which is aimed to respect the child and his/her (growing) capacities. Although parents or guardians have an indisputable role in the inclusion of children in research, assent is orientated towards the child. Even though a positive relationship between child and parent is desirable and helpful in engaging the child, it is not a requirement for assent. It is up to the researcher to assess what the role of the parent or guardian should be in the assent procedure in that particular situation.

Second, Waligora invites us to reflect on the practicality of personalized assent. He indicates that there is an alarming situation because of the variation in general organization of research ethics committees (RECs) in the European Union, and he argues that therefore personalized assent would be hard to fulfill. However, personalized assent allocates the responsibility to engage the child towards the researchers. Thus, even with a poor general organization of RECs, the researcher can obtain personalized assent. Waligora illustrates his claim with a study on Polish children, who participated in the Gabriel project, which is a project aimed to identify the genetic and environmental origin of asthma. In the study, 706 questionnaires from children between 6 and 14 years were collected about their participation in the Gabriel project. Overall, 42% of the children said they were not asked for their opinion on participation, whereas 39% of the children felt that both parents and children should be asked for permission and another 33% thought that children of their age should always give permission.[3] This study is an excellent illustration of children who have, unfortunately, not been involved in the decision-making process and it underscores our notion of assent. We agree with Waligora that in order to foster and safeguard the engagement of children in the decision-making process, practical guidance is needed. Although an age limit seems attractive from a practical point of view, it entails the risk of working counterproductively. Instead of making sure that children are asked for assent, it may result in excluding children who want to and can be engaged but are not old enough. Moreover, what matters are the child's capabilities, and although age can be a guide to this, other factors determine the actual development of capabilities,[4] for example, life experience. In addition, it is important to note that personalized assent is not so much a legal but a moral concept.

Thus, an age limit will not be of assistance to achieve appropriate engagement of the child in the decision-making process. We must, however, be mindful that personalized assent does not become an empty concept. Guidance should be provided to researchers on how to implement personalized assent.

CONFLICT OF INTEREST

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Types of array findings detectable in cytogenetic diagnosis: a proposal for a generic classification

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Array testing reveals different types of clinically relevant results. A CNV (copy number variant) classification is already proposed and published by several authors.[1–3] However, none of these proposals defined any subcategories of clinically significant findings. We think that defining subcategories is a crucial basis for developing generic consent, if the patients may choose the kind of information they wish to be informed about. Moreover, there is no consensus concerning the name of the category of disease-causing array findings. Some authors call these CNVs 'clinically relevant',[4] 'clinically significant',[5] while others speak of 'pathological findings'[6,7] or 'pathogenic CNVs'.[8] Most authors do not subcategorize the clinically relevant CNVs,[9,10] while others distinguish subtypes of pathogenic CNVs and for instance report microdeletion and microduplication syndromes with reduced penetrance separately.[11,12] Finally, some classify CNVs with reduced penetrance (susceptibility loci) as variants of unknown clinical significance (VOUS).[8] CNVs classified as 'incidental findings' are also reported in the literature;[13] however, many authors do not describe the definition of the term used[14,15] and others simply include such findings in one group of clinically significant array findings.[10] A recent review on incidental findings in genetic testing also underlines the problem of unclear definitions and the problematic terminology for this type of results.[16]

We suggest using a uniform name for disease-causing array findings, namely, pathogenic, which means that 'the CNV is documented as clinically significant in multiple peer-reviewed publications, even if penetrance and expressivity of the CNV are known to be variable'.[1]

Based on our experience we recommend using three subcategories of pathogenic array findings: causative array findings, unexpected diagnoses and susceptibility loci for neurodevelopmental disorders (Table 1).

We introduce the term 'unexpected diagnoses' for findings that are often classified by others as 'incidental findings',[13] because they do not fit the phenotype or the indication for testing. The reason for this is that 'an incidental finding' means 'a diagnosis found unintentionally'. In case an affected proband is tested with a whole-genome array technique to detect CNVs, one can hardly describe a pathogenic CNV as unintentional; indeed the aim of array testing is finding CNVs! However, it may represent a pathogenic CNV that does not match the indication or phenotype.

We propose to include susceptibility loci for neurodevelopmental phenotypes in a separate subcategory of pathogenic array findings. It is well established that the incidence of such CNVs among affected individuals is increased in comparison with the general population. Therefore, they may be classified as pathogenic[2,17] in spite of their variable phenotypes and inheritance from normal parents. A susceptibility locus should represent a separate subcategory, as the disorders of extreme phenotypic heterogeneity or variable expressivity probably partly depend on the presence of a second-site variant.[18–20] If a susceptibility locus is found prenatally, the risk for developing the disease is still unquantified and little can be offered in a prenatal setting, as neurodevelopmental phenotypes most often cannot be ascertained by ultrasound examination.

