Current controversies in prenatal diagnosis 2: The 59 genes ACMG recommends reporting as secondary findings when sequencing postnatally should be reported when detected on fetal (and parental) sequencing.

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Conflicts of interest

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What is already known?

- In clinical exome and genome sequencing, there is potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for sequencing but of potential medical value for patient care.
- The American College of Medical Genetics and Genomics (ACMG) has guidelines that state that when offering sequencing, secondary findings should be sought and reported in 59 genes because when found, surveillance and early treatment may prevent disease or improve outcomes.
- Individuals can opt out of receiving this information and the ACMG guidelines exclude prenatal sequencing.

What did this debate add?

- The majority (55%) of audience members polled remained in favour of reporting

secondary findings in the prenatal setting.

- However, the debate highlighted research indicating that parents may not want, or may struggle to deal with this additional information, as well the challenges of ensuring this information is passed to the child.
- In the prenatal setting, pregnancy termination is a potential consequence of reporting secondary findings.
- Additional challenges arise when reporting secondary findings in the prenatal setting, and health services may not be equipped to deal with the additional counselling that will be required.
- The debate highlighted the need for further research to generate evidence upon which to base prenatally appropriate guidelines.

Abstract

Genome sequencing is increasingly being used to aid genetic diagnosis in fetuses with structural abnormalities detected on ultrasound examination. However, with clinical exome and genome sequencing, there is potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing, but of potential medical value for patient care. In the postnatal setting, the American College of Medical Genetics and Genomics (ACMG) has clear guidelines that state that when offering sequencing, secondary findings should be reported in 59 genes for which ACMG consider there is clinical evidence that pathogenic variants may result in disease that might be prevented or treated, with the option to opt out of receiving this information. However, these guidelines specifically exclude prenatal sequencing. Here we report the debate on whether or not pathogenic findings in these 59 genes should or should not be reported in the prenatal setting. Although more were in favour of reporting before the debate, there was no significant consensus from the audience. After the debate there was a swing towards not reporting, but a slim majority (55%) remained in favour, indicating that this is an area requiring further research and the development of evidence-based guidelines applicable to prenatal proband and trio sequencing.

Introduction

In clinical exome and genome sequencing, there is potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing, but of potential medical value for patient care. In response to the increasing use of exome and genome sequencing for genetic research and postnatal diagnostic purposes, the ACMG convened a group of experts to develop a list of genes for which they considered there is clinical evidence that those variants classified as pathogenic result in a high likelihood of disease for which preventative measures and/or treatments are available. These disorders include many where individuals with pathogenic variants might be asymptomatic for long periods of time. Such findings may therefore have medical benefit for the patients and families of patients undergoing clinical sequencing. An expert group developed a policy statement, published in 2013, which mandated that diagnostic laboratories performing exome and genome sequencing seek and report mutations in 57 genes for known pathogenic (KP) and expected pathogenic (EP) variants.¹ Subsequently one gene was removed. Of note, this guidance applied to all clinical germline (constitutional) exome and genome sequencing, but specifically excluded fetal samples.

In response to a 2014 report from the Presidential Commission on Bioethical Issues² and results from a survey of the ACMG membership,³ the recommendations were modified to include an “opt out” option for receiving these results, whilst also noting that it was not practical to offer an option of receiving results for only a subset of the genes on this list. In addition, the ACMG clarified that these results should not be referred to as “incidental” findings, but rather “secondary” findings, because they are sought intentionally.⁴ Finally, by 2015, some genes were removed and others added to generate a current list of 59 genes (ACMG59, Table 1), but the recommendation with regard to fetal samples was not changed.⁵

What issues might arise when applying these guidelines in the prenatal setting, where typically both parents and the fetus have their genomes sequenced simultaneously? Issues that must be considered include that this knowledge may result in parents choosing to terminate a pregnancy, along with our duties to the unborn child from whom we may remove the right to choose whether or not to have these results.⁶ Other points to consider include variable penetrance without a clear phenotype, counselling and valid informed consent, management and feedback of information. Questions also arise as to who should be responsible for follow-up and family studies if required. Further, the ACMG guidelines state “We recommend that laboratories performing clinical sequencing seek and report mutations”. Does this mean that, since this guidance specifically states that we should ‘seek’ these mutations, targeted clinical sequencing focused on genes presenting prenatally should not be offered as this will exclude the majority of the ACMG59 genes?

Here we report the debate on “Secondary findings in the 59 genes, that ACMG recommends reporting when sequencing postnatally, should also be reported when they are detected on fetal (and parental) samples during prenatal sequencing”, presented at the 2019 annual ISPD meeting.

