Published in final edited form as:

Dev Disabil Res Rev. 2011 ; 17(1): 27–31. doi:10.1002/ddrr.135.

Prenatal Testing for Intellectual Disability: Misperceptions and Reality with Lessons from Down syndrome

Kruti Acharya, MD

Assistant Professor of Pediatrics and Medicine, Section of Developmental and Behavioral Pediatrics, Faculty, MacLean Center for Clinical Medical Ethics, The University of Chicago Medical, Center 950 East 61st Street SSC 207, Chicago Illinois 60637, Telephone: 773/702-3095, Fax: 773/702-0208

Kruti Acharya: kacharya@peds.bsd.uchicago.edu

Abstract

Down syndrome is the most common cause of intellectual disability. In the United States, it is recommended that prenatal testing for Down syndrome be offered to all women. Because of this policy and consequent public perception, having Down syndrome has become a disadvantage in the prenatal period. However, in the postnatal period, there may be some advantage to having Down syndrome. In order to help parents make informed decisions about screening and testing, it is crucial to reconcile divergent prenatal and postnatal perspectives. Advancements in genetic technologies will also impact the informed consent process and need to be considered.

Keywords

Down syndrome; intellectual disability; prenatal testing; genetic testing

Introduction

Pregnancy is fraught with uncertainty: Will my baby be healthy? Will my baby develop normally? What kind of person will my child become? Throughout pregnancy, expectant parents mull over these questions with hope, anticipation, and anxiety. Although these questions can only be resolved with certainty once the baby is born and often only after the child is several years old, prenatal testing can provide expectant parents with some answers.

In the United States, prenatal testing has become synonymous with Down syndrome and Down syndrome has become synonymous with intellectual disability. This conflation of terms is artificial and does not accurately represent the true intent of current screening and testing practice. In this manuscript, I will argue that having Down syndrome is a disadvantage prenatally, reinforced by current policy and public perception; whereas, having Down syndrome can be relatively advantageous in childhood and adulthood. Lastly, I will explore how new genetic screening technologies may influence parents' decisions regarding prenatal testing.

Prenatal testing for ID

Prenatal testing for intellectual disability (ID) can inform parents about their child's genotype- either normal or abnormal. False positive and false negatives not with standing, a

prenatal diagnosis obtained via invasive testing, either amniocentesis or chorionic villus sampling, allows for an estimation of a plausible range of a child's developmental outcomes but usually cannot predict the severity of a child's disability. Whereas it is clear that a fetus with Trisomy 13 will have profound intellectual disability, a range of phenotypes can be described for a fetus with Down syndrome, Turner syndrome, or Klinefelter's syndrome, meaning the child's actual cognitive potential cannot be known in utero. Prenatal diagnosis is at once specific yet ambiguous.

Despite the ambiguity, many parents still opt for prenatal testing and consider it a useful tool. Parents use test results to prepare for raising a child with disability and to guide decisions about continuing or terminating a pregnancy according to their personal values and beliefs. Awareness of a diagnosis, either positive or negative, may reduce parental anxiety. Parents may also gain psychological benefit from prenatal testing because they feel they have done everything in their power to make informed decisions about the pregnancy. For those that undergo prenatal testing, prenatal diagnosis affords a sense of agency and control amidst the uncertainty of pregnancy. Other parents decline testing based their own tolerance of risk in order to avoid potential harm to the fetus and procedure-related pregnancy loss. Timing of prenatal testing and cultural beliefs also influence parents' refusal of testing (Rapp, 1999). Regardless of which choice is made, deciding to pursue or decline testing is an emotional decision for parents situated within their personal and social context of disability.

