Arrays in Postnatal and Prenatal Diagnosis: An Exploration of the Ethics of Consent

SPECIAL ARTICLE

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Arrays in Postnatal and Prenatal Diagnosis: An Exploration of the Ethics of Consent

Wybo Dondorp,[1]* Birgit Sikkema-Raddatz,[2] Christine de Die-Smulders,[3] and Guido de Wert[1]

[1]*Department of Health, Ethics and Society, CAPHRI and GROW Research Schools, Maastricht University, Maastricht, The Netherlands;* [2]*Department of Genetics, University of Groningen, University Medical Centre Groningen, The Netherlands;* [3]*Department of Clinical Genetics, University Hospital Maastricht, GROW Research School, Maastricht University, Maastricht, The Netherlands*

For the Focus on CNV Detection with Diagnostic Arrays

Received 8 November 2011; accepted revised manuscript 21 February 2012.
Published online 6 March 2012 in Wiley Online Library (www.wiley.com/humanmutation).DOI: 10.1002/humu.22068

ABSTRACT: The introduction of genome-wide arrays in postnatal and prenatal diagnosis raises challenging ethical issues. Here, we explore questions with regard to the ethics of consent. One important issue is whether informed consent for genome-wide array-based testing is in fact feasible, given the wide range of possible outcomes and related options. The proposed alternative of "generic consent" will have to be studied in practice. From an ethical point of view, the question is whether consent would still be sufficiently "informed" in a generic approach. Another issue that has not yet been given much attention is how far parents, or pregnant women and their partners, should be allowed to determine the range of possible outcomes that will or will not be reported back to them. The scope and limits of parents' and prospective parents' right to know or not to know are far from clear. The complex normative issues on the content and weight of these rights can only be answered by taking full account of the rights and interests of all the parties involved: prospective and actual parents, children, and relatives. This paper is the result of a working group meeting preceding the European Society of Human Genetics 2011 Conference, where these issues were addressed.

Hum Mutat 33:916–922, 2012.

KEY WORDS: unsolicited findings; informed consent; testing children; prenatal diagnosis; ethics

Introduction

Genome-wide array technology is rapidly gaining ground both in postnatal and prenatal diagnosis. Postnatally, this mainly concerns the clarification of unexplained intellectual disability and other heterogeneous conditions affecting young children [Vissers et al., 2010]. Prenatally, genome-wide arrays are increasingly being used in pregnancies with ultrasound abnormalities [Vetro et al., 2012], while proposals have also been made for using this technology as an alternative for karyotyping in low-risk pregnancies [Ogilvie et al., 2009]. The introduction of genome-wide arrays in these settings promises to have far-ranging implications for clinical genetics, but also raises challenging questions from an ethical point of view. A vexing issue for clinical practice concerns the ethics of consent [Netzer et al., 2009]. The question involves not just whether, or to what extent, informed consent for genome-wide array-based testing is in fact feasible, given the wide range of possible outcomes and related options it may yield, but also to what extent parents or pregnant women and their partners should be allowed to determine the range of possible outcomes that will or will not be reported back to them [Dondorp and De Wert, 2010]. This question, referring to the application in these specific contexts of rights or presumed rights both "to know" and "not to know," has until now not been paid much attention. This paper is the result of a working group meeting preceding the European Society of Human Genetics (ESHG) 2011 Conference in Amsterdam, where these issues were addressed. In line with the nature of the workshop, this paper is exploratory. It gives an overview of ethical issues and challenges relevant to policy development in this highly dynamic field, focusing on the contexts of postnatal and prenatal testing. When speaking of "postnatal testing," we mean testing of young children. Testing of adults raises different issues than those discussed in the workshop and in this paper. Another theme beyond the scope of this paper is how to deal with the still theoretical possibility of genetic findings meaningfully associated to non-health-related traits such as intelligence, musicality, and so on.

The structure of this paper is as follows. We start out with a separate section briefly presenting the outline of the ethical concept of "informed consent." Corresponding to the themes of the workshop, the next two main sections are on issues of consent in postnatal and prenatal testing. Both are divided in three subsections. In the first of those, we discuss the challenge of obtaining meaningful informed consent for genome-wide array-based testing. In the second, we discuss whether and to what extent the pretest consent procedure should include the option for parents or pregnant women to indicate that they do not want to be informed about specific outcomes. In the third, the opposite issue of their right to know specific outcomes is addressed. The final section consists of a brief conclusion.

