Prenatal chromosomal microarray for the Catholic physician

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Prenatal chromosomal microarray (CMA) is a test that is used to diagnose certain genetic problems in the fetus. While the test has been used in the pediatric setting for several years, it is now being introduced for use in the prenatal setting. The test offers great hope for detection of certain genetic defects in the fetus so that early intervention can be performed to improve the outcome for that individual. As with many biotechnical advances, CMA comes with certain bioethical issues that need to be addressed prior to its implementation. This paper is intended to provide guidance to all those that provide counseling regarding genetic testing options during pregnancy.

Keywords: Chromosomal microarray, Prenatal diagnosis

INTRODUCTION

A recent article in the December 6, 2012, edition of the *New England Journal of Medicine* showed that chromosomal microarray (CMA) in the setting of prenatal diagnosis revealed more clinically significant genetic information regarding the fetus compared with standard karyotyping (G-banded karyotyping) alone (Wapner et al. 2012). There were some limitations such as the inability to diagnose balanced translocations and triploidies, but overall, it appears to be a better test for prenatal diagnosis. Currently, standard karyotyping identifies all cases of fetal triploidy and balanced translocations (if they are large enough).

CMA has the ability to detect almost all of the genetic deviations that can be detected with standard karyotype, but can also detect genetic deletions and

duplications that are at least 1 kb in size (Dugoff 2012). CMA has been studied for its potential use in prenatal diagnosis in the past. However, this study certainly not only brings the technology to the forefront, but also validates its use clinically in the setting of prenatal diagnosis in the pregnant patient with an increased risk of aneuploidy (Maya et al. 2010; Park et al. 2010; Strebniak et al. 2011).

CMA has been used in clinical practice over the past decade in pediatrics to diagnose genetic abnormalities in children with neurodevelopmental delays and congenital anomalies (Mefford, Batshaw, and Hoffman 2012). In fact, the International Standard Cytogenetics Array (ICSA) Consortium held two international workshops on CMA. These workshops appeared to be held in response to the increasing utilization of CMA in individuals with unexplained developmental

delay/intellectual disability (DD/ID), autism spectrum disorders (ASD), or multiple congenital anomalies (MCA). Prior to the use of CMA, standard karyotyping (G-banded karyotyping) was widely used. The ICSA Consortium released a consensus statement in May 2010 that stated,

Available evidence strongly supports the use of CMA in place of G-banded karyotyping as the first-tier cytogenetic diagnostic test for patients with DD/ID, ASD, or MCA. G-banded karyotype analysis should be reserved for patients with obvious chromosomal syndromes (e.g., Down syndrome), a family history of chromosomal rearrangement, or a history of multiple miscarriages. (Miller et al. 2010)

The principle reason for this statement was that after a very thorough review that included 33 studies and 21,698 patients, they found that CMA offered a higher diagnostic yield than G-banded karyotyping in individuals with unexplained DD/DI, ASD, or MCA (15–20% versus ~3%).

A meta-analysis in 2009 reported similar findings. In a population of individuals with ID and/or MCA, the overall diagnostic rate for chromosomal abnormalities was 10 percent (Sagoo et al. 2009). In this population, most of the individuals had a normal standard karyotype. We will see in Wapner et al.'s paper that this finding of an abnormal CMA result in the setting of an individual with a normal standard karyotype and some type of congenital abnormality seen on ultrasound is common. The goal of this paper is to provide guidance for the Catholic physician with regard to this type of prenatal testing. The guidance relates not only to a better understanding of this new technology, but also to the moral concerns that arise from its use. This subject is really important to all who counsel patients

regarding genetic testing options during pregnancy.

WHAT IS MICROARRAY?

Microarray is a technology that is able to determine what are called copy number variants (CNVs). These structural deviations are small deletions or duplications in the DNA that result in variation in the number of copies of a gene or particular DNA sequence that vary from one person to the next (Feero, Guttmacher, and Collins 2010). With microarray, one can study many genes at once. Many of these CNVs may not be known to cause a disease (variant of unknown clinical significance), although many people may have the particular defect. To add further variation to the CNV interpretation, it may be difficult to predict the phenotype of a CNV that is associated with a disease due to epigenetic, genetic, or environmental modifiers (Bodurtha and Strauss 2012). Much of this is due to the variation in our DNA as individuals. For example, two individuals may have the same CNV result obtained from a CMA, but appear or act differently from each other.

