JOURNAL
OF THE CANADIAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY / DE L'ACADÉMIE CANADIENNE DE PSYCHIATRIE DE L'ENFANT ET DE L'ADOLESCENT

COMMENTARY

Whole Genome Sequencing as a Genetic Test for Autism Spectrum Disorder: From Bench to Bedside and then Back Again

Michael J. Szego PhD, MHSc[1,2,3]; Ma'n H. Zawati LLB, LLM[4]

Abstract

Autism spectrum disorder (ASD) is characterized by repetitive patterns of behaviour and impairments in social interactions and communication abilities. Although ASD is a heterogeneous disorder, it is a highly genetic condition for which genetic testing is routinely performed. Microarray analysis is currently the standard of care genetic test for ASD, however whole genome sequencing offers several key advantages and will likely replace microarrays as a frontline genetic test in the near future. The 2nd Consultation on Translation of Genomic Advances into Health Applications took place in the spring of 2014 to broadly explore the current and potential impacts of genomic advances in supporting personalized and family-centered care for autism and related developmental conditions. In anticipation of WGS becoming a standard of care test, we examine the policy landscape and highlight the lack of consistency among guidelines regarding what genomic information should be returned to patients and their families. We also discuss the need to create the infrastructure to share clinical WGS data with researchers in a systematic and ethically defensible manner.

Key Words: *autism spectrum disorder, return of results, whole genome sequencing, database, research ethics*

Résumé

Le trouble du spectre de l'autisme (TSA) est caractérisé par des comportements répétitifs et des déficiences dans les aptitudes aux interactions sociales et à la communication. Bien que le TSA soit un trouble hétérogène, c'est une affection hautement génétique pour laquelle un test génétique est régulièrement mené. L'analyse par microréseau est présentement la norme de pratique pour le TSA; cependant, le séquençage du génome entier (SGE) offre plusieurs avantages clés et remplacera probablement les microréseaux comme test génétique de première ligne dans un avenir rapproché. La 2e Consultation sur la conversion des progrès de la génomique en applications de santé a eu lieu au printemps de 2014 afin d'explorer largement les effets actuels et potentiels des progrès de la génomique pour soutenir les soins de l'autisme personnalisés et axés sur la famille, et les troubles du développement connexes. En prévision que le SGE devienne la norme de pratique des tests, nous examinons le paysage normatif et soulignons l'absence de cohérence des lignes directrices à l'égard de l'information génomique qui devrait être retournée aux patients et à leurs familles. Nous discutons également du besoin de créer l'infrastructure pour partager les données cliniques du SGE avec les chercheurs de manière systématique et éthiquement défendable.

Mots clés: *trouble du spectre de l'autisme, retour des résultats, séquençage du génome entier, base de données, éthique de la recherche*

[1]Centre for Clinical Ethics, St. Joseph's Health Centre, Toronto, Ontario

[2]The Centre for Applied Genomics, The Hospital for Sick Children, Toronto, Ontario

[3]Department of Family and Community Medicine, The Dalla Lana School of Public Health, and The Joint Centre for Bioethics, University of Toronto, Toronto, Ontario

[4]Centre of Genomics and Policy, McGill University, Montreal, Quebec

Corresponding E-Mail: michael.szego@utoronto.ca

Submitted: May 6, 2015; Accepted: March 26, 2016

Background

Autism spectrum disorder (ASD) is characterized by repetitive patterns of behaviour and impairments in social interactions and communication abilities (Anagnostou et al., 2014). Individuals with ASD can present with a wide variety of features, with symptoms ranging from mild to severe (Carter & Scherer, 2013; Scherer & Dawson, 2011). ASD affects approximately 1% of the population and the most recent surveillance data suggest the prevalence is one in 68 among children (Anagnostou et al., 2014; Developmental Disabilities Monitoring Network, 2014). Currently, there are no pharmaceutical agents available to treat the core symptoms of ASD, although there are several promising experimental therapeutics being tested (Anagnostou et al., 2014).

ASD is diagnosed clinically following an extensive assessment (Anagnostou et al., 2014). The diagnostic workup usually includes a detailed medical history, a systematic interactive assessment, an evaluation of other co-morbidities, and genomic testing (Anagnostou et al., 2014). Genomic testing is included in the diagnostic workup since ASD is a highly genetic condition with many known genetic risk factors (Anagnostou et al., 2014; Carter & Scherer, 2013). While no single laboratory test is sufficient for the diagnosis of ASD, identification of genetic risk factors can influence patient management, availability of services, and accuracy of recurrence risk estimates (Carter & Scherer, 2013; Shen et al., 2010).

