosis is made, consent is sought for the analysis of de novo and inherited variants. During counseling, parents are informed that the likelihood of UFs increases in the second step, and they can reconsider their UF choices or even withdraw consent after the first stage. The diagnostic yield from the first step ranges from approximately 25–50% [25], meaning that many children may receive a diagnosis while minimizing the chance of encountering UFs. This approach reduces parental decisional deadlock, facilitating access to care. Even when parents are not in a Catch-22 scenario, staged consent supports better-informed decision-making by allowing them to reconsider their UF choices and weigh the benefits of timely diagnosis against the potential harms of discovering UFs [26].

Returning UFs according to confidence in the child's future autonomy

The second key feature links the disclosure or withholding of specific UFs to the level of confidence regarding a child's ability to develop autonomous decision-making capacities. Clinicians must make predictions about the child's potential to develop autonomy, considering factors such as current health conditions, the prognosis of these conditions, developmental progress, and age.

When there is low or no confidence that a child will be unable to develop autonomous capacities, a cautious approach should be taken regarding UFs related to carrier status, conditions that are only medically actionable in adulthood, and adult-onset conditions without available interventions. Conversely, when there is high confidence that a child will not develop autonomous capacities, decisions should prioritize the child's welfare, granting parents greater discretion.

Allowing parental discretion respects their autonomy. Our research showed that rigid, uniform policies cannot accommodate the diversity of family circumstances, and that offering choices fosters informed consent. Moreover, providing options encourages parents to reflect on potential consequences—such as emotional impact or insurance implications—helping them weigh alternatives thoughtfully and make more informed decisions about receiving or declining genetic information.

Default options, provisional choices, and multidisciplinary oversight

When parents are given choices regarding unsolicited findings (UFs), our guidelines recommend providing default policy options, such as "recommend returning, but allow opt-out" or "recommend withholding, but allow opt-in." These defaults help parents consider additional factors that they might not have initially reflected on, thereby supporting more informed decision-making.

Trio-analysis introduces an additional complexity that can create potential conflicts between parental preferences and the child's best interests—whether interpreted through future autonomy or welfare considerations. Specifically, if a UF is inherited from a parent, it cannot be disclosed for the parent without also being revealed for the child, due to how sequencing data are analyzed. To address this, our guidelines differentiate between inherited UFs and de novo UFs in the child. In situations where there is low confidence that a child with DD cannot develop autonomous capacities, parental discretion over de novo UFs is limited to help protect the child's emerging autonomy.

Furthermore, parents' UF choices under these guidelines are "provisional." In some cases, it may be ethically necessary to override these decisions if competing interests are present. Consistent with Holm *et al.,* we recommend that all UF cases be reviewed by a multidisciplinary committee to determine whether parents' provisional choices should be maintained or modified [8].

When a UF is temporarily withheld, clear protocols for data storage and potential future disclosure should be in place. The committee is responsible for evaluating and advising on these disclosure plans. We acknowledge current legal and practical challenges in storing UFs and the absence of an adequate IT infrastructure. Nevertheless, our guidelines emphasize the moral responsibility to explore ways to implement these systems. Several bio-banking initiatives are already using dynamic consent frameworks, allowing individuals to

update preferences for receiving results over time [20]. Our approach adopts the principles of dynamic consent while recommending restrictions on the range of choices for children, reflecting their unique ethical considerations.

Low confidence in the child's future autonomy and returning unsolicited findings

For cases where there is low confidence that a child with developmental delay will be unable to develop autonomous decision-making capacities, disclosure of UFs should aim to preserve the child's potential for future autonomy. The guidelines provide the following directives:

a) Severe, medically actionable conditions in childhood

Disclosure of these UFs is always in the child's best interest. Protecting life and ensuring good health during childhood are prerequisites for future autonomy. This aligns with current pediatric guidelines [3–11]. Examples include child-onset cancers or congenital heart conditions.

b) Severe, medically actionable conditions in adulthood

For adult-onset conditions like BRCA1 or BRCA2 mutations, disclosure depends on whether the variant is de novo or inherited. De novo variants should be stored for potential future disclosure, as it is uncertain whether the child could make autonomous decisions later. If it becomes clear the child will remain under parental care, parents may then receive the information. Inherited variants are medically relevant for parents and relatives; disclosure may sometimes be delayed due to contextual considerations, such as insurance or family health. Committee deliberations should also consider the child's interest in growing up with healthy parents and the potential impact on family members.