Informed Consent

The ethical concept of "informed consent" for medical treatment consists of two normative elements [Beauchamp and Childress, 2009]. Firstly, it requires doctors to obtain the patient's consent prior to initiating medical treatment (or testing). This requirement connects to the ethical principle of respect for patient autonomy;

*Correspondence to: Wybo Dondorp, Department of Health, Ethics and Society, Faculty of Health, Medicine and Life Sciences, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. E-mail: w.dondorp@maastrichtuniversity.nl

Contract grant sponsor: CSG Centre for Society and the Life Sciences; Netherlands Genomics Initiative; Research Project "The $1000 Genome: Ethics of Whole Genome Sequencing in Public Health Care" (70.1.070).

patients should be allowed to remain the authors of their own lives. If the patient is incompetent, his or her relatives (proxies) or legally appointed representatives must (whenever realistically possible) be asked to decide in his or her place. However, these persons do not then simply take over as fully autonomous decision makers. As representatives, their role is to decide what is in the best interest of the patient, taking account, when applicable, of what they know about the patient's own views and preferences. In terms of ethical principles, proxy consent has a strong, direct link with the principle of beneficence, and a weaker, indirect one with the principle of respect for patient autonomy. Secondly, the qualification "informed" stresses that for consent to be meaningful, it must be based on an adequate understanding on the part of the patient or his or her representatives of what the proposed treatment involves, what is at stake in terms of possible burdens, benefits and drawbacks, and how this relates to any realistically available alternatives. According to the norm of "informed consent", it is the responsibility of the professional to provide this information. This does not entail telling the patient or his or her representative about every possible detail, as that would undermine rather than facilitate meaningful informed consent. Instead, the information should be tailored to what the patient or representative needs to know in order to make a well-informed decision. The basic criterion for this is the perspective of the "reasonable person." Especially with regard to decisions with possibly far-ranging consequences, professionals should invite patients to indicate whether they would have any specific additional information needs based on their personal values, ideals, and preferences.

Parental Consent for Genome-Wide Array-Based Testing of Children

Genome-wide array-based testing aimed at uncovering the genetic basis of a child's hitherto unexplained intellectual disability or other complex disorder may be the only way to arrive at a diagnosis necessary for the adequate treatment and care of that child [Vissers et al., 2010]. If so, beneficence-based professional obligations toward the child may justify the provision of such testing, even though it comes at the price of possibly also generating outcomes that may sometimes lead to difficult decision making.

As the child cannot decide upon the testing offer, the parents are asked to give their proxy consent. Other things being equal (e.g., costs), it is part of their parental responsibility to consent to medical testing that is clearly in the interests of their child [Buchanan and Brock, 1989]. Since doctors and counselors cannot fulfill their own duty of providing good care without the parents also being prepared to accept their responsibility in this regard, persuading them to consent may, if necessary, be appropriate. If the interests of the child are at stake, nondirectiveness cannot be the final word.

Meaningful Informed Consent for Postnatal Testing

The fact that (other things being equal) parents can be expected to consent to testing that is in the interest of their child, should not take away the importance of properly informing them about the nature and possible outcomes of the test. Providing this information is a matter of taking them seriously in their role as representatives of the best interest of their child. From an ethical point of view, that is why professionals should always try to obtain well-informed parental consent.

In order for their consent to be meaningful, parents must be provided with adequate pretest information about the possible outcomes and implications of genome-wide array-based testing. Apart from findings that may help to resolve the clinical problem, there may also be outcomes of unclear clinical significance and unsolicited findings. Here we use "unsolicited findings" to refer to outcomes of clinical significance (mutations and risk factors) that are not related to the health problem that prompted the testing.

However, even with regard to clinically relevant findings, the range of possible outcomes is far too wide to be able to discuss all the possibilities prior to testing. The problem is, in part, of a practical and economic nature; even if it were possible for medical professionals to have a complete overview, they simply do not have the time to provide detailed pretest information to patients, parents, or prospective parents about every possible outcome. But there is also a limit to the information that patients or their representatives (in this case, the parents of the child to be tested) can be expected to absorb, understand, and reflect upon. "Information overload" is a serious concern, signaling that not just too little, but also too much information may undermine well-informed decision making [Van Zwieten, 2006].