The argument in favour - Ignatia Van den Veyver

The primary objective of reporting KP and EP variants in the ACMG59 genes is to “*prevent high likelihood of severe disease by identifying them before symptoms occur*”,¹ because there are interventions available that can mitigate or avert adverse, occasionally fatal, health outcomes. This goal, to provide information that can lead to prevention of potentially serious harm, is by itself the strongest argument to report secondary findings for anybody who undergoes exome sequencing, including prenatally. Variants of uncertain significance in those genes are not reportable,¹ and thus the concern that those might generate additional uncertainty in an already complicated pregnancy does not need to be considered here.

When examining the genes included and their associated conditions, the first striking characteristic that is not always appreciated, is that only seven genes are associated with diseases that have their onset and age of intervention exclusively during adulthood (BRCA1 and BRCA2 for hereditary breast and ovarian cancer; MLH1, MSH2, MSH6 and PMS2 for Lynch syndrome, and MUTYH for familial adenomatous polyposis type 2) (Table 1, Figures 1A and 1B). Of the remaining genes, some have onsets that are always in childhood, with some as early as in the neonatal period. The latter comprises TSC1 and TSC2, which are associated with tuberous sclerosis; WT1, which predisposes to Wilms tumours; ATP7B, which is associated with Wilson disease; and X-linked OTC, which is associated with ornithine transcarbamylase deficiency, with a severe neonatal phenotype in males and variably severe disease in females. For others the onset may be either in childhood or adulthood (Figure 1A, Table 1).⁵ In addition, current recommendations for the majority of these conditions are to start preventive or therapeutic measures during childhood, including as early as in the neonatal period for a subset of them (Figure 1B; Table 1). Thus, there is great benefit for most of these diseases of knowing about individual risks as early as possible. This supports the disclosure of this potentially lifesaving information when prenatal exome sequencing is performed.

In order to facilitate accuracy and speed of variant interpretation, most prenatal genome- wide sequencing is performed as trios, whereby DNA from both parents is sequenced concurrently with the fetal sample and sequence data from parental samples are primarily used to help interpret the inheritance pattern and potential pathogenicity of variants detected in the fetal DNA.⁷ Thus, we also need to consider the implications for the parents of reporting KP and EP variants in the ACMG59 genes detected in the fetus when delivering prenatal trio exome sequencing. Each parent transmits one copy of all autosomal genes to the fetus. A mother also transmits one copy of all X-linked genes to her male and female offspring, while males transmit either their X or Y chromosome, depending on the fetal sex. Fifty-five of the ACMG59 genes are associated with diseases that are predominantly autosomal dominant, two with X-linked disorders (*OTC* and *GLA*), and two with autosomal recessive disorders (*MUTYH* and *ATP7B*, for which ACMG recommends only reporting on individuals with bi-allelic mutations) (Table 1). This means that if a KP or EP variant is identified in one of the parents, for the majority, there is a 50% risk that the fetus has

this variant. For autosomal dominant genes on the ACMG59 list, the majority are inherited rather than arising de novo. Thus the identification of a KP or EP variant in the fetus for one of these conditions carries a very high likelihood of being inherited from one of the parents. Not reporting such finding in the fetal sample is therefore a potentially missed opportunity for a lifesaving intervention for one of the parents.

Table 1 here

Figures here

An argument used against reporting KP and EP variants in the ACMG59 genes is that the list was developed because such variants are “medically actionable” in children and/or adults, but that the “medical action” of prenatal diagnosis includes the potential consequence of termination of the pregnancy. This was not intended to be one of the actions considered when the gene list was created. Nevertheless, authoritative reviews for each of these conditions⁹ include prenatal diagnosis and preimplantation diagnosis with appropriate genetic counselling, as valid options to manage at risk pregnancies. It is ethically difficult to justify that families in which the disease has been identified to cause risk to a pregnancy deserve different options than those in whom the disease is identified as a secondary finding on exome or genome sequencing. Furthermore, to date, most sequencing is performed for pregnancies in which the fetus already has birth defects or other phenotypes, such as intrauterine growth restriction, and not for screening of healthy pregnancies. Depending on the precise fetal phenotype, an additional secondary KP or EP variant in one of the ACMG59 genes may well change the prognosis and treatment options for the fetal condition for which sequencing was done. From this perspective, the secondary finding is not “secondary,” but rather a component of a comprehensive evaluation that will help the care team and parents make better-informed decisions about pregnancy management.