c) Severe, medically inactionable child-onset conditions

For these conditions, parents may provisionally choose to receive information for both de novo and inherited variants. When child-onset conditions carry a high risk of severe cognitive impairment or fatality, future autonomy cannot justify withholding the information. Returning these findings aligns with welfare-based best interests, may prevent further diagnostic delays, and can significantly affect parental or family reproductive decisions.

d) Severe, medically inactionable adult-onset conditions

De novo variants in this category are generally not disclosed to preserve the child's future autonomy. Inherited variants are also generally withheld, though exceptions may apply if the findings have substantial implications for parents' or adult relatives' reproductive decisions. Parents may provisionally opt to receive this information. Examples include adult-onset neurodegenerative diseases such as ALS.

e) Carrier status for severe X-linked or autosomal recessive conditions

Carrier-status findings are primarily relevant for reproductive decision-making. Female carriers of X-linked conditions usually have low or mild risk, but sons have a 50% chance of being affected. Parents may provisionally opt to receive inherited carrier-status findings for reproductive planning, while a cautious approach is recommended for de novo variants when low confidence exists regarding the child's autonomy. Autosomal recessive carrier-status poses risks only if both parents are carriers. If a child inherits both variants and is predisposed to a severe condition, disclosure should follow the relevant UF category guidelines. The committee should also consider whether other children in the family could be affected, which may justify overriding parental preferences not to receive such information.

Carrier-Status UFs and reproductive implications

Unsolicited findings (UFs) for carrier-status of severe X-linked or autosomal recessive conditions are grouped separately to emphasize their primary relevance for reproductive decision-making. For most female carriers of X-linked conditions, personal risk is minimal, and if symptoms do occur, they are typically milder than in affected males. However, sons of these carriers have a 50% chance of being affected. Parents may provisionally choose to receive inherited carrier-status results for reproductive planning, while disclosure of de novo variants should be approached cautiously when confidence in the child's autonomous capacities is low.
In contrast, autosomal recessive carrier-status UFs do not pose risks to carriers themselves and only have

significant reproductive implications if both parents are carriers. Because of the way sequencing data are analyzed, this can only be identified if the child is predisposed to the condition. If a child is predisposed to a severe condition due to both parents' carrier status, disclosure should follow the relevant UF category guidelines. Our recommendations allow parents to provisionally opt to receive inherited UFs with major reproductive significance. In some cases, parents may prefer not to know their own carrier-status while still wanting UFs for their child's predisposition; the committee should consider whether other children in the family could be affected, which may justify overriding parental preferences.

High confidence in the child's lack of autonomous capacities

For some children with developmental delay, there is strong evidence that they will not develop autonomous capacities. In these cases, parents can be granted broader provisional discretion over more UF categories, provided decisions align with the child's welfare. UFs for severe, medically actionable childhood conditions should always be disclosed to protect immediate health.

For severe, medically actionable adult-onset conditions, disclosure is generally warranted for both the child and parents, as children benefit from having healthy caregivers. Parents of younger children may choose to delay learning about de novo UFs until interventions are possible; the committee should ensure plans are in place for future disclosure and consider any potential risks to other family members.

For de novo and inherited UFs related to severe, medically inactionable conditions—whether child- or adult-onset—and carrier-status for X-linked or autosomal recessive conditions, parents may exercise substantial provisional discretion. Decisions may be guided by nonmedical utility or reproductive considerations, provided they do not conflict with the child's welfare.

Conclusion

A distinctive feature of these guidelines, absent from previous policies for WES and WGS, is that disclosure requirements are tailored according to the degree of confidence regarding a child's potential for autonomous decision-making. This approach explicitly addresses uncertainty in developmental potential, particularly for young children with developmental delay.

The guidelines incorporate staged consent and default options (provisional opt-ins/opt-outs) to promote well-informed parental decision-making [24, 27]. While default choices are common in genetics, our empirical findings underscore their role in assisting parents to make thoughtful, context-specific decisions. Collectively, these elements help resolve ethical challenges arising when children undergo genomic sequencing in trio-analysis for clarifying developmental delay.

Future research should address practical challenges, including secure information storage, re-contact procedures, and formalizing multidisciplinary committee deliberations. It should also evaluate whether staged consent is appropriate in all pediatric WES contexts, particularly when rapid diagnosis is critical—such as in neonates with severe conditions in intensive care. Guideline development should remain iterative, continuously updated as scientific knowledge and ethical insights evolve.

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