Genome-wide testing is a part of the standard diagnostic assessment for patients with ASD (Anagnostou et al., 2014; Miller et al., 2010). The discovery that copy number variants – large regions of DNA (>1kb) that can differ in copy number between an individual and a reference genome (Redon et al., 2006) – are more common in patients with ASD has been the driver for this molecular diagnostic approach (Devlin & Scherer, 2012). Historically, cytogenetic analysis was performed to directly visualize chromosomes for any rearrangements, including gains and losses (Miller et al., 2010). Chromosomal microarray technology has replaced cytogenetic analysis as a molecular diagnostic tool for ASD (Miller et al., 2010). Chromosomal microarrays have greater resolution and can detect copy number variants across the entire genome in a single test. However, a limitation of both cytogenetic analysis and chromosomal microarrays is the inability to detect single nucleotide changes.

Single nucleotide changes are more common in single gene disorders, which account for 10% of patients with ASD (Devlin & Scherer, 2012). With the development of next generation sequencing, it is now cost effective to sequence individual genomes (Wetterstrand, 2014). Two common applications of next generation sequencing are whole genome sequencing (WGS), which involves elucidating the complete genomic sequence of an individual, and whole exome sequencing (WES), which involves elucidating the protein coding regions of the genome (about 2-3% of the entire genome). WGS will likely be used for the molecular diagnosis of ASD in the near future since it can detect both copy number variants and single nucleotide changes across the entire genome in a single test (Tammimies et al., 2015; Jiang et al., 2014).

The 2nd Consultation on Translation of Genomic Advances into Health Applications took place in the spring of 2014 to broadly explore the current and potential impacts of genomic advances in supporting personalized and family-centered care for autism and related developmental conditions. The consultation event was attended by 50 basic, clinical, and social scientists, health practitioners, ethicists, jurists, economists and community stakeholders from the UK and Canada. The purpose of this commentary is to discuss some ethical issues associated with WGS relevant to ASD that were presented as part of the panel discussion on ethics, public policy and health economics. Although many ethical issues have been discussed in the context of WGS (Presidential Commission for the Study of Bioethical Issues, 2012; Tabor, Berkman, Hull, & Bamshad, 2011; Wolf, 2013), for the purposes of this commentary we will focus on the return of results and how using WGS in a clinical context- provided the right infrastructure is in place- could accelerate the pace of ASD research advances.

ASD genomics: from the bench to the clinic

Genomic studies have revealed several features of ASD. First, rare genomic variants, which are present in less than 1% of the general population, account for a large proportion of genetic risk factors associated with ASD (Levy et al., 2011; Marshall et al., 2008; Neale et al., 2012; Sanders et al., 2012). Examples of rare variants that have been associated with ASD risk include single nucleotide variants (SNVs), chromosomal abnormalities and an abnormal number of repeats of specific DNA regions called copy-number variants (Devlin & Scherer, 2012). Secondly, both inherited and *de novo* mutations have been implicated in ASD with *de novo* mutations present in 10-15% of ASD cases (Devlin & Scherer, 2012). While inherited mutations are transmitted from parents to their children, *de novo* mutations represent genetic changes that occur for the first time in the affected individual as a result of a mutation in the germ cell of one of their parents or in the early embryo itself.

Third, there are likely hundreds of genes associated with ASD-risk (Devlin & Scherer, 2012; Pinto et al., 2014).

Some ASD-risk variants are associated with single gene disorders in which patients often exhibit ASD as part of their phenotype. For example, genetic disorders such as Fragile X, tuberous sclerosis, Rett syndrome, and neurofibromatosis are present in 10% of patients with ASD (Devlin & Scherer, 2012). Additional high impact single nucleotide variants and copy number variants have been identified and account for an additional 10% of cases (Scherer & Dawson, 2011).