The human genome contains over 6 billion base pairs and approximately 20,000 protein encoding genes (Clamp et al. 2007). These genes are able to code for proteins through the use of RNA. The central dogma of biology has traditionally held that this process of genes coding for protein went from DNA to RNA to protein. This tradition has been re-visited as the regulatory process of gene to protein is controlled by many processes other than what has been stated above. This gene regulation is complex, being controlled by other proteins and RNA molecules that act as regulators to a gene's transcription and translation (Davidson and Levine 2008).

There does not appear to be an overall “normal” DNA sequence with which to compare an individual’s DNA. Humans are 99.6 percent similar to each other at the DNA sequence level, yet this 0.4 percent gives tremendous variation to our DNA and each other as individuals (Kidd et al. 2008). Therefore, there can be up to a 24 million base pair difference between two “normal” individuals. Even looking at CNVs, we see a tremendous potential for variation. Conservative estimates show that approximately 10 percent of our genome is subject to copy number variation (Redon et al. 2006; Wong et al. 2007).

CMA IN PRENATAL TESTING

The study by Wapner et al. (2012) best illustrates how CMA will be used in prenatal genetic testing. The researchers enrolled women who had an indication for invasive prenatal testing in 29 prenatal diagnostic centers across the US. These indications were advanced maternal age (≥ 35 at time of delivery), a positive aneuploidy screening result, or structural abnormalities on an ultrasound. This study did not enroll patients that were having invasive testing for any other reason, such as elective genetic testing.

The participants went through an informed consent process that included both pre- and post-test counseling. They were thoroughly counseled regarding the advantages and disadvantages of this type of testing, as well as the possibility of receiving a result for which there was uncertain clinical significance or a result that may have been passed on to the fetus by the mother or father. The counseling for this study appeared to be very thorough and complete. The invasive testing was performed by either an amniocentesis or a chorionic villus sampling

procedure. The standard used in this study was the standard karyotype, and the microarray results were compared with this result. The primary outcome was the microarray being analyzed as a true positive or true negative or false positive or false negative. Secondary outcomes were related to the CNVs and the microarray.

The results were reported to the patient after review. Those that were known to be implicated with a disease were classified as “pathogenic” and were reported to the patient as such. If the microarray result was known to be a benign CNV, then it was reported to the patient as such. All other CNVs were reported as “uncertain clinical significance.” These results were then further reviewed by the study’s clinical geneticists and laboratory directors. They determined whether any should be classified as “likely benign,” and if so, they were reported to the patient. If they were not reported as “likely benign” then they were sent for further review by an independent clinical advisory group. The group then could classify the results as “likely benign.” Those that could not be reported as “likely benign” could be reported as potential clinical significance and were reported to the patient as such. As one can see, the results were carefully reviewed by a team of experts due to the somewhat unknown nature of the results.

A total of 4,406 women had invasive testing, of which 4,391 (99.7%) had an adequate sample for analysis. Essentially, all of the aneuploidies and unbalanced rearrangements that were found in a standard karyotype were identified with microarray. Microarray did not identify balanced translocation and fetal triploidy. Of those patients who were either of advanced maternal age or had a positive screen result for aneuploidy and had a normal standard karyotype, 1.7 percent of their CMA results had a clinically relevant

CNV. If the fetus had a structural anomaly and a normal standard karyotype, 6 percent of the microarray results had a clinically relevant microarray result.

There were 3,822 fetuses that had a normal karyotype. Of these 3,822 fetuses, 1,399 (36.6%) had CNVs on microarray. Of these 1,399 CNVs, 1,234 (88.2%) had a common benign CNV and were not reported to the study participant. Of the 1,399 CNVs, 35 were pathogenic and reported to the patient. The remaining 130 were initially determined to be of unknown clinical significance. Of these 130, 61 were then determined, by further review, to have the potential for clinical significance. Overall, of the 3,822 fetuses that had a normal karyotype, 96 (2.5%) had a CNV that was of clinical significance. So, for every 100 women who would have received normal results with standard karyotyping, 2.5 would now receive an abnormal CNV result with CMA that is felt to be clinically relevant.