Some may argue that this applies only for a subset of the conditions caused by pathogenic variants in the ACMG59 genes and that in particular those with uniquely or primarily adult-onset do not fall into the above category. Yet, considering the high degree of heritability, identifying adult-onset disorders can lead to improvements in parental health through interventions. These parents may become the primary caregivers of children with special needs, who were prenatally diagnosed with structural birth defects and other developmental disabilities; optimising their health will benefit the care of those children. Furthermore, the extended family will also benefit, as each first degree biological relative has a 50% chance of carrying the same variant in case of dominantly inherited conditions.

The potential harm that can be done by presymptomatic testing for adult-onset conditions, or for conditions that only become symptomatic later in adolescence, to a child’s autonomous “right to an open future” is often used to argue against it¹². However, although research is ongoing, emerging data from studies investigating this concern have shown that children do not appear to incur significant adverse

effects to their psychosocial well-being from presymptomatic genetic testing information.^{12,13} In their recent position statement, the ASHG, has pointed out that the earlier guidance against presymptomatic testing has been interpreted in a more restrictive way than originally intended.¹⁵ Finally, since exome sequencing is currently done for fetuses with birth defects or other features raising suspicion for monogenic disorders, the fetuses from the tested pregnancies have already been diagnosed with serious health conditions that could be limiting their future potential, and it can be argued that withholding additional health information limits their and their parents' autonomy to help them shape a future that is most optimally aligned with the child's individual potential. Garrett et al. have also recently elegantly argued that there are limitations to the "right to an open future" and they propose a new paradigm that considers that children rather than having a right, have an "interest in an open future" that must be weighed against all other interests of the child and family.¹² From this perspective they argue that predictive genetic testing is ethically permissible in principle, as long as the interests promoted outweigh potential harms. I believe that this is the case for the disorders caused by KP and EP variants the ACMG59 genes, which are severe conditions for which specific interventions can improve prognosis.

In conclusion, if we consider the medical ethical principles of autonomy and the "respect for persons" ethical principle, offering the parents the autonomy to make decisions on behalf of their unborn fetus should apply for result disclosure of secondary findings in these genes. Considering the preventive and therapeutic measures that can be taken for affected fetuses, their similarly affected parent(s) and other relatives when a secondary finding in the ACMG59 genes is detected, the benefits of this information far outweigh the harms. The implications for the health of parents and other family members seem to support the non-maleficence principle's associated duty to warn. Finally, although one may argue that the cost and burden on the healthcare system is such that the ethical principle of justice, or the need to make such services available to all stakeholders in the same way (distributive justice), cannot be satisfied. I believe that it is unjust to use this challenge as an excuse not to offer the option to receive information on these secondary findings for those for whom it is possible, especially in view of the recommendations to test family members of affected individuals for most of these conditions. Instead, it should be the motivation to optimise systems to increase access to genetic testing services in a more equal way.

The case against - David J Amor

The introduction of new medical interventions should be supported by evidence of clinical utility, cost-effectiveness and feasibility. Whilst acknowledging that potential benefits might arise from the interrogation of prenatal exome and genome tests for ACMG59 secondary findings, there are also a number of downsides, suggesting that an alternative approach is needed.

The ACMG59 was not designed for prenatal use and is poorly suited to this purpose, due to the heterogeneity of disorders tested and ages of onset ranging from the neonatal period to typically in adulthood (Table 1). Of the 59 genes, 18 (30.5%) are for disorders in which the onset is typically in adulthood,⁹ although for 11 of these disorders there is recommendation for intervention to be considered in childhood or adolescence.⁹ (Table 1, Figure 1B) Yet these figures do not convey the complete picture, because adult onset cancer syndromes are overrepresented amongst the disorders actually detected when the ACMG59 are analysed: 41.5% of the times when an ACMG59 KP or EP variant is detected, it will be for an adult onset disorder¹⁰ (Figure 1C). If actionable secondary findings are to be sought in the prenatal setting, why not design a new list, focusing on the genes with childhood onset?

With the inclusion of adult onset disorders in the ACMG59, its use in the prenatal setting can be viewed as an 'extreme' form of predictive genetic testing in children. The ethical, legal, social and psychological arguments against predictive genetic testing in children are well documented and have led professional societies to recommend that such testing be deferred until adulthood.^{15,16} An additional complexity in the prenatal setting is that such findings might lead to pregnancy termination,¹⁷ an outcome contrary to the original conceptualisation of 'actionability,' which emphasises benefit to the individual tested.