Interestingly, no single locus accounts for more than 1% of ASD cases (State & Sestan, 2012). Underscoring the genetic heterogeneity of ASD is the finding that in approximately 69% of cases when multiple affected siblings are present in a family, they carry different ASD-relevant mutations (Yuen et al., 2015). This situation is in stark contrast to monogenic disorders when affected siblings would likely have inherited the same mutation. To complicate the picture further, most of the genetic abnormalities associated with ASD are also associated with highly variable phenotypes (Devlin & Scherer, 2012). One suggested explanation for the phenotypic variability is the key role of genetic interactions between rare variants in some individuals (Risch et al., 1999). Ongoing studies such as the autism sequencing project aim to identify the full cadre of variants associated with ASD (Buxbaum et al., 2012). Such efforts will greatly impact patients since a better understanding of the genetic basis of ASD will improve our ability to molecularly diagnose ASD.

Currently, mircroarray analysis leads to the identification of an ASD-associated variant in about 12% of cases (Miller et al., 2010). Given the genetic complexity associated with ASD, more sensitive techniques may be needed in cases where clinical microarray analysis does not yield any results. WES has been shown to be an effective approach to identify variants associated with ASD risk (Jiang et al., 2014; Rodriguez-Flores et al., 2014). Recently, the diagnostic yield of chromosomal microarray analysis was shown to be comparable to WES, demonstrating the utility of WES (Tammimies et al., 2015). Non coding regions of DNA, which are not interrogated by WES, have been shown to play a role in some cases of ASD (Turner et al., 2016; Walker & Scherer, 2013). As a result, WGS (which interrogates both coding and non coding regions of the genome) will likely replace clinical microarrays as a frontline genetic test in the near future (Jiang et al., 2014). As such, we will focus the next two sections on some ethical issues raised by WGS in the clinical context.

What WGS results to return: exploring the policy landscape

The translation of ASD research tools into the paediatric clinical setting has prompted discussion surrounding the ethical issues of reporting whole-genome sequencing (WGS) results back to patients and families. Consequently, a series of proposals were put forward by various national and international organisations, but no clear consensus exists on the matter. Before exploring this policy landscape, it is important to note that most of the documents featured in this section are, for the most, not binding in nature, but help shape the legal standard of care. In other words, the laws existing in the jurisdiction in question will frame the application of such ethics norms.

In 2013, the European Society of Human Genetics (ESHG) recommended avoiding unsolicited findings by filtering out known genetic variants with limited or no clinical utility (van El et al., 2013). Respect for patient autonomy was a matter of intense debate following the release of the American College of Medical Geneticists (ACMG) recommendations on the reporting of incidental findings from clinical WGS/WES in 2013 (Burke et al., 2013; Green et al., 2013). Most noticeably, the ACMG proposed feeding back results emanating from the analysis of 56 medically actionable genes associated with 24 inherited conditions when a patient undergoes WGS/WES. Moreover, they adopted a more permissive approach than the ESHG recommendations by determining that resulting incidental variants should be reported regardless of the age of the patient. More recently, the ACMG revised their initial recommendations (Green et al. 2013) through a series of clarifications and updates (ACMG Board of Directors, 2013a; ACMG Board of Directors, 2013b; ACMG Board of Directors, 2015). These revisions eventually led to the inclusion of an opt-out alternative to the routine analysis of an evolving subset of genes (ACMG Board of Directors, 2015). However, the ACMG proposes that the patient's decision shall apply to the entire set of genes deemed actionable (ACMG Board of Directors, 2015).

In the Canadian context, Zawati et al. presented a Canadian-specific proposal for a policy on the use of WGS and more explicitly for the return of results (Zawati, Parry, Thorogood, et al., 2014). Ultimately, in Canada, it is recommended to communicate to parents all "results revealing a clinically significant condition that is actionable during childhood", and this, without the option to opt-out (Zawati, Parry, Thorogood, et al., 2014). However, for the communication of adult-onset genetic conditions, it is suggested that this should be withheld "unless disclosure to the parents could prevent serious harm to their health or that of

family members as determined on a case-by-case basis, and if such disclosure is desired by the parents" (Zawati, Parry, & Knoppers, 2014). It is important to consider the child's views in the decision-making process depending on age and maturity (Zawati, Parry, & Knoppers, 2014). Subsequently, the Canadian College of Medical Geneticists (CCMG) formed two working groups tasked with emitting a position statement on the clinical application of genome-wide sequencing for monogenic diseases (Zawati, Parry, Thorogood, et al., 2014). The criteria set forth for the communication of incidental findings in children primarily revolves around the assessment of medical-actionability during childhood. Ethical decision-making as presented in the national and international proposals mentioned above evoke the consideration of four guiding principles: integrity, beneficence, non-maleficence and justice (Zawati, Parry, & Knoppers et al., 2014). That said, the child's best interests will fundamentally guide all current recommendations regarding the return of WGS results in the clinical paediatric setting.