This study shows that most of the CNV results are benign and will not need to be reported to the patient. The study also shows that many of the CNV results will be of unknown clinical significance. This result allows for much ambiguity with regard to the patient's interpretation of what the effects on the fetus may be. Some of the results that are reported as potential for clinical significance may be somewhat ambiguous as well. These CNVs may involve genes that are connected in some way to learning disabilities or autism or other developmental delays.

Even then, it is very difficult to determine how severely affected the neonate will be. One can easily see a mother getting a result that her newborn may be affected with some type of learning disability or other developmental delay or autism. Imagine taking this child home and not knowing what the future will hold. Always worrying that this child may

have a learning disability or some other problem can lead to vulnerable child syndrome. Vulnerable child syndrome can lead to overprotection and other parent-child difficulties on the part of a parent(s) who has a child that is perceived to be at risk for intellectual, developmental, or behavioral problems (Leslie and Boyce 1996).

PLACING CHROMOSOMAL MICROARRAY IN ITS PROPER CONTEXT

For Catholic physicians who desire to practice medicine in keeping with Catholic moral thought, this testing will present certain moral problems. Many times, we do not know what many of these CNV results mean from a clinical standpoint because we have not had the time to follow the natural progression of an individual with these CNV results. Imagine taking a child home from the hospital with a genetic defect and not knowing if that child will ever show any adverse effects from this genetic defect. Another moral problem deals with the selective termination of fetuses with abnormal CNV results. In addition to fetuses being aborted due to abnormalities that we can currently detect on standard karyotyping such as Down syndrome, we will now see fetuses being aborted for abnormal CNV results.

The Congregation for the Doctrine of the Faith wrote in *Donum vitae* (CDF 1987, n. 1), “the human being must be respected—as a person—from the very first instant of his existence.” In the world of prenatal diagnosis, many times, the dignity of the fetus is not acknowledged by healthcare providers. The mother of the fetus is more likely to acknowledge its God-given dignity than the healthcare providers that actually provide care for the patient. As physicians, sometimes we are

hesitant to speak of the fetus as a “person” until we have determined what the parent thinks of the status of the fetus. In other words, if the parent does not look at the fetus as a person, then speaking in terms of personhood with respect to the fetus may offend the patient. This is especially true in the setting of a genetic defect. It may be that the possibility of uncovering a genetic defect through this CMA testing may cause the patient to keep emotional or mental distance from the fetus by not acknowledging its human dignity.

With respect to prenatal diagnosis and fetal treatment, several conditions that were either lethal to the fetus or could cause some serious, significant disability, have been improved with *in utero* therapy. Two conditions come to mind. The first is the treatment of Rh alloimmunization with *in utero* fetal blood transfusions. In 1981, an intravascular transfusion was reported in *The Lancet* for the treatment of Rh alloimmunization (Rodeck et al. 1981). The second is in the case of a fetal myelomeningocele (spina bifida). In March 2011, a randomized control trial validated the use of *in utero* fetal surgery in the setting of a fetal myelomeningocele (Adzick et al. 2011). These two examples tell of the immense benefits that can come with prenatal diagnosis and fetal treatment.

In the above two examples, I would expect that the parent had already assigned “personhood” to the developing fetus. I do not mean this in some deep philosophical sense. Rather, if you were to ask the mother if she considers the fetus a person or her child, she would respond with a “yes.” Here, it is easy to recognize the dignity of the developing fetus since it is considered a person by the mother.

Dignitas personae states in the first line, “The dignity of a person must be recognized in every human being from conception to natural death.” This

instruction builds upon what was written in the instruction *Donum vitae*. Under the heading, “Respect for Human Embryos,” it states very clearly that the human being must be respected from the very first instance of his existence (CDF 1987, n. I.1). Regardless of how we view the fetus as physicians, it has dignity that is given to it by God. This dignity is intrinsic and inviolable. It is given to the weakest and the strongest members of society. It cannot be taken away by the healthcare provider, or anyone else for that matter.

The act of recognizing this human dignity makes it more difficult for the physician to act in an immoral way when he or she is counseling the patient regarding her options.