As a solution for this problem, which arises in several contexts in genetic testing, the model of "generic consent" has been proposed [Elias and Annas, 1994]. This involves providing information about generalized outcome categories and related options, instead of more specific information across the full range of possible outcomes. The recent proposal by Berg et al. [2011] for what they call a "binning system for incidental findings," seems to come close to this idea. Whether generic consent is a feasible alternative is very much an open question, requiring empirical research to see how this as-yet untested model works in practice. Of course, further in-depth ethical analysis of this concept is also required. From an ethical point of view, the issue is whether this approach allows counselors to steer clear of information overload, on the one hand, without ending up with what is in fact "uninformed consent," on the other. It would seem that in order for generic consent for genome-wide array-based testing to be sufficiently informed, pretest information will at least have to differentiate between unsolicited findings with early or late-onset health implications, and further break these down into outcome categories accounting for level of risk, burden of disease, and options for treatment or prevention. Parents should also be made aware that the interpretation of certain unclear outcomes may also require themselves to be tested, and that genome-wide testing of their child may reveal something that affects themselves as well as other relatives, for example, being at an increased disease risk [Vermeesch et al., 2011].

Parental Right Not to be Informed About Specific Test Outcomes

Another question is whether, as part of the consent procedure, parents should be given the option of indicating that they do not want to be informed about specific outcomes beyond those answering the clinical problem prompting the test. It is generally acknowledged that, in principle, competent adults have a right to remain ignorant with regard to genetic information about themselves [Wilson, 2005]. But can parents claim "a right not to know" with regard to certain outcomes of genome-wide array-based testing of their child? Here, again it is important to acknowledge that they themselves are not the patient to be tested, but his or her representatives. According to the recommendations of the ESHG, "health care professionals have the responsibility to defend the interests of the minor if the decision of the minor's parents or legal guardians is not to the direct benefit of the minor" [European Society of Human

Genetics, 2009]. Therefore, if there is such a thing as a "parental right not to know," it cannot cover findings that, even though they are unsolicited, are of clinical relevance, in the sense of requiring treatment, prevention, or surveillance.

However, in some consent protocols for array-based testing of children that we have seen (coming from university hospitals in the Netherlands), parents are simply given the option of indicating that they do not want to be informed about unsolicited findings, with no further qualification or condition. In an article reflecting on new challenges for informed consent arising from whole-genome array testing, Netzer et al. [2009] also included this option in their proposal to ask:

> patients or their parents [prior to testing] whether they wish to be informed about any additional genetic findings (without direct connection to the phenotype in question) with predictive value for the health of the proband and potentially her/his family; [whether] they only wish to be informed about such additional genetic findings if effective treatment options or surveillance programmes are available; [and also whether] they wish to be informed about a carrier status for an autosomal recessive disease—that is, about a condition which may have implications for reproductive decisions of the proband and/or family members. [Netzer et al., 2009]

It is telling that in this quotation, the authors fail to differentiate between what a patient may decide for himself or herself and what parents may decide for their children. Of course, had we been speaking about testing competent adults, respect for autonomy would also have included their right to determine the scope of the information they want to receive, regardless of whether receiving that information would be in their best interests. But asking parents to provide proxy consent does not come under this principle. It is not a matter of respecting their informational privacy, but of taking them seriously in their role of parents representing their children's interests. Giving them the option of not being informed of any clinically relevant findings regarding the health of their child ignores this parental responsibility. The issue here is not one of parental autonomy, but of parental and professional duties of beneficence. To suggest otherwise is to make a mockery of the principle of respect for autonomy.

With regard to unsolicited findings indicating a high risk of an adult-onset disorder, the question is whether, on balance, the disclosure of this information is in the best interest of the child. Severity and treatability are important factors in this respect, where treatability should be specified in terms of whether the course and burden of the disease can be significantly altered by starting treatment and prevention prior to the first symptoms. According to current guidelines, asymptomatic children should not be tested for adult-onset disorders, unless treatable in this sense [European Society for Human Genetics, 2009]. If, for instance, a BRCA (hereditary breast cancer) mutation is found in a girl, this information need not be acted upon before she reaches adulthood. Since nothing can be done with this information as long they are children, it is not in their interest to be tested at that time. Moreover, it is felt that letting these girls grow up knowing this information would be at odds with respecting their future autonomy to decide for themselves about whether or not to be tested.

However, these guidelines do not yet discuss the issue of unsolicited findings indicating a high risk of such a disorder. Typically, the background document to the recommendations of the ESHG on testing asymptomatic children states that "the problem of incidental findings (such as a deletion affecting BRCA1) needs to be discussed urgently. For practical purposes, and before consensus is reached on the reporting of incidental findings, it may be advisable to ignore data that are not relevant for the pathology in the patient" [Borry et al., 2009]. In anticipation of this urgently needed debate, we think that it would be in line with the general principles behind those same guidelines (stressing parental responsibility to always serve the best interests of their child) to defend the following.