WGS and ASD: from bedside to bench

Research and clinical care are typically regarded as separate endeavors. In the discussion above, we explored the policy landscape guiding the return of WGS results to patients. Once WGS becomes an established clinical test, the resulting sequence data could be of great utility to the research community. In particular, access to clinical WGS data sets could accelerate current gene-finding efforts, provide more data on genotype-phenotype relationships and serve as a potential source of longitudinal data. In anticipation of the broad use of WGS in ASD genetic testing, models of data sharing between clinical and research environments should be explored.

Currently, when a clinical microarray is ordered as a genetic test for ASD, the data cannot automatically be used for research. The secondary use of clinical data for research purposes requires research ethics board approval and under most circumstances explicit research subject consent (Canadian Institutes of Health Research et al., 2014). As WGS replaces microarray technology, maintaining the status quo entails putting the onus on individual investigators to apply for access to clinical data. A more standardized approach to research data collection could benefit researchers and patients alike. One such approach involves emulating a database model in which clinical WGS and phenotypic data of patients undergoing testing would be collected and stored for future use in research.

Explicit consent is usually required when prospectively collecting patient data for research purposes (Canadian Institutes of Health Research et al., 2014). At the time of clinical consent for WGS, patients could be asked whether they would agree to allow their clinical information to be included in a research database. This additional research consent would include a discussion of the potential benefits and risks of participating, including privacy risks. Prospective participants would also be assured that they could continue to receive the same standard of clinical care regardless of their decision to participate in research. An assent process would also need to be created for paediatric patients who do not yet have the capacity to consent; however, given that ASD genetic testing usually occurs at a young age, substitute decision makers would normally be consenting. Furthermore, if the database is intended as a long-term project, then a process to re-consent participants when they gain the capacity to do so would need to be established.

Databases require an appropriate governance structure and procedures to obtain data and to share data. Creating a data access committee to scrutinize data access requests is one way to control the flow of information. Data sharing is another consideration and organizations like the Global Alliance for Genomics and Health are working towards standardizing ethics review and data harmonization internationally (Knoppers, 2014). A significant advantage of depositing clinical WGS data for research purposes is that a healthcare professional has already returned clinically relevant data. Researchers will have a more manageable task of creating provisions to return any clinically relevant data identified in the future.

Conclusion

ASD is a complex disease for which genomic testing can reveal useful clinical information for patients, families, and healthcare providers. In the near future, WGS will likely replace microarrays as being the standard of care genomic test for ASD. For paediatric patients who have their genome sequenced there is a lack of consistency among guidelines regarding what genomic information should be returned to patients and their families. With the wealth of information generated by WGS, we have an opportunity to improve the health of children by testing for variants associated with actionable childhood disorders in addition to ASD-associated variants. However, before this additional testing occurs consistently, laboratories need guidance so they can build the necessary bioinformatics pipelines. In anticipation of WGS becoming a standard of care genomic test, we have the opportunity to creating new infrastructure to share clinical data with researchers in a systematic and ethically defensible manner. Data sharing could increase the pace of genetic discoveries, which would benefit current and future patients.

Acknowledgements / Conflicts of Interest

MJS is supported by funding from a Genome Canada Large Scale Applied Research Project grant, "Autism Spectrum Disorders: Genomes to Outcomes" (Principal investigators S. Scherer and P. Szatmari). MHZ is supported by the Réseau de medicine génétique appliquée du Québec (RMGA). The authors would like to thank Me Erika Kleiderman, Academic Associate at the Centre of Genomics and Policy, for her assistance. The authors have no financial relationships to disclose.

References

ACMG Board of Directors. (2013a). Incidental findings in clinical genomics: A clarification. *Genetics in Medicine, 15*(8), 664-666. doi: 10.1038/gim.2013.82

ACMG Board of Directors. (2013b). Points to consider for informed consent for genome/exome sequencing. *Genetics in Medicine, 15*(9), 748-749. doi: 10.1038/gim.2013.94

ACMG Board of Directors. (2015). ACMG policy statement: Updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genetics in Medicine, 17*(1), 68-69. doi: 10.1038/gim.2014.151