It would be difficult for the Catholic or non-Catholic physician to both recognize the God-given human dignity of the developing fetus and, at the same time, counsel the patient on termination of this individual with that God-given human dignity.

Furthermore, there is responsibility on the part of the physician for the act of termination. If the physician counsels her regarding termination of the fetus, then the physician is playing a role in the termination itself. In *Evangelium vitae* (1995), Pope John Paul II quotes Genesis 9:5, “From man in regard to his fellow man I will demand an accounting.” In this instance, the fellow man is the fetus.

John Paul II was certainly prophetic when he addressed the role of the healthcare provider with respect to the protection of human life. He talks of the unique responsibility of the healthcare provider in this setting. Our profession calls for us to be “guardians and servants of human life” (John Paul II 1995, n. 89). As healthcare providers, we can lose focus on this. John Paul II uses the terms, “manipulators of life” and “agents of death” in

describing some of the tempting roles that we can take on while providing counsel for a patient for anything but a normal result in the setting of prenatal diagnosis, such as CMA. This temptation is greater with the ambiguity of results that will be obtained from the use of CMA. This increase in temptation must be met with an increase in responsibility while counseling the patient, both prior to and after the testing. With the advent of CMA, we are now able to receive genetic information on the fetus that was not available several years ago. In Wapner et al.'s study, what percentage of women who received a diagnosis of a variant of unknown clinical significance terminated the pregnancy? If CMA had not been used with these patients, these pregnancies would have not ended in termination. In a systematic review published in 2012 of termination rates in fetuses with Down syndrome from 1995 to 2011, the average termination rate was 67 percent, and in some studies was as high as 85 percent (Natoli et al. 2012). It is difficult to extrapolate this termination rate to CMA results, but it is not a preposterous idea to think that this testing will result in an increase in the termination rate of fetuses with genetic defects.

When we diagnose Down syndrome in the fetus, we as healthcare professionals have to be guardians of human life. A pregnant woman can give consent to an amniocentesis in order to get a diagnosis of Down syndrome. This is not an immoral action. This is done many times so that the patient can be prepared for a child with Down syndrome or so that special considerations can be made after delivery. Father Tad Pacholczyk argues that if a patient does this testing with the idea in mind of having an abortion if the diagnosis is Down syndrome, then she is committing a sin (even with a normal result). The idea is twofold: If the patient is planning on having an abortion if the

test results are abnormal, then this act of consenting to an amniocentesis is a sin. As well, for the physician, if they participate in this planning and perform the procedure when they know that the patient already has plans for an abortion, then he or she may be committing a sin (Pacholczyk 2006).

CMA has the ability not only to give us more genetic information about the fetus, it also greatly increases the amount of uncertainty with regard to this genetic information. This uncertainty is not limited only to determining how the genetic defect will present, but also includes the determination of whether or not a genetic defect is even a disease. As stated above, we are now able to get genetic information on the fetus and also not have the knowledge to tell the patient whether or not this will even affect the child as it develops. Therefore, many times when we are able to detect a genetic defect in the fetus, there will be corresponding times when we will have to say that there is a certain percentage of individuals with this mutation who will develop autism or some other type of neurodevelopmental disorder. Furthermore, if we receive a result that is a variant of unknown clinical significance, we are not able to tell the patient if the child will even be affected in any way (ACOG 2007). Not only is there uncertainty in defining what the prognosis will be for a genetic defect, there is also uncertainty in even stating that the genetic defect is a disease. For many of these genetic defects that can now be detected with CMA, some cannot be fully explained with respect to disease state or variability in presentation. Therein lies one of the ethical problems with microarray.

Already there are articles written recommending what is to be told or withheld from the patient with regard to these ambiguous results. McGillivray et al.

(2012) argue, in a recently published expert opinion, that although these variants of unknown clinical significance can be distressing to the patient, they should be disclosed to the patient. Their main argument for this is patient autonomy and that to withhold this information would be paternalistic in the sense that physicians would be trying to take responsibility for a woman's healthcare decisions and whether or not to terminate a pregnancy. The authors of this study do not take into account the principle of nonmaleficence. They admit that what makes the process distressing is the ambiguity of the results. We have an obligation to first do no harm. Providing patients with ambiguous results can cause harm and potentially lead to termination of the pregnancy due to this ambiguity. With more research into the natural progression of these uncertain results, we can alleviate much of this ambiguity. This research should be done under the protection of an institutional review board.

