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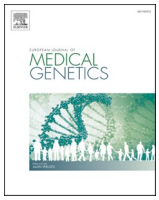

Response to the comment on Diderich et al. "The role of a multidisciplinary team in managing variants of uncertain clinical significance in prenatal genetic diagnosis" (EJMG 66(10),104844)

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We thank dr. Chen and dr. Li for their comment on our recent report on our experience in dealing with variants of uncertain significance (VUS) in a prenatal setting (Diderich et al., 2023b). We agree with the general policy on not reporting VUS in a prenatal setting, however VUS disclosure in exceptional cases is included in our pre-test counseling (Diderich et al., 2023a). The VUS disclosure was considered in a few cases, because of potential benefits for the prospective parents.

We appreciate that it would be interesting to get insight into how many VUS were uncovered. Most VUS, however, are not discussed within the multidisciplinary team (MDT) and these variants are not systematically registered in the patient files. The papers, dr. Chen and dr. Li refer to, concern reported VUS and not all VUS uncovered during analysis. Furthermore, reported cases did not all concern ongoing pregnancies.

Finding a VUS in a gene that does not explain the abnormal phenotype (incidental finding) can indeed be especially problematic. We have considered reporting VUS in these cases as not all disorders can be prenatally diagnosed (or excluded based) on ultrasound imaging and some disorders are treatable as illustrated in case 6–8. Cases 7 and 8 concerned metabolic disorders for which functional tests (for which cooperation of parents is necessary) and treatment were available. Moreover, the variant if pathogenic would result in a high recurrence risk for following pregnancies, therefore it was important to exclude the pathogenicity in these cases. Case 6, the most challenging case, concerned a fetus with an omphalocele and bilateral choroid plexus cysts. Exome sequencing showed compound heterozygous variants in the COQ8B gene associated with "Nephrotic syndrome, type 9" (OMIM 615573, AR) with an onset in the first or second decade of life. The paternal sequence variant was classified as pathogenic and the maternal variant as a VUS. This variant was reported only once in combination with another pathogenic variant in a patient with nephrotic syndrome (Lolin et al., 2017). The disorder is steroid treatment-resistant and usually progresses to end-stage renal disease requiring transplantation. The MDT concluded that the severity of the disease and the possibility of early treatment with CoQ10 supplementation to delay the proteinuria outweighed the uncertainty for the parents. The couple was extensively counseled and supported by a psychologist from our department. After consultation with a child nephrologist, the parents decided that the combination of the omphalocele with the possibility of nephrotic syndrome in childhood was not the future they wished for their child. After termination of the pregnancy, the parents reported that they were grateful that they were given the opportunity to be included in this difficult dilemma. Later we received a formal letter from one of the parent's father, who found reporting this variant was a good choice that allowed the family being part of the decision-making.

In all cases further testing of family members was considered. In case 1 with the VUS in SMC1A the maternal brother (who lived abroad) was tested as the sole living male relative, but was not found to be a carrier. The mother herself had no features that could either confirm or exclude her being a carrier of X-linked Cornelia de Lange syndrome (Huisman et al., 2017).

In all relevant cases, the advanced ultrasound examination was repeated or reanalyzed with the knowledge of the VUS. However, an additional ultrasound examination can also only be performed with the parents knowing the reason behind this additional investigation.

So called "not actionable VUS", when no additional examinations were possible and the only strategy would be "wait and see" whether the future child's development is normal, were never considered for reporting.

The purpose of our paper was to raise awareness that even a general policy not to report VUS in prenatal settings can create dilemmas that cannot be solved by an individual laboratory specialist or clinical specialist. Health care is not a black-and-white science. We hope this paper will stimulate other specialists to share their difficult cases and that based on all shared experience the future guidelines on dealing with uncertainty can be improved (Klapwijk et al., 2021). A multidisciplinary and multicenter approach to minimize the burden of VUS is necessary as we are just one step from whole genome fetal sequencing that will reveal many more (structural) variants. Sharing experience, phenotypes and variants is necessary to ensure diagnosis and limit the burden of genomic testing for fetal anomalies.

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Table 1
LOVD Accession ID and variant IDs.

Variant	LOVD.Uniq. Acc. Variant-ID	LOVD.Variant. ID
NM_006306.3(SMC1A): c.598A > C; p. (Lys200Gln)	#0000619701	SMC1A_000095
NM_020436.3(SALL4): c.2260G > A, p. (Val754Met)	#0000618210	SALL4_000045
NM_005257.5(GATA6): c.271C > T, p. (Pro91Ser)	#0000931632	GATA6_000003
NM_004387.3(NKX2-5): c.701C > G, p. (Ser234Trp)	#0000689482	NKX2-5_000358
NM_000098.2(CPT2): c.502_508delinsT, p. (Ala168_Leu170delinsPhe)	#0000931633	CPT2_000055
NM_024876.3(COQ8B): c.645delT, p. (Phe215fs)	#0000808879	ADCK4_000004
NM_024876.3(COQ8B): c.649G > A, p. (Ala217Thr)	#0000808878	ADCK4_000016
NM_172250.3(MMAA): c.433C > T, p. (Arg145*)	#0000801520	MMAA_000003
NM_172250.3(MMAA): c.1079G > A, p. (Arg360Gln)	#0000801523	MMAA_000006
NM_000292.2(PHKA2): c.1490G > A, p. (Arg497Gln)	#0000856508	PHKA2_000099
NM_014305.4(TGDS):c.714_716del, p. (Val239del)	#0000853704	TGDS_000006
NM_014305.4(TGDS):c.964G > A, p. (Glu322Lys)	#0000853703	TGDS_000005

Ethical approval and consent to participate

Our research represents a retrospective patient records study that does not fall under the scope of the WMO (The Medical Scientific Research with Humans Act), and therefore it did not need to be assessed by an accredited Medical Ethical Committee or the CCMO (Central Committee on Research Involving Human Subjects). According to the Research Codes of Erasmus MC and the FMWV Code of Conduct for Health Research the data that cannot be traced to an individual may be used for research.

All presented (supplementary) data are anonymous and do not allow identification of the individual patients and were obtained during routine diagnostic procedures. Patients are informed that we may investigate/publish their medical data as long as all data remain anonymous and cannot lead to the identification of the individual persons. Every patient had the opportunity to decline the use of their data/material. No objections were made.

Consent for publication

Not applicable.

Funding information

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Availability of data and materials

All variants were submitted to Leiden Open Variation Database (LOVD) (lovd.nl). The variant IDs and the unique variant accession ID are given in Table 1.

CRediT authorship contribution statement

Karin E.M. Diderich: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Jasmijn E. Klapwijk:** Formal analysis, Investigation, Writing – review & editing. **Vyne van der Schoot:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Myrthe van den Born:** Formal analysis, Investigation, Writing – review & editing. **Martina Wilke:** Formal analysis, Investigation, Writing – review & editing. **Marieke Joosten:** Formal analysis, Investigation, Writing – review & editing. **Kyra E. Stuurman:** Formal analysis, Investigation, Writing – review & editing. **Lies H. Hoefsloot:** Formal analysis, Investigation, Writing – review & editing. **Diane Van Opstal:** Formal analysis, Investigation, Writing – review & editing. **Hennie T. Brüggenwirth:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Malgorzata I. Srebniak:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

All authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Not applicable.

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Glossary

MDT: multidisciplinary team
VUS: variant(s) of uncertain significance

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