In the case of a test result revealing a high risk of a late-onset disorder that is treatable in the sense indicated, and where presymptomatic treatment or surveillance would have to be initiated during childhood, parents must be informed and cannot be granted a right not to know with regard to such outcomes. If the disease is treatable in the sense indicated, but not yet during childhood, it may still be in the child's interest that the information about its being at a high risk is kept for use at the appropriate time. Whether this would then require informing the parents, depends on the availability of alternative ways for effectively safeguarding this interest, for instance, by leaving the information "in trust" until the children are older.

As a further complication, it will often be the case that not just the interest of the child is at stake, but also the health and/or reproductive interests of the parents themselves and, possibly, of other relatives. Although, in principle, the parents have a right not to be informed about findings about themselves, this again does not overrule their parental responsibility to be given information that reveals a serious and treatable condition in their child. Nor can they be granted the right to decide that the possible health and/or reproductive interests of other family members need not be taken into account. However, this is what the quotation from Netzer et al. [2009] seems to propose. And in one of the consent protocols we have seen, the possibility of opting for not to be given information about unsolicited findings is brought up without even referring to the possible interests of wider family members.

Parental Right to be Informed About Specific Test Outcomes

With regard to the very rare cases where, as an unsolicited outcome of array-based testing, a high risk may be found for a severe and untreatable late-onset disorder, the issue seems to become one of not so much whether the parents have a right not to know, but whether they have a right to know. If it can be expected that the child will grow into a competent adult, revealing that he or she is at risk of a serious, late-onset disorder infringes upon what Feinberg has called the child's "right to an open future" [Feinberg, 1980]. Unless there are possible benefits of presymptomatic treatment or prevention (see above), professionals have a prima facie moral duty not to share such findings with the parents. Prima facie means that this duty is not absolute. Professionals should also take account of possible harm to third parties that not conveying this information may entail. Given the scenario of a high risk for a serious, nontreatable, late-onset disorder, the dilemma arises that although the child's relatives (including the parents) may have a strong reproduction-related interest in this information, telling them will most certainly also be harmful because of what this would mean for their own health prospects. Given this moral complexity, it is not evident that a case can be made for telling the parents against the clear interests of the child. In the light of this, the suggestion by Netzer et al. [2009] that parents should be given the option to indicate whether they want to receive predictive information about untreatable disorders, without distinguishing between childhood and adult-onset disorders, is at least problematic.

Of course, if the child is expected to remain incompetent as an adult (which will be the case if testing is done to reveal the genetic basis of serious intellectual disability), no future autonomy rights are at stake. However, it may still be questionable whether it is in the

child's interest that the parents know that it is at risk of a serious, untreatable, late-onset disorder. To the extent that this can indeed be doubted, an unqualified parental "right to know" is still not self-evident.

A further issue regards parents' right to learn of outcomes of unclear clinical significance. As a detailed discussion of this is beyond the scope of this paper, we only make the following remarks. Where such outcomes require further testing of the parents themselves, they will of course have to be reported. But if no such testing is necessary, the interests of the child should determine whether to tell the parents or not.

Consent for Genome-Wide Array-Based Prenatal Testing

Genome-wide array-based testing of children with an intellectual disability or other hitherto unclarified complex condition is performed with the clear aim of contributing to better care for these children. But what precisely is the aim of using similar testing in the prenatal context, either as follow-up to an abnormal ultrasound outcome or as an alternative for karyotyping in low-risk pregnancies? Here, the primary aim of such testing is to better inform pregnant women and their partners about fetal abnormalities that they may regard as relevant in deciding whether to let the pregnancy continue or not. Hence the reference in the article by Vetro et al. [2012] to the "limited timeframe" for decision making in the prenatal context due to the laws on abortion in different countries. With this aim, we enter a different moral landscape compared to that governing postnatal testing. As we have seen, parents may, if necessary, be persuaded to consent to testing that is necessary for arriving at a diagnosis of their child's disorder, but if testing is done to contribute to better-informed reproductive decisions, no such directivity is acceptable. It is not for professionals to determine whether a woman should consider having an abortion. Professional nondirectiveness and value neutrality are core values in the traditional normative framework for prenatal diagnosis and screening [De Wert and Dondorp, 2006]. These are based on a concern that abortion decisions may otherwise be turned into instruments for achieving professional or societal goals such as preventing the birth of children whose health and welfare needs will place a high financial burden on society.