The case of Down syndrome: Prenatal Disadvantage

Down syndrome is the most common known cause of ID. In 1959, Lejeune identified an extra chromosome as the genetic abnormality (Lejeune, Gautier, & Turpin, 1959). Until that time, amniocentesis was primarily used to treat Rh incompatibility and later to identify male fetuses at risk for hemophilia and Duchenne Muscular Dystrophy, both X-linked conditions. As cytogenic technology improved, physicians were able to use amniocentesis to identify fetuses with aneuploidy; however, physicians did not universally offer the procedure. In late 1970s, several high profile wrongful life and wrongful birth lawsuits were brought against obstetricians by parents of children with Down syndrome (Ossorio, 2000). The parents claimed they were not fully informed nor were they offered amniocentesis, which could have allowed them to avoid the birth of a child with disability in the case of a wrongful birth suit or the burden of raising a child with Down syndrome in wrongful life suits. Because of these lawsuits and in accordance with new recommendations of the American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG), prenatal care providers began to offer prenatal testing more routinely (Cowan, 2002).

In 2001, ACOG officially recommended that women over 35 be offered prenatal diagnosis for fetal aneuploidy, which included Down syndrome (Trisomy 21), Edwards Syndrome (Trisomy 13), and Patau Syndrome (Trisomy 18) (American College of Obstetricians and Gynecologists Committee on Genetics, 2011). The age cut-off of 35 was chosen because it was at this age that invasive testing could be justified because the risk of having a fetus with Down syndrome balanced the risk of losing a fetus during an amniocentesis. As the safety of amniocentesis improved, the risk of the procedure became less than the fetal risk of Down syndrome. Therefore, in 2007, ACOG revised their practice guidelines about prenatal screening and testing for chromosomal abnormalities to recommend that fetal aneuploidy screening be offered to all pregnant women irrespective of age (American College of Obstetrics & Gynecology, 2007). Now, there are a host of acceptable screening strategies with different false positive and false negative rates (American College of Obstetrics & Gynecology, 2007). The testing algorithms are geared towards the early detection of Trisomy 21, 13 and 18; however, Down syndrome is the most common target of screening

because of its higher prevalence in live births. Even though Down syndrome is less impairing than the other trisomies, there is a prevalent misperception that prenatal testing for ID means prenatal testing for Down syndrome (Edwards & Ferrante, 2009).

Screening for Down syndrome gives parents a numerical risk assessment that the fetus will be affected based on an arbitrary cut-off: $>1/250$ is considered low risk and $<1/250$ is high risk. The risk categorization helps physicians decide which testing algorithm to recommend. However, for some parents, the exact number may be more persuasive than the risk category; $1/300$ chance can seem too risky despite the incremental risk being exceedingly small. Moreover, many parents do not fully understand what the numerical risks actually signify, and parents interpret risk differently depending on whether it is presented as percentages or odds (Keller & Siegrist, 2009). Since there is so much confusion about what the results of screening mean, using these tests for reassurance is dangerous. Despite our best efforts, parents are not fully informed.

The revised ACOG policy and the publicity it garnered has given Down syndrome an unfortunate notoriety; highlighting it in the minds of expectant parents as the disability to universally consider avoiding. Among the known causes of ID, Down syndrome is the most common. Yet the most prevalent cause of ID is ID of unknown etiology. Overall, 1% of children in population studies have ID (Leonard & Wen, 2002). Yet Down syndrome has a prevalence of approximately 1 per 1000 (Parker, et al., 2011); therefore, 90% of ID is not attributable to Down syndrome. Parents may now incorrectly perceive Down syndrome as the biggest threat to their child's wellness and cognitive development. In actuality, it is only the biggest threat we have the technology to test for. The policy does not acknowledge other potential causes of ID that remain even if prenatal testing for fetal aneuploidy is negative and it is unknown how explicitly genetic counselors and physicians state this fact. Regardless of the prenatal diagnosis regarding chromosomal abnormalities, uncertainty about the fetus remains. Unless we make explicit the limitations of prenatal genetic technologies we may give prospective parents the erroneous assumption that their baby will be typical and "free" of developmental disabilities. Something other than Down syndrome could potentially affect the baby and that condition, at this time, may be unidentifiable.