Anagnostou, E., Zwaigenbaum, L., Szatmari, P., Fombonne, E., Fernandez, B. A., Woodbury-Smith, M.,...Scherer, S. W. (2014). Autism spectrum disorder: Advances in evidence-based practice. *Canadian Medical Association Journal, 186*(7), 509-519. doi: 10.1503/cmaj.121756

Burke, W., Antommaria, A. H., Bennett, R., Botkin, J., Clayton, E. W., Henderson, G. E.,...Zimmern, R. (2013). Recommendations for returning genomic incidental findings? We need to talk! *Genetics in Medicine, 15*(11), 854-859. doi: 10.1038/gim.2013.113

Buxbaum, J. D., Daly, M. J., Devlin, B., Lehner, T., Roeder, K., State, M. W., & Autism Sequencing, C. (2012). The autism sequencing consortium: Large-scale, high-throughput sequencing in autism spectrum disorders. *Neuron, 76*(6), 1052-1056. doi: 10.1016/j.neuron.2012.12.008

Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. (2014). Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Carter, M. T., & Scherer, S. W. (2013). Autism spectrum disorder in the genetics clinic: A review. *Clinical Genetics, 83*(5), 399-407. doi: 10.1111/cge.12101

Developmental Disabilities Monitoring Network; Centers for Disease Control and Prevention. (2014). Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveillance Summaries, 63*(2), 1-21.

Devlin, B., & Scherer, S. W. (2012). Genetic architecture in autism spectrum disorder. *Current Opinions in Genetics & Development, 22*(3), 229-237. doi: 10.1016/j.gde.2012.03.002

Green, R. C., Berg, J. S., Grody, W. W., Kalia, S. S., Korf, B. R., Martin, C. L.,...Genomics. (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine, 15*(7), 565-574. doi: 10.1038/gim.2013.73

Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T.,...Risch, N. (2011). Genetic heritability and shared environmental factors among twin pairs with autism. *Archives in Genetic Psychiatry, 68*(11), 1095-1102. doi: 10.1001/archgenpsychiatry.2011.76

Jiang, Y. H., Wang, Y., Xiu, X., Choy, K. W., Pursley, A. N., & Cheung, S. W. (2014). Genetic diagnosis of autism spectrum disorders: The opportunity and challenge in the genomics era. *Critical Reviews in Clinical Laboratory Sciences, 51*(5), 249-262. doi: 10.3109/10408363.2014.910747

Knoppers, B. M. (2014). International ethics harmonization and the global alliance for genomics and health. *Genome Medicine, 6*(2), 13. doi: 10.1186/gm530

Levy, D., Ronemus, M., Yamrom, B., Lee, Y. H., Leotta, A., Kendall, J.,...Wigler, M. (2011). Rare de novo and transmitted copy-number variation in autistic spectrum disorders. *Neuron, 70*(5), 886-897. doi: 10.1016/j.neuron.2011.05.015

Marshall, C. R., Noor, A., Vincent, J. B., Lionel, A. C., Feuk, L., Skaug, J.,...Scherer, S. W. (2008). Structural variation of chromosomes in autism spectrum disorder. *American Journal of Human Genetics, 82*(2), 477-488. doi: 10.1016/j.ajhg.2007.12.009

Miller, D. T., Adam, M. P., Aradhya, S., Biesecker, L. G., Brothman, A. R., Carter, N. P.,...Ledbetter, D. H. (2010). Consensus statement: Chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *American Journal of Human Genetics, 86*(5), 749-764. doi: 10.1016/j.ajhg.2010.04.006

Neale, B. M., Kou, Y., Liu, L., Ma'ayan, A., Samocha, K. E., Sabo, A.,... Daly, M. J. (2012). Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature, 485*(7397), 242-245. doi: 10.1038/nature11011

Pinto, D., Delaby, E., Merico, D., Barbosa, M., Merikangas, A., Klei, L.,...Scherer, S. W. (2014). Convergence of genes and cellular pathways dysregulated in autism spectrum disorders. *American Journal of Human Genetics, 94*(5), 677-694. doi: 10.1016/j.ajhg.2014.03.018

Presidential Commission for the Study of Bioethical Issues. (2012). Privacy and Progress in Whole Genome Sequencing, from http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf. Accessed [December 6, 2014].