However, prenatal testing may also serve the additional aim of contributing to a better pregnancy outcome for the pregnant woman and her future child. When offering array-based testing to clarify abnormal ultrasound outcomes, professionals should take account of the moral implications of these different aims. Although they should refrain from persuading women to consent to testing if the aim is to contribute to better-informed abortion decisions, a directive offer of a test may well be acceptable if it is clear that the information will not be used for an abortion (either because the couple has indicated that no matter what, they want to carry the pregnancy to term, or because the legal limit for abortion has elapsed), and if the test is expected to contribute to better prenatal and perinatal care, which is also in the interest of the future child. This latter expectation is of course crucial; if testing can be deferred until after birth, women should not be persuaded to consent to prenatal testing they do not particularly want to have.

Vetro et al. [2012] refer to the interests of the future child, but without drawing the conclusion that where his or her interests are clearly at stake, the traditional framework of nondirectiveness does not apply. They say that the parents should be helped "to make their own decision based on the ethical concept of the fetus as a patient." If the word "decision" in this phrase refers to decision making about testing with a view to a possible abortion, it is unclear how this could possibly be based on the concept of "the fetus as a patient." If it refers to decision making about testing that is also in the interest of the future child, it may indeed be appropriate in a sense to speak of the presence of a second patient. But if this is the case, how would that not affect the responsibility of professionals to also take the interests of that patient into account, thus limiting the scope for nondirectiveness?

However, we do not think that formulating this in terms of "the fetus as a patient" is very helpful [Health Council of the Netherlands, 2009]. By putting the emphasis on the supposed interests of the fetus, this notion leads into a debate about the moral status of the unborn, which is better left out of this discussion [Brown, 2008]. Whatever the status of "the fetus as fetus," it is enough to acknowledge that if the fetus can be expected to grow into a child, the interests of this future person should already be taken into account whenever decisions are made that can be expected to affect its interests [Murray, 1987].

Meaningful Informed Consent for Prenatal Testing

As in the postnatal context, the question arises how meaningful consent is possible in light of the wide range of possible outcomes of genome-wide array-based testing. But the problem is even greater in prenatal testing, at least when it is offered with the aim of enabling informed and autonomous abortion decisions. Although a possible lack of sufficiently informed consent of the parents for postnatal testing is an issue of moral concern, it does not make testing the child morally problematic, at least not as long as having the test is in the clear interests of the child. But if the aim of testing is to enable informed reproductive decisions, a lack of sufficiently informed consent on the part of those having the test means that this aim will not be achieved, thus undermining the moral justification of offering such testing in the first place. Much, therefore, depends on whether a form of generic consent or some other model of consent for genome-wide array-based prenatal testing is possible that would indeed allow decision making to be sufficiently informed and autonomous. Elsewhere we have suggested that in this context, relevant categories may have to be included: congenital lethal disorders, early- or late-onset disorders requiring intensive medical care, early- or late-onset disorders requiring limited medical care, susceptibilities for complex disorders, conditions involving only minor health problems, and abnormal findings with unknown clinical implications [De Jong et al., 2011]. One problem with this approach is that any list of categories may not sufficiently account for the variable expression of many disorders. A further concern is that the severity of different diseases is perceived differently between and among professionals [Wertz and Knoppers, 2002] and pregnant women [Bryant et al., 2010]. As indicated, the practical feasibility of such alternative models of informed consent needs to be tested in empirical studies.

The alternative option of using filters in order to minimize findings that may be unclear or otherwise difficult to handle is perhaps more appropriate with regard to array-based testing offered as an alternative for karyotyping in low-risk pregnancies (screening) than if the technology is being used for clarifying unexplained ultrasound abnormalities (diagnosis). In the latter context, the use of platforms with a targeted design would not only require frequent updating, but would also risk missing abnormalities relevant to answering the diagnostic problem [Vetro et al., 2012]. We will return to this issue later.

Pregnant Women's Right Not to be Informed About Specific Test Outcomes

On a consent form for array-based testing offered to pregnant women with an abnormal ultrasound used in one of the Dutch university hospitals, women can indicate whether they want to be informed about (1) only outcomes explaining the ultrasound abnormality, or also (2) findings likely to lead to health effects early in life, (3) findings likely to lead to health effects later in life, and/or (4) findings likely to affect their own health.