A further consideration is that even in adults, clinical utility of ACMG59 analysis has not been demonstrated. Whilst the approach 'makes sense' in theory, the realisation of predicted health benefits depends on a number of downstream variables, including confirmation of the diagnosis and the initiation of follow up screening and interventions; yet due to individual and health service factors these may not occur.¹⁰ Meanwhile any clinical benefit must be balanced against possible harms including overtreatment, high cost of care, increased parental anxiety, complications of unnecessary interventions and stigmatisation.^{18,7} In health systems with limited resources and existing inequities, the question must be asked whether prenatal testing of ACMG59 represents a high-value healthcare intervention?

It is also not clear that parents actually want this information. Evidence from the prenatal diagnosis setting is limited, but suggests that at least 40% of women having prenatal diagnosis wish to limit the amount of genetic information about their fetus that is returned to them.¹⁹ More research has been undertaken in the postnatal setting, in which it is clear that parental attitudes vary greatly, with subsets of parents wanting all information, some information or no information.²⁰ Newborn genomic screening research shows that more than one third of parents choose not to receive additional findings, for reasons that include feeling overwhelmed, concern about abnormal results, insurance and privacy, and discomfort with genetic testing more broadly.²¹ Further, within a couple, there is frequently discordance between parents' interest in receiving secondary findings for their child.²²

Whilst it might seem that a simple solution is to offer choice to couples about whether to receive secondary findings, there is evidence that asking couples to make this choice is itself a burden. Anderson

et al. (2017) showed that parents offered secondary findings in the paediatric setting experienced conflict between a perceived moral obligation 'to do the best for their child', and their own preference not to know this information.²³ They coined the term 'inflicted ought' to describe the burden generated by the provision of choice in this setting. It is clear that in the prenatal setting, both the provision of additional findings and the provision of choice about additional findings are significant stressors occurring at a time where couples are likely to already be feeling overwhelmed.

The routine offer of ACMG59 secondary findings analysis will also present practical challenges for the clinic. Prenatal genomic counselling is already complex and the additional challenges of counselling for secondary findings in patients of diverse educational and cultural backgrounds are immense. Prenatal services are neither set up nor resourced to provide this service.

In the absence of new evidence to the contrary, I argue that the prenatal use of the ACMG59 is inappropriate; it is the wrong test at the wrong time. Rather, analysis during pregnancy should focus on the primary indication of the test and should specifically exclude adult onset disorders.

If there is a strong desire to undertake additional analysis for secondary findings, an alternative pathway could be developed, customised for the prenatal setting. A suggested approach is to defer the offer of secondary analysis until after the pregnancy, and to restrict initial analysis of the ACMG59 to the parental samples. Only if an actionable secondary finding is identified in a parent would it be necessary to consider analysis for that variant in the child, with decision making taking into account parental wishes and the age of onset of the disorder. Such an approach would preserve most potential benefits of secondary analysis whilst minimising the disadvantages.

Discussion

Prior to the debate, 66% of the audience voted in favour of the argument with subsequent discussion adding to the debate. One gave the example of finding balanced translocations prenatally and commented that we tend to give that information to the parents, saying "tell your child about this when they are older so they can seek genetic counselling before reproductive planning," but in reality, the parents often don't even remember that this information existed by the time the child is old enough to discuss it. So this raises a logistical issue: if we do report secondary findings how do we actually ensure the transfer of that information to relevant family members and to the unborn child when they are older? A further point was raised that recent qualitative work from the 100,000 Genomes Project participants shows that many people, when followed up later, did not recall their decision regarding consenting for secondary findings.²⁴ They also felt it was too much for them to be expected to consider that in the same conversation as consenting for sequencing and primary findings in the first place. The final point raised by the audience gave the ethical perspective - "if you know it, how can you not disclose it to the family?". To which our

opposer responded that targeted analysis of genomic data (largely) avoids identifying secondary findings in the first place. He would not advocate withholding information if we do have it – for example, parental BRCA2 status in fetal Fanconi anaemia.

Summary

In summary, the argument in favour focussed on considering the preventative and therapeutic measures that can be taken for affected fetuses and their parent(s) and other relatives, with the benefits of this information far outweighing the harm. The argument against pointed out that the clinical utility of the ACMG59 genes has not yet been proven even in adults. In other settings, a significant proportion of parents did not want the burden of deciding whether or not to have secondary findings revealed. The challenges of pre-test counselling in the prenatal setting were considerable, with current services not yet equipped to cope with the demands.

