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COMMENTARY

Next Generation Sequencing and Health Technology Assessment in Autism Spectrum Disorder

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Abstract

Next generation sequencing (NGS) is a new genome-based technology showing great promise in delineating the genetic basis of autism thus facilitating diagnosis and in the future, the selection of treatment. NGS can have a targeted use as well as provide clinically important findings from medically actionable variants regarding the risk of other disorders. As more is learned about the genomic basis of autism, the clinical utility of the risk information will increase. But at what cost? As the medical management that ensues from primary and secondary (incidental) findings grows, there will be increased pressure on sub-specialists with a longer and more circuitous pathway to care. This will result in higher costs to health care systems and to families. Health technology assessment is needed to measure the additional costs associated with NGS compared to standard care and to weigh these costs against additional health benefits. Well-designed data collection systems should be implemented early in clinical translation of this technology to enable assessment of clinical utility and cost-effectiveness and to generate high quality evidence to inform clinical and budget allocation decision-making.

Key Words: *autism, next generation sequencing, diagnosis, health technology assessment, cost-effectiveness*

Résumé

Le séquençage de nouvelle génération (SNG) est une nouvelle technologie basée sur le génome qui promet beaucoup pour délimiter la base génétique de l'autisme, facilitant ainsi le diagnostic et à l'avenir, le choix du traitement. Le SNG peut avoir une utilisation ciblée et procurer d'importants résultats cliniques de variantes médicalement actionnables à l'égard du risque d'autres troubles. À mesure que nous en apprenons davantage sur la base génomique de l'autisme, l'utilité clinique de l'information sur le risque va s'accroître. Mais à quel prix? Comme la prise en charge médicale qui suit les découvertes primaires et secondaires (connexes) s'intensifie, plus de pression s'exercera sur les surspécialistes qui ont une trajectoire de soins plus longue et indirecte. Il en résultera des coûts plus élevés pour les systèmes de santé et les familles. L'évaluation de la technologie de la santé est nécessaire pour mesurer les frais additionnels associés au SNG comparativement aux soins standards et pour mettre ces frais en balance contre les avantages additionnels pour la santé. Des systèmes de collecte de données bien conçus devraient être mis en œuvre au début de la traduction clinique de cette technologie pour permettre l'évaluation de l'utilité clinique et de la rentabilité, et pour produire des données probantes de grande qualité afin d'éclairer la prise de décisions cliniques et l'allocation budgétaire.

Mots clés**:** *autisme, séquençage de nouvelle génération, diagnostic, évaluation de la technologie de la santé, rentabilité*

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Autism Spectrum Disorder (ASD) is a condition that spurs active debates regarding the optimal method for screening children, which tools should be used for diagnosis and by whom, and which treatments should be initiated and when. Despite disagreements regarding assessment and treatment strategies, there is converging evidence that the earlier a diagnosis is made and treatment – typically a behavioural intervention -- can be applied, the better the short- and long-term outcomes for the child (Perry et al., 2008; Reichow, Barton, Boyd, & Hume, 2012; Virues-Ortega, 2010; Weitlauf et al., 2014). This commentary will introduce the principles of health technology assessment and present its role in evaluating novel genome-based technologies for the diagnosis of ASD.

Genomics and autism

In recent years research into the genomic basis of ASD has uncovered rare variants that explain approximately 20% of susceptibility for ASD (Scherer & Dawson, 2011). As the condition is highly heritable, it is hypothesized that there may be hundreds of genes implicated in the cause of this neurodevelopmental condition (Egger et al., 2014; Griswold et al., 2012; Jiang et al., 2013; Scherer & Dawson, 2011). This in turn has triggered research into how these genes are expressed and translated to affect neurocognitive development and function (Chaudhry et al., 2014; Cukier et al., 2014; Leblond et al., 2014; Lee et al., 2013; Merikangas et al., 2014; Pinto et al., 2014; Vaags et al., 2014). The discovery of genomic involvement in the etiology of ASD has made this condition a strong candidate for genome-based diagnostic testing, including chromosomal microarrays and next generation sequencing (NGS), comprised of whole exome sequencing and whole genome sequencing.