Redon, R., Ishikawa, S., Fitch, K.R., Feuk, L., Perry, G.H.,...Hurles, M. E. (2006). Global variation in copy number in the human genome. Nature, *444*, 444-454. doi:10.1038/nature05329

Risch, N., Spiker, D., Lotspeich, L., Nouri, N., Hinds, D., Hallmayer, J.,...Myers, R. M. (1999). A genomic screen of autism: Evidence for a multilocus etiology. *American Journal of Human Genetics, 65*(2), 493-507. doi: 10.1086/302497

Rodriguez-Flores, J. L., Fakhro, K., Hackett, N. R., Salit, J., Fuller, J., Agosto-Perez, F.,...Crystal, R. G. (2014). Exome sequencing identifies potential risk variants for Mendelian disorders at high prevalence in Qatar. *Human Mutatation, 35*(1), 105-116. doi: 10.1002/humu.22460

Sanders, S. J., Murtha, M. T., Gupta, A. R., Murdoch, J. D., Raubeson, M. J., Willsey, A. J.,...State, M. W. (2012). De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature, 485*(7397), 237-241. doi: 10.1038/nature10945

Scherer, S. W., & Dawson, G. (2011). Risk factors for autism: Translating genomic discoveries into diagnostics. *Human Genetics, 130*(1), 123-148. doi: 10.1007/s00439-011-1037-2

Shen, Y., Dies, K. A., Holm, I. A., Bridgemohan, C., Sobeih, M. M., Caronna, E. B.,...Autism Consortium Clinical Genetics, D. N. A. D. C. (2010). Clinical genetic testing for patients with autism spectrum disorders. *Pediatrics, 125*(4), e727-735. doi: 10.1542/peds.2009-1684

State, M. W., & Sestan, N. (2012). Neuroscience. The emerging biology of autism spectrum disorders. *Science, 337*(6100), 1301-1303. doi: 10.1126/science.1224989

Tabor, H. K., Berkman, B. E., Hull, S. C., & Bamshad, M. J. (2011). Genomics really gets personal: how exome and whole genome sequencing challenge the ethical framework of human genetics research. *American Journal of Medical Genetics A, 155A*(12), 2916-2924. doi: 10.1002/ajmg.a.34357

Tammimies, K., Marshall, C. R., Walker, S., Kaur, G., Thiruvahindrapuram, B., Lionel, A. C.,...Fernandez, B. A. (2015). Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder. *Journal of the American Medical Association, 314*(9):895-903. Doi:10.1001/jama.2015.10078

Turner, T. N., Hormozdiari, F., Duyzend, M. H., McClymont, S. A., Hook, P. W., Iossifov, I., . . . Eichler, E. E. (2016). Genome Sequencing of Autism-Affected Families Reveals Disruption of Putative Noncoding Regulatory DNA. *Am J Hum Genet, 98*(1), 58-74. doi: 10.1016/j.ajhg.2015.11.023

van El, C. G., Cornel, M. C., Borry, P., Hastings, R. J., Fellmann, F., Hodgson, S. V.,...Professional Policy, C. (2013). Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. *European Journal of Human Genetics, 21*(Suppl 1), S1-5.

Walker, S., & Scherer, S. W. (2013). Identification of candidate intergenic risk loci in autism spectrum disorder. *BMC Genomics, 14*, 499. doi: 10.1186/1471-2164-14-499

Wetterstrand, K. A. (2014). DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP), from http://www.genome.gov/sequencingcosts. Accessed [January 14, 2015].

Wolf, S. M. (2013). Return of individual research results and incidental findings: facing the challenges of translational science. *Annual Review of Genomics and Human Genetics, 14*, 557-577. doi: 10.1146/annurev-genom-091212-153506

Yuen, R. K., Thiruvahindrapuram, B., Merico, D., Walker, S., Tammimies, K., Hoang, N.,...Scherer, S. W. (2015). Whole-genome sequencing of quartet families with autism spectrum disorder. *Nature Medicine, 21*(2), 185-191. doi: 10.1038/nm.3792

Zawati, M. H., Parry, D., & Knoppers, B. M. (2014). The best interests of the child and the return of results in genetic research: International comparative perspectives. *BMC Medical Ethics, 15*, 72. doi: 10.1186/1472-6939-15-72

Zawati, M. H., Parry, D., Thorogood, A., Nguyen, M. T., Boycott, K. M., Rosenblatt, D., & Knoppers, B. M. (2014). Reporting results from whole-genome and whole-exome sequencing in clinical practice: A proposal for Canada? *Journal of Medical Genetics, 51*(1), 68-70. doi: 10.1136/jmedgenet-2013-101934