Deletions revealing carrier status for recessive diseases may also be found in array testing and these are a separate category of findings. According to the American College of Medical Genetics[1] comprehensive reporting of heterozygous recessive mutations is outside the scope of genomic array testing and, in general, is not recommended. It is also not feasible to check all genes in large deletions. However, there are some situations when reporting such findings is clinically important. We do agree with Kearney *et al.*[1] that carrier status in case of a well-characterized recessive disorder with a reasonably high population frequency and/or with clinical features consistent with the patient's reason for referral, may be considered for disclosure.[21]

We recommend using the term incidental findings for a separate category of pathogenic array findings that are found in the parents. Targeted array testing of parental DNA can be performed in both prenatal and postnatal settings to determine inheritance of CNVs found in the proband. If by chance a pathogenic abnormality in the parental array profile is found, such a finding is truly incidental as

Table 1 A proposal for a generic classification of array findings

Finding category	*Subcategory*	*Definition and/or subclasses*	*Examples*
Pathogenic for the proband (ie, fetus)	**Causative findings**	Pathogenic finding explaining the phenotype or matching the indication	• 22q11 microdeletion in a proband with a tetralogy of Fallot • Trisomy 21 in a fetus referred for cytogenetic testing due to an abnormal first trimester screening (1:20 risk for Down syndrome) • Mosaic terminal duplication 2q31.1q37.3 in a child with ASD (detected on B-Allelic frequency plot, not detected with routine karyotyping and on LogR ratio plot)[22] • UPD (7) in a proband with failure to thrive[22]
	Unexpected diagnoses	Pathogenic findings NOT explaining the phenotype or NOT matching the indication. (a) early-onset treatable diseases (b) early-onset untreatable diseases (c) late-onset treatable diseases (d) late-onset untreatable diseases	(a) a deletion in band 10q11.21 including RET gene associated with multiple endocrine neoplasia IIA (b) DMD deletion in a male fetus referred for prenatal diagnosis because of an abnormal first trimester screening (c) a deletion in CHEK2 associated with a moderately increased risk of breast cancer and risk of other cancers in a proband with severe global developmental delay[13] (d) microdeletion of 17p12 (PMP22 gene) associated with a hereditary neuropathy with liability to pressure palsies (HNPP)
	Susceptibility loci	Variants associated with neurodevelopmental disorders, but of extreme phenotypic heterogeneity and/or variable expressivity.[20]	16p12.1 deletion in a patient with developmental delay[19]
VOUS (variants of unknown clinical significance)	—	(a) potentially pathogenic (without 'enough' evidence)[1,20] (b) truly VOUS (unknown significance)[1] (c) likely benign (without 'enough' evidence for benign)[1]	
Benign findings	—	(a) benign (found in many healthy individuals)[1] (b) polymorphic (found in $>1\%$ of the general population)[1]	
Status for recessive diseases	—	Comprehensive reporting of heterozygous recessive mutations is not recommended. However, carrier status in case of a well-characterized recessive disorder with a reasonably high population frequency and/or with clinical features consistent with the patient's reason for referral, may be considered for disclosure.[21]	Deletion of CFTR gen
Incidental findings	—	Abnormalities found by chance, unintentionally, in parents of probands	Mosaic Turner syndrome discovered on B-allelic frequency plot during quality control of the array profile of a pregnant woman referred for prenatal diagnosis due to foetal ultrasound abnormalities

Examples without references refer to clinical examples from our own center.

array diagnosis is not meant to find pathogenic abnormalities in the parents. These incidental findings do not particularly refer to the target regions, which were the indication for testing, but to other findings encountered by chance (Table 1, last row), for example during the quality control of the array profiles.

Finally, as SNP arrays are nowadays more often employed in diagnostic settings, not only CNVs but also abnormal B-allelic frequencies can indicate a pathogenic finding.[22] Therefore, we suggest broadening the classification to array findings and not narrowing it to CNVs only. Moreover, the proposed classification is generic and potentially may also be applicable for massive parallel sequencing (MPS) findings.

If the classification is to contribute to generic consent, based on which a patient may choose which information he/she wishes to be informed about, the subcategory of pathogenic unexpected diagnoses should be further divided into subclasses as suggested in Table 1. Otherwise such a heterogeneous subcategory might be misunderstood by patients leading to incorrect choices and frustrations if a certain pathogenic array finding is not reported.

An international classification and terminology for array findings are indispensable in order to avoid miscommunication, to facilitate comparing cohorts studied by different researchers and to optimize pre-test counseling. We hope that our suggestion will contribute to the establishment of a generic array and ultimately also to MPS findings classification.

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