Washington State Health Care Authority

FINAL key questions and background

Genomic micro-array and whole exome sequencing

Background

Chromosomes, the genetic structures of a cell, are constructed of deoxyribose nucleic acid (DNA) and the proteins and other elements that protect, regulate, and package the DNA. Humans normally have 23 pairs of chromosomes, with half inherited from each parent. During cell replication, chromosomes are sometimes lost or gained, or broken and rearranged. Rearrangements vary in size and complexity, and may be balanced, with no loss or gain of genetic material, or unbalanced.

Unbalanced chromosomal rearrangements that are present at conception or that occur during fetal development have profound consequences for the developing fetus, resulting in fetal death, structural defects, genetic diseases, or intellectual impairment.[4] Chromosomal abnormalities occur in 43.8 per 10,000 births that survive to 20 weeks gestation or later.[5] Trisomies 21, 18, and 13; 45, X, and other sex chromosome abnormalities account for most abnormalities. Excluding these, the prevalence of more rare abnormalities is 7.4 per 10,000 births.[5] Small pathological duplications or deletions occur in 1 of 270 pregnancies.[6] Studies examining the prevalence of chromosomal abnormalities have focused on the prenatal period,[5] the prevalence at birth,[7] or the prevalence among individuals with specific structural defects[8] or developmental disabilities.[9]

The number of living children or adults with a chromosomal abnormality is unknown. Although the life expectancy for individuals with a chromosomal abnormality may be significantly shortened by birth defects and other conditions, the life span of affected individuals has increased in recent years

Policy context

This health technology assessment (HTA) will review the efficacy, cost, and potential harms in the use of genomic microarrays (GAs) or whole exome sequencing (WES) to identify chromosomal abnormalities, including aneuploidies, rearrangements, and copy number variants for the diagnosis and management of children with autism, intellectual disability, birth defects, or undiagnosed genetic disease. When present at conception or acquired during prenatal development, chromosomal abnormalities can cause genetic diseases, congenital structural defects, or developmental disabilities.[1, 2] GAs or WES can identify smaller rearrangements and copy number variants than karyotype or fluorescent in-situ hybridization (FISH) analysis.[3]

Proposed scope

Population: Children and fetuses diagnosed with or suspected of having congenital defects, autism, intellectual disability or developmental disability.

For question 1 only: Populations not at increased risk of chromosomal rearrangements, including unselected prenatal or newborn populations.

Interventions: Genomic micro-array testing and whole exome sequencing.

Comparators:

Questions 1 – 2: Are descriptive.

Question 3: Management before and after diagnosis; management of similarly affected undiagnosed children.

Question 4: No genetic diagnostic testing OR genetic diagnostic testing did not include GA or WES.

Outcomes:

1. Earlier diagnosis
2. Mortality during infancy or childhood
3. Development of co-morbidities
4. Functional achievement
5. Medical or educational interventions

Time period: 2000 to 1017

Settings: Clinical genetic laboratories, medical genetic clinics, general and specialty pediatric clinics

Key questions

1. What, if any, safety issues do GA and WES pose beyond those associated with phlebotomy?
2. How often do GA or WES return an informative result?
3. For what types of conditions are GA or WES most useful?
4. Does the diagnosis of a chromosomal disorder change the child's management?
5. Do children with congenital defects, autism, intellectual disability or developmental disability tested with GA or WES have better health outcomes?
6. What is the cost and cost-effectiveness of genetic diagnostic testing for these conditions with GA or WES?

References

1. Schaefer GB, Mendelsohn NJ, Professional P, Guidelines C. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013 May;15(5):399-407.
2. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet. 2010 May 14;86(5):749-64.
3. Patel A, Cheung SW. Application of DNA Microarray to Clinical Diagnostics. In: Li PCH, Sedighi A, Wang L, editors. Microarray Technology Methods and Applications. New York, NY: Humana Press; 2016. p. 111-32.

4. Watson CT, Marques-Bonet T, Sharp AJ, Mefford HC. The genetics of microdeletion and microduplication syndromes: an update. Annu Rev Genomics Hum Genet. 2014;15:215-44.
5. Wellesley D, Dolk H, Boyd PA, Greenlees R, Haeusler M, Nelen V, et al. Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population-based congenital anomaly registers in Europe. Eur J Hum Genet. 2012 May;20(5):521-6.
6. Srebniak MI, Joosten M, Knapen M, Arends LR, Polak M, van Veen S, et al. Frequency of submicroscopic chromosome aberrations in pregnancies without increased risk for structural chromosome aberrations: a systematic review of literature and meta-analysis. Ultrasound Obstet Gynecol. 2017 May 27.
7. Nielsen J, Wohlert M. Chromosome abnormalities found among 34,910 newborn children: results from a 13-year incidence study in Arhus, Denmark. Hum Genet. 1991 May;87(1):81-3.
8. Lammer EJ, Chak JS, Iovannisci DM, Schultz K, Osoegawa K, Yang W, et al. Chromosomal abnormalities among children born with conotruncal cardiac defects. Birth Defects Res A Clin Mol Teratol. 2009 Jan;85(1):30-5.
9. Mundhofir FE, Winarni TI, van Bon BW, Aminah S, Nillesen WM, Merkx G, et al. A cytogenetic study in a large population of intellectually disabled Indonesians. Genet Test Mol Biomarkers. 2012 May;16(5):412-7.

Public comment and response

No comments were received on the draft key questions.