Indeed, microarray testing that examines gross chromosomal structural abnormalities is now considered standard practice in ASD diagnosis (Anagnostou et al., 2014). Microarrays can detect a variety of copy number variants which are associated with ASD and other neurodevelopmental disorders (Carter & Scherer, 2013). In contrast, NGS detects mutations in the sequence of genes coding for proteins that may be present in children with ASD and absent in others (Jiang, et al., 2013). The use of microarrays, NGS and more traditional single-gene genetic tests can also be useful for ruling out ASD or other conditions (Carter & Scherer, 2013). While research into the genomic basis of ASD continues, a positive result on a genetic test does not alone confer a diagnosis, nor does it reveal information about cognitive function, language skills, adaptive or social interaction ability. Assessment tools such as the Autism Diagnostic Observation Schedule are still required to render a complete diagnosis and fully understand a child's particular deficits (Lai, Lombardo, & Baron-Cohen, 2014; Ozonoff, Goodlin-Jones, & Solomon, 2005).

Cost-effectiveness of genome-based testing

This raises the question of the clinical utility of genome-based diagnostic testing in ASD and whether it adds value for the money invested in it by health care systems, health insurance plans, institutions and families. The field of health technology assessment (HTA) is one that examines the social, legal, ethical and economic consequences of emerging technologies (Canadian Agency for Drugs and Technologies in Health, 2006). Technologies can include new screening interventions, diagnostic tests, medical treatments, or health or educational programs or services. A centrepiece of HTA is a cost-effectiveness analysis which examines the additional costs associated with a new technology compared to standard care and weighs those costs against the additional benefits. The type of health benefits that are measured depend on whether the technology is for screening, diagnosis or treatment. Benefits such as rate of identification of high-risk patients, true ASD cases identified and improved social skills are examples of outcomes for novel ASD screening, diagnostic or treatment interventions, respectively. There are also universal outcome measures, such as quality-adjusted life years, which consider additional years of life that accrue within a target population as a result of a new technology and adjust the added life years by changes in the quality of life of these patients, who may be better or worse off as a result of the technology (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005).

Clinical translation and the costs of next generation sequencing

As more is learned about the genomic basis of ASD and how it translates into neurodevelopment, the clinical utility of the risk information from NGS will increase. Furthermore, while NGS may be applied in a targeted fashion to aid diagnosis in patients deemed high risk for ASD, a major potential benefit of NGS lies in its ability to provide secondary clinically important findings from medically actionable variants regarding the risk of other related or unrelated disorders, allowing secondary prevention or early treatment for those disorders (Wright et al., 2011). It may also generate incidental findings of unknown or not-yet-known significance (Bennette, Gallego, Burke, Jarvik, & Veenstra, 2014). Thus the potential benefits of NGS testing cross multiple clinical sub-disciplines.

While the potential benefits of the application of NGS to the diagnosis of ASD are apparent, one must ask at what cost? The start-up costs for NGS technologies are substantial. These include:

- Equipment and depreciation
- Materials, reagents and supplies
- Laboratory space and overhead

- Laboratory personnel and training
- Bioinformatics expertise and training
- Bioinformatics software development, implementation and updating
- Data storage and management
- Clinical interpretation expertise

The US National Human Genome Research Institute (NHGRI) Genome Sequencing Program has been tracking the costs of genome sequencing. Their figures demonstrate a dramatic reduction in costs from US $95.3 million in September 2001 to US $4,905 in July 2014 per genome sequenced (Wetterstrand, 2014). These estimates can be misinterpreted by individuals arguing in favour of adoption. The NHGRI has been forthright about the items *not* included in these costs, such as quality assessment of sequencing projects; research and development to improve equipment, software, bioinformatics tools and sequencing processes; management of sequencing projects; informatics equipment; data analysis downstream of initial data processing (e.g., sequence assembly, sequence alignments; identifying variants) and interpretation of results. Nor does the cost estimate include downstream effects such as medical services and consultations, genetic counseling and patient and family productivity costs.