At the end of the debate the proportion voting in favour fell by 11% to 55% – thus, whilst the majority remained in favour, there was a small swing against indicating that there are still questions to answer. Maybe for now we should do as Dr. Amor suggested, and defer the offer of secondary analysis until after the pregnancy, and to restrict initial analysis of secondary findings to the parental samples. Only if an actionable secondary finding is identified in a parent would it be necessary to consider analysis for that variant in the child. However, using this approach, occasionally we may not report on findings for which there would be an early benefit from prenatal detection. The alternative is to use a targeted approach, which precludes analysis of most of the ACMG59 genes.⁶ Whatever approach, is taken it is clear that expert pre- and post-test counselling will be required to ensure informed parental consent.²⁵

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Table 1. List of 59 ACMG genes with mode of inheritance, age of disease onset, and age of intervention implementation (adapted from Kalia et al. (2017)⁸ and Milko et al. (2019)⁹.

AD – autosomal dominant; AR – autosomal recessive; XL – X-linked

Phenotype	Gene s	Inheritance	Disease onset	Surveillance onset
Hereditary breast and ovarian cancer	<i>BRCA1, BRCA2</i>	AD	Adult	Adult
Li-Fraumeni syndrome	<i>TP53</i>	AD	Child/adult	Child
Peutz-Jeghers syndrome	<i>STK11</i>	AD	Child/adult	Child
Lynch syndrome	<i>MLH1, MSH2, MSH6, PMS2</i>	AD	Adult	Adult
Familial adenomatous polyposis	<i>APC</i>	AD	Child/adult	Child
<i>MYH</i> -associated polyposis	<i>MUTYH</i>	AR	Adult	Adult
Juvenile polyposis	<i>BMPR1A, SMAD4</i>	AD	Child/adult	Child
Von Hippel–Lindau syndrome	<i>VHL</i>	AD	Child/adult	Child
Multiple endocrine neoplasia type 1	<i>MEN1</i>	AD	Child/adult	Child
Multiple endocrine neoplasia type 2	<i>RET</i>	AD	Child/adult	Child
Familial medullary thyroid carcinoma	<i>RET</i>	AD	Child/adult	Child
<i>PTEN</i> hamartoma tumour syndrome	<i>PTEN</i>	AD	Child/adult	Child
Retinoblastoma	<i>RB1</i>	AD	Child	Neonate
Hereditary paraganglioma- pheochromocytoma syndrome	<i>SDHD, SDHAF2, SDHC, SDHB</i>	AD	Child/adult	Child
Tuberous sclerosis complex	<i>TSC1, TSC2</i>	AD	Child	Neonate
WT1-related Wilms tumor	<i>WT1</i>	AD	Child	Neonate
Neurofibromatosis type 2	<i>NF2</i>	AD	Child/adult	Child
Ehlers-Danlos syndrome, vascular type	<i>COL3A1</i>	AD	Child/adult	Child
Marfan syndrome, Loeys-Dietz syndromes and familial thoracic aortic aneurysms and dissections	<i>FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2</i>	AD	Child/adult	Neonate
Hypertrophic cardiomyopathy, dilated cardiomyopathy	<i>MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2</i>	AD XL (GLA)	Child/adult	Neonate
Catecholaminergic polymorphic ventricular tachycardia	<i>RYR2</i>	AD	Child/adult	Child
Arrhythmogenic right ventricular cardiomyopathy	<i>PKP2, DSP, DSC2, TMEM43,</i>	AD	Child/adult	Child
Romano-Ward long-QT syndrome types 1, 2, and 3, Brugada syndrome	<i>KCNQ1, KCNH2, SCN5A</i>	AD	Child/adult	Neonate
Familial hypercholesterolaemia	<i>LDLR, APOB, PCSK9</i>	AD	Child/adult	Neonate

Wilson disease	<i>ATP7B</i>	AR	Child	Neonate
Ornithine transcarbamylase deficiency	<i>OTC</i>	XL	Child	Neonate
Malignant hyperthermia susceptibility	<i>RYR1, CACNA1S</i>	AD	Child/adult	Neonate

Figure legend

Figure 1: Characteristics of genes on the ACMG59 list: A. Onset of the associated diseases; and B. Approximate ages by which earliest screening and/or interventions that can improve health are recommended (A and B adapted from the classification of Kalia et al. (2017)⁸ and Milko et al (2019)⁹; C. ACMG59 genes by age of intervention, adjusted according to disorder prevalence using data from Milko et al. (2019)⁹ and Hart et al. (2019)¹⁰.

A

ACMG59 genes by age of onset

B

ACMG59 genes by age of intervention

C

ACMG59 genes by age of intervention
adjusted for disorder prevalence

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