Prenatal screening for Down syndrome is widespread. A year after the new guidelines were implemented, 95% of prenatal providers offered screening to all their pregnant patients and 48–82% of patients who were offered testing accepted it (Driscoll, Morgan, & Schulkin, 2009). The estimated acceptance rates of patients differed based on region, age, and type of prenatal provider (maternal fetal specialist vs. obstetricians-gynecologists). The increased uptake of prenatal screening and subsequent testing has led to changes in birth rates for Down syndrome. Internationally and in the United States, there has been dramatic decrease in the number of babies who are born with Down syndrome, leading some to speculate if babies with Down syndrome will eventually disappear (B. G. Skotko, 2009).

The Down syndrome Advantage

Within the larger context of Western culture, disability is rarely a value neutral term. Along the spectrum of disability, there are conditions that are viewed as better than others. It is ironic that Down syndrome has such negative connotation in the prenatal setting since postnatally Down syndrome is said to afford affected individuals and their families an advantage.

The Down syndrome advantage refers to the enhanced well being reported by mothers raising a child with Down syndrome compared to mothers of children with other developmental disabilities... Data about the magnitude and reason for this difference are not definitive. (Abbeduto et al., 2004; Corrice & Glidden, 2009; Esbensen & Seltzer, 2011).

Child-specific mediators of the Down syndrome advantage have been proposed such as the child's positive temperament and social responsiveness, relatively limited maladaptive behavior, and relatively strong adaptive skills (Bourke et al., 2008; Esbensen & Seltzer, 2011). Several confounding variables including older maternal age and greater social support have also been suggested to account for this advantage (Corrice & Glidden, 2009; Esbensen & Seltzer, 2011). Importantly, these postnatal data may reflect that the child's intellectual disability is not profound, but most often mild to moderate.

In Down syndrome, child health is also an important indicator of maternal stress and well-being (Bourke et al., 2008). Since 1950, the life expectancy for individuals with Down syndrome has improved dramatically. Bittles and Glasson (2004) found the life expectancy of individuals with Down syndrome is approaching that of the general population in Western Australia. Reasons for the improvements are better outcomes in congenital heart surgery and improvements in routine medical care like antibiotics. Like other developmental disabilities, immobility decreases life expectancy in individuals with Down syndrome; however, most individuals with Down syndrome have near normal functional mobility skills. With age, individuals with Down syndrome are at risk of developing chronic medical conditions like obesity, sleep apnea, Alzheimer's (Steingass, Chicoine, McGuire, & Roizen, 2011). Therefore, comprehensive medical care is key to optimizing quality of life.

The benefits of Down syndrome extend to the entire family. Urbano and Hodapp (2007) have demonstrated lower divorce rates among parents with a child with Down syndrome compared to those without. Skotko et al (2011a; 2011b) conducted a series of cross-sectional studies surveying parents and siblings of individuals with Down syndrome about their experiences. (B. G. Skotko, Levine, & Goldstein, 2011a; B. G. Skotko, Levine, & Goldstein, 2011b) The majority of parents and siblings were proud of and loved their family members with Down syndrome. These feelings did not differ based on the functional level of the child or sibling, respectively, with Down syndrome. Almost 80% of parents reported having a more positive life outlook because of their child with Down syndrome. (B. G. Skotko, Levine, & Goldstein, 2011a) A majority of siblings also endorsed being better people as a result of having a brother or sister with Down syndrome. (B. G. Skotko, Levine, & Goldstein, 2011b). Additionally, Skotko et al (2011c) surveyed individuals aged 12 and older with Down syndrome. Their self-perceptions closely resemble the sentiments of other family members and reflect what most parents hope for their children regardless of diagnosis or neurocognitive potential.

So which is it: disadvantage or advantage?

An objective answer to this question does not exist. Of course, there is always validity to the perceptions of families raising a child with Down syndrome and pregnant women and their partners faced with the possibility of raising a child with Down syndrome. Some people view disability prenatally and postnatally as a continuum (Asch, 2000); whereas, others view the potential of disability that can be avoided as different than the actual challenges of managing a disability (Bailey, 2000). Proponents of either perspective endorse the value and support the rights of persons with disabilities.