If prenatal testing is offered with the aim of enabling informed and autonomous abortion decisions, women should indeed be allowed to indicate prior to testing what outcomes they would not consider relevant to such a decision and therefore would rather not be informed about. But the way that idea is elaborated in this protocol invites the following comments: Firstly, it seems clear that this requires a more detailed list of possible outcomes than the rudimentary one in this protocol. Secondly, it is not obvious why women should, without allowing for further differentiation, accept to be informed about all possible outcomes explaining the ultrasound abnormality. Thirdly, the protocol does not indicate that there may also be limits to the right not to know. Although, in principle, the woman/couple has the right to indicate not to want to receive information relevant to their own health, the possibility of avoiding serious consequences for the health and/or reproductive interests of their relatives may limit the professional's obligation to heed this request [Lacroix et al., 2008]. Moreover, it should be acknowledged that a new situation arises if the woman either decides to carry the pregnancy to term or if the test results are only known after the legal limit for abortion. In those cases, the interests of the future child limit the scope for the right not to know of the parents to be. Professionals cannot ignore test results that are important for adjusting prenatal or perinatal care to the health interests of the future child. As an example, one may think here of test results indicating a congenital heart disease that would require adapted postpartum care. In future, one may increasingly also think of test results indicating conditions for which prenatal treatments are available. Ethically, it is important that professionals are aware that the moral framework determining their responsibilities changes as soon as the interests of the future child come into play.

Pregnant Women's Right to be Informed About Specific Test Outcomes

Do pregnant women and their partners also have a right to be informed about outcomes of unclear clinical significance? A difference with postnatal testing is that due to the time constraints in prenatal testing, the parents-to-be will usually already have been tested as well. This makes it easier to withhold results of unclear significance. Moreover, the range of possible results that are difficult to interpret is even greater in the prenatal context than in the postnatal context. Professionals are reluctant to report such results in order not to induce unnecessary anxiety and to avoid abortions of fetuses based on outcomes of which the exact health implications are still unclear [Vetro et al., 2012]. Although this paternalistic stance is understandable and may even be justified with reference to the notion of helping pregnant women to make well-informed rather than ill-informed reproductive decisions, there is still a tension with the ideal of reproductive autonomy. As some women or couples may want to have more information than others, including outcomes of which the precise implications are still unclear, a case can perhaps be made for addressing these preferences in the context of pretest counseling.

A difficult dilemma arises with regard to possible outcomes indicating a high risk of a serious, nontreatable, late-onset disorder. On the one hand, the woman or the couple can be said to have a right to this information if the knowledge of bearing a child with this risk would be a reason to terminate the pregnancy for them. On the other hand, if they decide to continue the pregnancy, a child will be born with a positive predictive test for serious health problems later in life. This may lay a cloud over its existence, affect the dynamics of the parent–child relationship, and infringe its right to make autonomous decisions about what to know or not to know about its health prospects once mature enough to do so. That the child is yet to be born does not change the fact that it may be harmed by information generated during pregnancy, which would affect its "right to an open future." Indeed, where the interests of the future child are at stake, "the timing of harm is irrelevant" [Murray, 1987].

The problem in question is familiar from the debate surrounding targeted prenatal testing for Huntington's disease. In the case of a positive result, most parents will choose to abort the pregnancy. If they do not, however, they will have a child known to be a carrier of this extremely severe and untreatable, late-onset disease. Given the generally supported consensus that postnatal testing of children for such conditions should not be allowed, the question is what this should mean for prenatal diagnosis. This problem arises for targeted prenatal testing for a number of other autosomal dominant conditions as well (e.g., the hereditary and often relatively early onset form of Alzheimer's disease). Contrary to standard practice for prenatal diagnostic testing, the solution proposed for updated guidelines from the International Huntington Association is to only allow the test to be performed on the condition that the woman indicates beforehand that she intends to abort the pregnancy in the event of a positive result [International Huntington Association, 1994; De Wert, 2002]. Of course, conditional access to prenatal diagnostic testing does not mean future parents can be forced to terminate the pregnancy in the event of an unfavorable result.

Applying this to genome-wide array-based testing, a distinction must be made between the (possible) scenario where such testing is offered as an alternative for karyotyping in low-risk pregnancies (screening) and the scenario of using genome-wide arrays to clarify abnormal ultrasound outcomes (diagnosis). We will first discuss the options for addressing the issue in the context of prenatal screening. By "prenatal screening" we mean the systematic offer of medical testing to women with low-risk pregnancies, regardless of the type of test. In this context, one may either opt for using targeted arrays in order to avoid the detection of a predisposition for a late-onset disorder as much as possible (with the drawback of denying women the possibility to use this information for abortion decisions), or allow access to nontargeted testing only to those who have expressed their intention to choose abortion if a predisposition for a late-onset disorder is found. Even though women cannot be forced to stick to this intention, this approach seems, at least in theory, to provide the optimal balance of respecting the autonomy of the woman (in view of a possible abortion decision) and those of her possible future child (its right to an open future). We say "in theory" because an important difference with the use of conditional access for the targeted prenatal diagnosis for Huntington's disease is that in a screening context, the pregnant women and their partners are not familiar with the nature and burdens of the disorders in question beforehand. As a consequence, it may be that many of

those given conditional access eventually decide not to abort, which would undermine the rationale of the approach, leading precisely to the kind of violations of the child's future autonomy that giving conditional access was meant to avoid.