As physicians, first we must do no harm to the patient, in this case by not having her deal with this much uncertainty. Furthermore, this uncertainty may have as an end result the termination of the pregnancy.

The authors further acknowledge that women who receive a diagnosis of a variant of unknown clinical significance will not only have anxiety with regard to the result, but also anxiety with regard to even partaking in the testing that leads to this diagnosis. Likewise, they acknowledge that physicians should be concerned about this maternal anxiety which will almost always accompany this diagnosis. Being able to evaluate these variants of unknown clinical significance in a research setting so that we could reduce the maternal anxiety would entail slowing down the introduction of this testing. The authors do not suggest this as a solution.

They suggest that the antidote to this anxiety is support and counseling following a disclosure of this result. How can one possibly counsel a patient when one does not know what will happen with this defect? Further counseling will not alleviate the uncertainty associated with some of the results because their natural course has never been described or studied.

Many will say that this level of uncertainty that we will see in CMA testing is something that we already deal with in obstetrics/maternal fetal medicine, particularly with the use of ultrasound (Beckman, Estivall, and Antonarakis 2007). Although I agree with Getz and Kirkengen (2003) in their assessment of the uncertainty in ultrasound with respect to Down syndrome, I do not think that this uncertainty is the same as the uncertainty that accompanies a diagnosis of a variant of unknown clinical significance. With an uncertain diagnosis or suspicion of Down syndrome brought about by a screening ultrasound, this uncertainty clearly is time-limited. Once the neonate is born, testing can be done to resolve this uncertainty. The parents will know as to whether or not their child has Down syndrome shortly after birth. With a variant of unknown clinical significance, birth offers little, if any, resolution to this uncertainty. In fact, in many instances, this uncertainty will follow the child into adulthood. Therefore, the time aspect of the uncertainty, which is often ignored, may be the most distressing part of the uncertainty.

To summarize, McGillivray et al. (2012) address the moral responsibility for an unnecessary termination of a pregnancy following an uncertain result. They acknowledge that clinicians may be concerned that an abortion may result following a diagnosis of a variant of unknown clinical significance. Their response to this concern is, again, patient autonomy. They state that it would be

paternalistic to suggest that a physician take responsibility for a patient's decision to terminate. They further state,

Even if a clinician feels that a woman's desire to terminate is disproportionate to the actual risk to the fetus or child, it is not the role of the clinician to assign a value to the fetus or to evaluate whether termination is reasonable: that falls clearly within the woman's sphere of autonomy. (McGillivray et al. 2012)

As Catholic physicians, we are morally obligated to acknowledge the human dignity of the developing fetus.

Pope Francis, in his encyclical, *Lumen fidei*, talks of the need for the light of faith in the search for Truth. He states that in modern times, this light of faith is not considered necessary in the search for truth and that faith was an "illusory light" in the quest for knowledge,

an illusion which blocks the path of a liberated mankind to its future.... The light of autonomous reason is not enough to illumine the future. (Francis 2013, nn. 2, 3)

There is a need for the light of faith in the search for Truth. Without this light, the light of autonomous reason is not able to guide us in any search for any truth, even in the setting of prenatal diagnosis.

In closing, CMA offers tremendous potential for early diagnosis of conditions that may truly benefit from early intervention. Imagine a scenario in which you know that your child will develop autism. Early intervention could impact this child so that his or her prognosis would clearly be better compared with not knowing this information. However, knowing this information may lead a patient to terminate the pregnancy due to not wanting to deal with this child. Up to this point, we have not had access to this information in a prenatal setting. Now we do, and we may not know exactly what to do with it. The

Catholic physician, guided by both faith and reason, may not have a precise answer for his or her patient. However, the Catholic physician, armed with the duty to protect all human life and uphold its dignity from conception to natural death, will be better equipped to be a light for his or her patient, even through the fog of uncertainty which this genetic testing brings.

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BIOGRAPHICAL NOTE

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