Acknowledging the postnatal and prenatal discrepancy, we need to consider this question from the perspective of what we can do as health care providers. There is consensus that balanced information should be provided to expectant parents (Edwards & Ferrante, 2009; K. B. Sheets, Best, Brasington, & Will, 2011; B. G. Skotko, 2009). Parents highly value understanding what life will be like for their child with Down syndrome, learning about the challenges likely to be encountered and potential solutions and supports. Parents and genetic counselors agree that multiple facts related to prognosis are vital to the initial discussion

about the diagnosis of Down syndrome, with both groups acknowledging the importance of printed information materials (K. B. Sheets et al., 2011a). Incorporating these essential items, The National Society of Genetic counselors have just published guidelines about prenatal and postnatal counseling of Down syndrome (K. Sheets et al., 2011b).

Yet, it is not clear how often balanced information is provided to or how information considered balanced by genetic counselors and health care providers is perceived by parents. In 2002, Roberts et al (2002) found 87% of pregnant women did not feel they got information about future quality of life for a child with disability and 83% felt they did not receive information about both positive and negative aspects of giving birth to a child with disability. Compared to parents and their postnatal counterparts, prenatal genetic counselors considered more negative aspects of Down syndrome as essential to include in an initial discussion (K. B. Sheets et al., 2011a). In a study of Spanish mothers, the majority felt that physicians did not provide adequate information, emphasizing the negative aspects of Down syndrome over positive ones, and did not provide printed information materials (B. Skotko & Bedia, 2005).

Initiatives are underway to improve the quality of information provided to parents. In 2008, the Kennedy-Brownback Pre- and Postnatally Diagnosed Conditions Awareness Act was signed into law to ensure families who receive a diagnosis of Down syndrome or any other condition would be offered up-to-date and accurate information about the condition and would be provided with contact information of support services that could offer assistance. However, this law has yet to be fully funded (Leach, 2011). The National Down Syndrome Society and National Down Syndrome Congress are also collaborating on an initiative to develop “gold standard” information brochures about Down syndrome to be distributed to parents. (Edwards & Ferrante, 2009).

Effective prenatal counseling about disability may be hindered by the lack of professional exposure to individuals with disabilities. Because of the populations they care for, obstetricians and prenatal genetic counselors may have different experiences and perceptions of individuals with disabilities than health care providers that care for children: pediatricians, pediatric subspecialists and genetic counselors that offer postnatal counseling. For example, what genetic counselors believe is the most salient information to discuss with parents differs based on whether they practice in the prenatal or postnatal setting (K. B. Sheets et al., 2011a). Regarding professional education, Driscoll et al (2009) found 40% of prenatal providers felt their residency training about the Screening for, and diagnosis of, Down syndrome “was less than adequate.” Exposure to the long-term outcomes of individuals with disabilities as well as the supports available to those individuals during OBGYN and pediatric residency and genetic counseling training could be helpful (Kirschner, Brashler, & Savage, 2007; Roberts et al., 2002; B. G. Skotko, Capone, & Kishnani, 2009). Having residents complete an interactive computer-based training program could be one solution (Ferguson II, Kleinert, Lunney, & Campbell, 2006).

The impact of new genetic technology

Technology often dictates policy. It has been demonstrated in newborn screening (The President’s Council on Bioethics, 2008) as well as in prenatal screening guidelines. Recently, non-invasive technology for prenatal testing for Down syndrome and fetal aneuploidy has been developed (Ehrich et al., 2011; Fan, Blumenfeld, Chitkara, Hudgins, & Quake, 2008; Papageorgiou et al., 2011). Fetal cells obtained from maternal blood in the 1st trimester of pregnancy are analyzed to determine karyotype information. Individuals who may have declined amniocentesis in the past because of the risk to the fetus may now consider non-invasive testing, which could lead to greater uptake of prenatal testing.