A further question regards the precise interpretation of the notion of the child's future autonomy rights. On maximum interpretation, one should try to avoid the generation of all kinds of genetic information (health as well as non-health related, causative mutations as well as susceptibilities) that becomes relevant for the child only later in life, except when this information will be used for an abortion decision. This indeed drives the notion of the child's "right to an open future" ad absurdum. On a weaker interpretation, the autonomy rights of the future child only stand in the way of generating information about serious and high-penetrance, late-onset disorders that are either nontreatable (e.g., Huntington's disease) or not amenable to treatment or prevention starting during childhood (e.g., BRCA mutation). Following this interpretation, prenatal screening using genome-wide arrays should either avoid such outcomes altogether (by using filters) or give conditional access to limit the use of such findings to make abortion decisions.

The above considerations may also be read as adding to the concern that obtaining meaningful and sufficiently informed consent for genome-wide prenatal testing will be too large a challenge to justify offering such testing as a form of screening in the first place.

Moving on to genome-wide array-based testing for clarifying ultrasound abnormalities, the problem is that the solutions discussed in the context of screening (filters, conditional access, etc.) may stand in the way of adequately solving the diagnostic problem. This means that the dilemma becomes even more poignant here. If solving the diagnostic problem is only possible with the use of tests that, in rare cases, may also lead to findings violating the child's future autonomy, the question becomes one of defining and weighing the different interests at stake. It does not necessarily follow from the need to also take the interests of the future child into account that pregnant women should be restricted in the use of tests needed to arrive at a diagnosis for an ultrasound abnormality. But neither does the mere presence of an abnormality justify the use of all possible means to arrive at a clarification. The question is why and for whom solving the diagnostic problem is regarded as so important. If the aim is to enable an informed abortion decision, a crucial question is whether the woman would indeed want to use a possible diagnosis for that purpose. If she makes it clear that whatever the outcome of the test, she would not have an abortion, the question becomes one of whether a mere wish to know on her part or a mere medical interest on the part of the professionals is enough to go ahead with a test that may lead to infringing the interests of the future child. But its relevance for a possible abortion decision need not be the only reason for finding a diagnosis so important. At this point, the additional aim of prenatal testing may come into the picture: to the extent that finding a diagnosis is also expected to contribute importantly to better prenatal and perinatal care in the interests of both the woman and her future child, the normative picture changes. In fact, the situation then becomes akin to that of genome-wide postnatal testing, as discussed earlier in this paper, where the need to solve the diagnostic problem in the interest of the child was seen to justify the use of a test that may lead to unsolicited and, in part, highly problematic findings as well.

But the fact that these different aims may both be at work here also leads to the possibility of difficult counseling situations and professional decision making. Although it is not in the interest of the child to inform its parents about the unsolicited finding of a serious, nontreatable, late-onset disorder, it may be in the interest of a pregnant woman wanting to be able to make an informed abortion decision not be denied this information. A possible approach is to only provide this information if the woman has indicated in pretest counseling that she indeed intends to ask for a termination if confronted with this type of finding. Clearly, the same reservations apply as raised earlier with regard to the idea of conditional access to genome-wide prenatal screening.

Conclusion

No doubt, genome-wide arrays will be increasingly used in the context of both postnatal and prenatal testing. They will be especially valuable for elucidating the genetic background of unexplained abnormalities. Even though facilitating a genetic diagnosis is an important advantage and, in principle, in line with the ethical principle of beneficence, at the same time it is clear that such genome-wide arrays raise moral questions that need ethical scrutiny. Of particular importance is the feasibility of informed consent, a central prerequisite of genetic testing. Generic consent may be a sound alternative type of informed consent, but this still has to be studied in practice. As we have shown, the scope and limits of parents' and prospective parents' right to know and not to know are far from clear. After considering some protocols regarding consent procedures for genome-wide array-based testing, we have the impression that there is a tendency to "solve" complex normative questions regarding the content and weight of these rights by sticking to one simple principle: respect for decisional autonomy of the parents or prospective parents. This one-dimensional approach, as we argue here, de facto disregards the ethical dilemmas at hand. Ethical analysis should take account of the rights and interests of all the parties involved: actual or prospective parents, children or future children, and relatives. We have pointed to some possible directions for more adequate solutions, but obviously, further discussion and fine-tuning is needed. *Festina lente* (make haste slowly).

