LETTERS

Is a requirement of personalised assent realistic? A case from the GABRIEL project

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Giesbertz *et al*¹ recent report regarding children decision-making status in paediatric research presents the interesting concept of personalised assent. The authors provide an excellent illumination of one of the aspects of paediatric research, among the many issues in the field of the regulation of research participated in by children which continue to await a meticulous study. There is a continued lack of a full explanation for many issues, including dissent, minimal risk, and the definition of same-population.

The participation of children in biomedical research is limited by many restrictions intended to guarantee them the greatest possible degree of safety. One of these methods is traditionally assent. However, Giesbertz *et al*¹ claim that this interpretation is incorrect. Better than assent in providing protection from harm are parental informed consent, strict regulations about acceptable risk, respect of dissent, researchers' integrity, and a high quality of RECs assessment. The authors argue that above all assent has educational value (as it fosters autonomy), and can also be an instrument making the communication of researchers with the child easier.

I have two doubts concerning this interpretation of the titular term. First, it assumes a positive, correct relationship of the children with their parents or guardians. Where this is not the case – in families in which the parent exploits the child – assent can still provide a form of protection. Yet, in this case, it will protect not so much from harm as from possible exploitation. Second, the idea of personalised assent with the idea of possible recontact and reconsent added seems rather unrealistic. In the EU itself, both the organisation and the

differentiation of protocol assessment by RECs means that such a recommendation would be very hard to fulfil.²

Let me give one example. An article was recently published on the participation of children in one of the stages of the Gabriel project. This large-scale genome-wide association study of asthma took place in 14 European countries. The part of the research carried out in Poland involved taking blood samples, nasal swabs, and prick skin tests. The research was conducted in schools located in rural areas and small towns. The Polish part of the study was also accompanied by an additional one on opinions about participation in medical genetic research, in which 706 children aged 6–14 years took part.³ This study showed that during the Gabriel study, no child was asked to express assent within the official study protocol. Only 42% of them were informed by their parents or the researchers about the genetic research in which they were to take part. Only slightly over half of them were asked by their parents for their opinion regarding participation. Overall, 31% received no information on the study. All the children stated that in their opinion both parental consent and the child's assent to the research should be expressed.

I therefore believe that the good idea of personalised assent should be complemented with a clear and unambiguous recommendation as to the age of a child from whom assent should definitely be obtained. Further discussion and research is needed in order to ascertain this age.

CONFLICT OF INTEREST

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Reply to Waligora

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We kindly appreciate the chance to reply to Waligora's¹ comments on what we call personalized assent. Assent understood from an

engagement point of view does justice to the specifics of childhood. In practice, this can be translated into personalized assent, which means that both the process and the content of the assent procedure are dynamic and adjusted to the individual child and research context.²

Waligora¹ expresses two doubts concerning personalized assent. First, he argues that a positive relationship between children and their parents is assumed, as assent can provide protection against exploitation. Even if assent would offer some form of protection against exploitation by parents, we do not think that it alters our interpretation of assent. Assent from an engagement perspective gives rise to the moral obligation of the researcher to involve the child,

1 Giesbertz NA, Bredenoord AL, van Delden JJ: Clarifying assent in pediatric research. *Eur J Hum Genet* 2013; e-pub ahead of print 12 June 2013; doi:10.1038/ejhg.2013.119.

2 Waligora M: A European consistency for functioning of RECs? We just lost our chance. *J Med Ethics* 2013; **39**: 408–409.

3 van der Pal S, Sozanska B, Madden D *et al*: Opinions of children about participation in medical genetic research. *Public Health Genomics* 2011; **14**: 271–278.

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).