Halliday et al. (2001) found 82% of women who refused amniocentesis would agree to non-invasive prenatal testing regardless of their stance on abortion. If there is greater uptake of prenatal testing, this new technology could contribute to the disappearance of babies with Down syndrome (B. G. Skotko, 2009).

Prenatal testing for Down syndrome is also becoming more accessible to parents in the form of preimplantation genetic screening (PGS). Infertility treatments like ICSI (intracytoplasmic sperm injection) and IVF (in vitro fertilization), allow individuals the opportunity to select for a fetus without aneuploidy; however, if this practice is ethical has been debated (Krahn, 2011). The timing of the decision to pursue prenatal testing fundamentally shifts from during pregnancy to in essence before a woman becomes pregnant. For some, this shift in timing makes it easier to pursue PGS compared to traditional prenatal testing. Twisk et al (2007) found that 42% of women undergoing ICSI or IVF who would not pursue prenatal testing for Down syndrome would elect to have PGS for Down syndrome. When deciding whether to pursue PGS, women considered the effect of PGS on their chance of getting pregnant and the sensitivity of the test (Twisk et al., 2007).

Comparative genomic hybridization (CGH, genetic microarray) is another technological advancement which could drastically alter practice. Presently, chromosomal karyotyping for aneuploidy is the standard of care. It can identify significant alterations in the amount of chromosomal materials, either the addition or absence of whole or partial chromosomes. Using karyotypes, an identifiable cause of ID is not found in most cases. Genetic changes on a smaller scale like microdeletions, duplications and trinucleotide repeats are not picked up routinely and are increasingly being found to be responsible for previously unexplained ID (Shaffer et al., 2007; Slavotinek, 2008). Although it cannot detect aneuploidy reliably, CGH can detect these more subtle changes in genetic material and can be used to evaluate the entire genome or targeted areas of interest.

While CGH is now the recommended test to evaluate childhood developmental delays and ID, the use of CGH in the prenatal setting is growing. (Evangelidou et al., 2010; Miller et al., 2010; Park et al., 2011; Sahoo et al., 2006). Although CGH may be able to provide some answers that karyotyping cannot, CGH also introduces additional uncertainty. The clinical significance of many of the changes picked up by CGH is unknown. To understand if the abnormality is normal variation or pathologic, additional testing of parents can be necessary in up to 5% of cases. (Darilek et al., 2008) Parental testing can reveal non-paternity, an added risk. In their article about the Baylor experience with prenatal CGH, Darilek et al (2008), described the time and labor intensive counseling that is undertaken to ensure that parents understand what CGH is and is not able to accomplish and what resultant potential uncertainty means. If CGH is incorporated into routine practice, similar counseling safeguards will need to be followed.

Despite the promise of new technology, some parents may be discouraged by the potential uncertainty and decline broad-scale testing. When posed with the theoretical option of full-scale testing with considerable uncertainty, fairly akin to that with CGH, 67% of women chose to decline testing and 20% more declined testing after being counseled about the limitations of the test (Pieters, Kooper, Smits, & De Vries, 2009). Pieters et al (2009) also found that a low educational level correlated with acceptance of full-scale testing. This emphasizes the importance of effective counseling for individuals at all educational levels.

A Down syndrome critical region has recently been identified on chromosome 21 (Yamamoto et al., 2011). Genotype-phenotype studies are being conducted to isolate more specific genes causing the disorder and establish which genes are responsible for which neurobehavioral phenotypes (Lyle et al., 2009). Whereas Down syndrome had previously

been diagnosed using karyotypes, specific mutations in this critical region, when identified, could be detected using CGH. Better genotype-phenotype correlations could improve prenatal counseling about prognosis, offer the promise of targeted therapeutic interventions and provide parents more certainty about the meaning of the prenatal diagnosis.