A sharp reduction in whole genome sequencing costs over the last thirteen years has arisen mainly due to improvements in the technology, such as the switch from Sanger sequencing to massively parallel throughput technologies (Wetterstrand, 2014; Wright et al., 2011). Further reductions in the cost per whole genome sequenced would also be expected to occur subsequent to the initial investment as the technology moves from a research application to a clinical platform, with the realization of economies of scale. However, sharp reductions in cost are not synonymous with value for money. One must recognize that as the medical management that arises as a consequence of primary and secondary findings from NGS becomes more complex, there will be an increased demand for services placed on subspecialists, leading to increased wait times and ultimately a lengthier, more circuitous pathway to treatment (Cuccaro et al., 2014; Kohane, Masys, & Altman, 2006). This will result in increased costs to public and private health insurance programs, greater out-of-pocket costs to patients and families, productivity costs to patients and families in the form of time losses from work, school and other activities, and unknown quality of life effects. All of these additional costs must be weighed in addition to sequencing costs against the additional health benefits of a possible earlier diagnosis and treatment of primary and secondary findings from NGS which would not otherwise have occurred.

Performing health technology assessment

While HTA provides a useful framework in which to view these issues, current HTA methods are not well equipped to measure effects of major practice change across multiple disciplines. Accurate data on outcomes and costs of ASD over the short-and long-term are required for both standard care and novel diagnostic approaches that include NGS. Large scale cohort studies such as the Pathways in Autism Spectrum Disorders Study are critical for generating high quality patient-level data (Georgiades et al., 2013). Modeling techniques such as discrete event simulation allow for examining specific questions related to the changes in costs, resource use and health outcomes in the wake of NGS (Zur, Carter, Scherer, & Ungar, 2014). HTA therefore provides essential evidence regarding value for money to health program decision-makers struggling with questions of payment and reimbursement for expensive new technologies.

In addition to delineating costs and outcomes of new technologies compared to standard care, HTA must allow for understanding of how clinical translation will occur and evolve. Early translational practices may change over time with respect to the sites for sequencing, bioinformatics and for clinical interpretation (which may all occur in different locations by different teams), the sub-specialists involved in filtering and interpreting bioinformatics, and most importantly, the actual recommendations that flow from primary and secondary findings (Cuccaro et al., 2014; Green et al., 2013; Schaefer & Mendelsohn, 2013). Changes in these aspects of practice will have significant implications for cost-effectiveness (Caulfield et al., 2013).

Once a decision is made to invest in NGS and offer it to patients, such as in the diagnostic pathway of ASD, the opportunity costs begin to accrue. Essentially the cost of making the "wrong" health investment decision, opportunity costs are the health benefits that are forgone because money was spent on NGS instead of another health program or service. Although difficult to measure, every investment decision is accompanied by opportunity costs that should never surpass the health benefits that flow from investment in the new technology.

Recommendations for enabling translational research

Genome-based diagnostic technologies in ASD are now in the early stages of clinical translation. A number of recommendations are made to ensure that high quality evidence to support clinical decision-making can be produced.

1. Design and implement electronic data collection systems to track all components of costs and downstream health resource use, such as further testing, physician assessments and consultations.

2. Record changes in in medical management policy decisions, such as the use of confirmatory genetic testing and the type of secondary findings that are divulged to families. Link changes in practice to changes in patient outcomes.
3. Establish uniform outcome measures for measuring the health benefits of new technologies. Measure improvement in terms of true clinical endpoints and changes in health status, not changes in volumes of health resources. For example, an increased number of referrals to clinical sub-specialists is not a "good" outcome unless improved health can be demonstrated.
4. Conduct cost-effectiveness analysis that incorporates the full gamut of costs and health resource use over the lifespan and that weighs additional costs against actual health improvements.
5. Perform full health technology assessments that address the social, legal and ethical issues, such as who will have access to this technology? Who will pay for it? Who will benefit? Who won't?

Conclusions

At the same time that clinicians raise concerns over an increasing incidence of autism, knowledge regarding the genomic basis of ASD is growing at an astonishing rate. An understanding of the functions of genes coding for ASD susceptibility can be harnessed to provide an efficient and streamlined diagnosis which in turn may dictate an individualized and highly effective treatment regimen. This process can be greatly aided by thoughtful and well executed translational research involving health technology assessment.

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