References

Beauchamp TL, Childress JF. 2009. Principles of biomedical ethics. Oxford, New York: Oxford University Press.

Berg JS, Khoury MJ, Evans JP. 2011. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genet Med 13:499–504.

Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K. 2009. Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG). Genetic testing in asymptomatic minors: background considerations towards ESHG recommendations. Eur J Hum Genet 17:711–719.

Brown SD. 2008. The "fetus as patient": a critique. Am J Bioeth 8:47–50.

Bryant LD, Green JM, Hewison J. 2010. The role of attitudes towards the targets of behaviour in predicting and informing prenatal testing choices. Psychol Health 25:1175–1194.

Buchanan AE, Brock DW. 1989. Deciding for others: The ethics of surrogate decision making. Cambridge, UK: Cambridge University Press.

De Jong A, Dondorp WJ, Frints SG, de Die-Smulders CE, de Wert GM. 2011. Advances in prenatal screening: the ethical dimension. Nat Rev Genet 12:657–663.

De Wert G. 2002. Ethical aspects of prenatal testing and pre-implantation genetic diagnosis for late onset neurogenetic disease: the case of Huntington's disease. In: Evers-Kiebooms G, Zoetewij M, Harper P, editors. Prenatal testing for late-onset neurogenetic diseases. Oxford, UK: Bios Scientific Publishers. pp 129–157.

De Wert G, Dondorp W. 2006. Ethical issues. In: Van Vugt M, Shulman K editors. Prenatal medicine. New York/London: Taylor & Francis. pp 575–604.

Dondorp W, de Wert G. 2010. The 'thousand-dollar genome': an ethical exploration. The Hague, the Netherlands: Health Council of the Netherlands. http://www.gezondheidsraad.nl/sites/default/files/201015E.pdf (last accessed 16 March 2012)

Elias S, Annas GJ. 1994. Generic consent for genetic screening. N Engl J Med 330:1611–1613.

European Society of Human Genetics. 2009. Genetic testing in asymptomatic minors: recommendations of the European Society of Human Genetics. Eur J Hum Genet 17:720–721.

Feinberg J. 1980. The child's right to an open future. In: Aiken W, Lafollette H, editors. Whose child? Children's rights, parental autonomy, and state power. New Jersey: Littlefield, Adams & Co. pp 124–153.

Health Council of the Netherlands. 2009. Care for the unborn child. The Hague, the Netherlands: Health Council of the Netherlands. http://www.gezondheidsraad.nl/sites/default/files/200901E.pdf (accessed 16 March 2012).

International Huntington Association and World Federation of Neurology. 1994. Guidelines for the molecular predictive test in Huntington's disease. Neurology 44:1533–1536.

Lacroix M, Nycum G, Godard B, Knoppers BM. 2008. Should physicians warn patients' relatives of genetic risks? Can Med Assoc J 178:593–595.

Murray TH.1987. Moral obligations to the not-yet born: the fetus as patient. Clin Perinatol 14:329–343.

Netzer C, Klein C, Kohlhase J, Kubisch C. 2009. New challenges for informed consent through whole genome array testing. J Med Genet 46:495–496.

Ogilvie CM, Yaron Y, Beaudet AL. 2009. Current controversies in prenatal diagnosis 3: for prenatal diagnosis, should we offer less or more than metaphase karyotyping? Prenat Diagn 29:11–14.

Van Zwieten M. 2006. The target of testing. Dealing with 'unexpected' findings in prenatal diagnosis. Amsterdam, the Netherlands: Buijten & Schipperheijn.

Vermeesch JR, Brady PD, Sanlaville D, Kok K, Hastings RJ. 2012. Genome-wide arrays: quality criteria and platforms to be used in routine diagnostics. Hum Mutat 33:906–915.

Vetro A, Bouman K, Hastings RJ, McMullan DJ, Vermeesch JR, Miller K, Sikkema-Raddatz B, Ledbetter D, Zuffardi O, van Ravenswaaij-Arts CMA. 2012. The introduction of arrays in prenatal diagnosis: a special challenge. Hum Mutat 33:923–929.

Vissers LE, de Vries BB, Veltman JA. 2010. Genomic microarrays in mental retardation: from copy number variation to gene, from research to diagnosis. J Med Genet 47:289–297.

Wertz DC, Knoppers BM. 2002. Serious genetic disorders: can or should they be defined? Am J Med Genet 108:29–35.

Wilson J. 2005. To know or not to know? Genetic ignorance, autonomy and paternalism. Bioethics 19:492–504.