Conclusion

There is a false perception that prenatal testing for ID is equivalent to prenatal testing for Down syndrome. Prenatal testing for Down syndrome does not identify the other 90% of ID. This misperception is reinforced by current policy and counseling practices that do not explicitly state the risk of other causes of ID. New genetic technologies can detect a wider array of CNV, deletions and duplications that may be involved in ID. With the introduction of these new genetic technologies, the uncertainty parents face with current testing options will be heightened. Moving forward, we need to be mindful about counseling expectant parents about the realities of living with a disability and the limitations of the test available. Only with this information can parents make truly informed decisions about prenatal testing.

References

- Abbeduto L, Seltzer MM, Shattuck P, Krauss MW, Orsmond G, Murphy MM. Psychological well-being and coping in mothers of youths with autism, down syndrome, or fragile X syndrome. *American Journal on Mental Retardation*. 2004; 109(3):237–254. [PubMed: 15072518]
- American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion no. 481: Newborn screening. *Obstetrics and Gynecology*. 2011; 117(3):762–765. [PubMed: 21343795]
- American College of Obstetrics & Gynecology. ACOG practice bulletin no. 77: Screening for fetal chromosomal abnormalities. *Obstetrics and Gynecology*. 2007; 109(1):217–228. [PubMed: 17197615]
- Asch, A. Why I haven't changed my mind about prenatal diagnosis: Reflections and refinements. In: Parens, Erik; Asch, Adrienne, editors. *Prenatal testing and disability rights*. Washington, DC: Georgetown University Press; 2000. p. 234–258.
- Baily, MA. Why I had amniocentesis. In: Parens, Erik; Asch, Adrienne, editors. *Prenatal testing and disability rights*. Washington, DC: Georgetown University Press; 2000. p. 64–71.
- Bittles AH, Glasson EJ. Clinical, social, and ethical implications of changing life expectancy in Down syndrome. *Developmental Medicine and Child Neurology*. 2004; 46(4):282–286. [PubMed: 15077706]
- Bourke J, Ricciardo B, Bebbington A, Aiberti K, Jacoby P, Dyke P, Leonard H. Physical and mental health in mothers of children with Down syndrome. *Journal of Pediatrics*. 2008; 153(3):320–326. [PubMed: 18534233]
- Corrice AM, Glidden LM. The Down syndrome advantage: Fact or fiction? *American Journal on Intellectual and Developmental Disabilities*. 2009; 114(4):254–268. [PubMed: 19642708]
- Cowan, RS. Women's roles in the history of amniocentesis and chorionic villi sampling. In: Kerr, A.; Shakespeare, T., editors. *Genetic politics: From eugenics to genome*. Berkeley, CA: New Clarion Press; 2002. p. 35–47.
- Darilek S, Ward P, Pursley A, Plunkett K, Furman P, Magoulas P, Eng CM. Pre- and postnatal genetic testing by array-comparative genomic hybridization: Genetic counseling perspectives. *Genetics in Medicine*. 2008; 10(1):13–18. [PubMed: 18197052]
- Driscoll DA, Morgan MA, Schulkin J. Screening for down syndrome: Changing practice of obstetricians. *American Journal of Obstetrics and Gynecology*. 2009; 200(4):459, e1–9. [PubMed: 19318157]
- Edwards, JG.; Ferrante, RR. *Toward concurrence: Understanding prenatal screening and diagnosis of down syndrome from the health professional and advocacy community perspectives*. Columbia, SC: University of South Carolina; 2009.

- Ehrich M, Deciu C, Zwiefelhofer T, Tynan JA, Cagasan L, Tim R, Van Den Boom D. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: A study in a clinical setting. *Obstetrical and Gynecological Survey*. 2011; 66(6):342–344.
- Esbensen AJ, Seltzer MM. Accounting for the “down syndrome advantage”. *American Journal on Intellectual and Developmental Disabilities*. 2011; 116(1):3–15. [PubMed: 21291307]
- Evangelidou P, Sismani C, Ioannides M, Christodoulou C, Koumbaris G, Kallikas I, Patsalis PC. Clinical application of whole-genome array CGH during prenatal diagnosis: Study of 25 selected pregnancies with abnormal ultrasound findings or apparently balanced structural aberrations. *Molecular Cytogenetics*. 2010; 3(1):24. [PubMed: 21110858]
- Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105(42):16266–16271. [PubMed: 18838674]
- Ferguson JE II, Kleinert HL, Lunney CA, Campbell LR. Resident physicians’ competencies and attitudes in delivering a postnatal diagnosis of down syndrome. *Obstetrics and Gynecology*. 2006; 108(4):898–905. [PubMed: 17012452]
- Halliday JL, Warren R, McDonald G, Rice PL, Bell RJ, Watson LF. Prenatal diagnosis for women aged 37 years and over: To have or not to have. *Prenatal Diagnosis*. 2001; 21(10):842–847. [PubMed: 11746126]
- Keller C, Siegrist M. Effect of risk communication formats on risk perception depending on numeracy. *Medical Decision Making*. 2009; 29(4):483–490. [PubMed: 19525484]
- Kirschner KL, Brashler R, Savage TA, Ashley X. *American Journal of Physical Medicine and Rehabilitation*. 2007; 86(12):1023–1029. [PubMed: 18090444]
- Krahn TM. Regulating preimplantation genetic diagnosis: The case of down’s syndrome. *Medical Law Review*. 2011; 19(2):157–191. [PubMed: 21531756]
- Leach, MW. [Accessed 11/3/11.] The prenatal testing sham. 2011. Retrieved from <http://www.thepublicdiscourse.com/2011/03/3008>
- Lejune J, Gautier M, Turpin R. Study of somatic chromosomes from 9 mongoloid children. [Etude des chromosomes somatiques de neuf enfants mongoliens]. *Comptes Rendus Hebdomadaires Des Séances De l’Académie Des Sciences*. 1959; 248(11):1721–1722.
- Leonard H, Wen X. The Epidemiology of Mental Retardation: Challenges and Opportunities in the New Millenium. *MRDD Research Reviews*. 2002; 8:117–134.
- Lyle R, Béna F, Gagos S, Gehrig C, Lopez G, Schinzel A, Antonarakis SE. Genotype-phenotype correlations in down syndrome identified by array CGH in 30 cases of partial trisomy and partial monosomy chromosome 21. *European Journal of Human Genetics*. 2009; 17(4):454–466. [PubMed: 19002211]
- Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, Ledbetter DH. Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics*. 2010; 86(5):749–764. [PubMed: 20466091]
- Ossorio, PN. Prenatal genetic testing and the courts. In: Parens, Erik; Asch, Adrienne, editors. *Prenatal testing and disability rights*. Washington, DC: Georgetown University Press; 2000. p. 308-333.
- Papageorgiou EA, Karagrigoriou A, Tsaliki E, Velissariou V, Carter NP, Patsalis PC. Fetal-specific DNA methylation ratio permits noninvasive prenatal diagnosis of trisomy 21. *Nature Medicine*. 2011; 17(4):510–513.
- Park S, Jung EH, Ryu R, Kang HW, Ko J, Kim HJ, Kang H. Clinical implementation of whole-genome array CGH as a first-tier test in 5080 pre and postnatal cases. *Molecular Cytogenetics*. 2011; 4:12. [PubMed: 21549014]
- Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Correa A. Updated national birth prevalence estimates for selected birth defects in the United States, 2004– 2006. *Birth Defects Research. Part A: Clinical and Molecular Teratology*. 2010; 88(12):1008–1016.
- Pieters JJPM, Kooper AJA, Smits APT, De Vries J. Parent’s attitudes towards full-scale prenatal testing for genetic disorders. *Journal of Psychosomatic Obstetrics and Gynecology*. 2009; 30(1): 42–47. [PubMed: 19308782]

- Rapp, R. Testing women, testing the fetus: The social impact of amniocentesis in america. New York, NY: Routledge; 1999.
- Roberts CD, Stough LM, Parrish LH. The role of genetic counseling in the elective termination of pregnancies involving fetuses with disabilities. *Journal of Special Education*. 2002; 36(1):48–55. [PubMed: 17333588]
- Sahoo T, Cheung SW, Ward P, Darilek S, Patel A, Del Gaudio D, Eng CM. Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. *Genetics in Medicine*. 2006; 8(11):719–727. [PubMed: 17108764]
- Shaffer LG, Theisen A, Bejjani BA, Ballif BC, Aylsworth AS, Lim C, Shaikh T. The discovery of microdeletion syndromes in the post-genomic era: Review of the methodology and characterization of a new 1q41q42 microdeletion syndrome. *Genetics in Medicine*. 2007; 9(9): 607–616. [PubMed: 17873649]
- Sheets KB, Best RG, Brasington CK, Will MC. Balanced information about Down syndrome: What is essential? *American Journal of Medical Genetics, Part A*. 2011a; 155(6):1246–1257. [PubMed: 21548127]
- Sheets K, Crissman B, Feist C, Sell S, Johnson L, Donahue K, Brasington C. Practice guidelines for communicating a prenatal or postnatal diagnosis of down syndrome: Recommendations of the national society of genetic counselors. *Journal of Genetic Counseling*. 2011b; 20(5):432–441.10.1007/s10897-011-9375-8 [PubMed: 21618060]
- Skotko B, Bedia RC. Postnatal support for mothers of children with Down syndrome. *Mental Retardation*. 2005; 43(3):196–212. [PubMed: 15882082]
- Skotko BG. With new prenatal testing, will babies with Down syndrome slowly disappear? *Archives of Disease in Childhood*. 2009; 94(11):823–826. [PubMed: 19531527]
- Skotko BG, Capone GT, Kishnani PS. Postnatal diagnosis of Down syndrome: Synthesis of the evidence on how best to deliver the news. *Pediatrics*. 2009; 124(4):e751–e758. [PubMed: 19786436]
- Skotko BG, Levine SP, Goldstein R. Having a brother or sister with down syndrome: Perspectives from siblings. *American Journal of Medical Genetics, Part A*. 2011a; 155(10):2348–2359. [PubMed: 21910244]
- Skotko BG, Levine SP, Goldstein R. Having a son or daughter with down syndrome: Perspectives from mothers and fathers. *American Journal of Medical Genetics, Part A*. 2011b; 155(10):2335–2347. [PubMed: 21915989]
- Skotko BG, Levine SP, Goldstein R. Self-perceptions from people with down syndrome. *American Journal of Medical Genetics, Part A*. 2011c; 155(10):2360–2369. [PubMed: 21910246]
- Slavotinek AM. Novel microdeletion syndromes detected by chromosome microarrays. *Human Genetics*. 2008; 124(1):1–17. [PubMed: 18512078]
- Steingass KJ, Chicoine B, McGuire D, Roizen NJ. Developmental disabilities grown up: Down syndrome. *Journal of Developmental and Behavioral Pediatrics*. 2011; 32(7):548–558. [PubMed: 21743353]
- The President's Council on Bioethics. The changing moral focus of newborn screening: An ethical analysis by the president's council on bioethics. 2008
- Twisk M, Haadsma ML, van der Veen F, Repping S, Mastenbroek S, Heineman M, Korevaar JC. Preimplantation genetic screening as an alternative to prenatal testing for Down syndrome: Preferences of women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment. *Fertility and Sterility*. 2007; 88(4):804–810. [PubMed: 17349641]
- Urbano RC, Hodapp RM. Divorce in families of children with Down syndrome: A population-based study. *American Journal on Mental Retardation*. 2007; 112(4):261–274. [PubMed: 17559293]
- Yamamoto T, Shimojima K, Nishizawa T, Matsuo M, Ito M, Imai K. Clinical manifestations of the deletion of Down syndrome critical region including DYRK1A and KCNJ6. *American Journal of Medical Genetics, Part A*. 2011; 155(1):113–119. [PubMed: 21204217]