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Background

Rare diseases (RD) posed an important public health issue greatly impacting the lives of patients, their family and caregivers, healthcare systems and society, and constituted a diagnostic challenge as they include a very heterogeneous group of disorders that can affect any system of the body. Rare diseases (RD) are a group of an estimated 6,000 to 9,000 known severe, chronic, degenerative, and often life-threatening conditions defined as diseases affecting less than 1 in 2,000 (5 in 10,000) people in Europe, while World Health Organization has suggested a frequency of less than 6.5 to 10 per 10,000 people to define RD. Majority of the countries defined RD as to be between 0.01% to 0.05% of their population. In Malaysia, RD as stipulated is a life-threatening and/or chronically debilitating rare condition affecting fewer than 1 in 4,000 people, as listed in the Malaysian RD list.

There are more than 6,000 genetic diseases, including single gene disorders, genomic structural defects and copy number variants, which are leading cases of childhood mortality and posed substantial financial implication. Estimated range of total inpatient charges for US pediatric patients related to suspected genetic diseases was US$ 14 to US$ 57 billion (2012), which is 11% to 46% of all pediatric inpatient charges.

Approximately 80% of RD have a genetic origin. However, more than half of these patients remain without a definite diagnosis. Twenty-five percent of patients with a RD are waiting from five to 30 years for confirmatory diagnosis and during this time 40% receive a misdiagnosis. The challenge is contributed by factors namely, genetic heterogeneity, clinical heterogeneity, frequent comorbidity and disease progression which is faster in children, switching the diagnostic odyssey to a race against time. Hence, establishing an early genomic diagnosis is important for timely management and optimal outcomes, particularly in guiding decision such as therapeutic selection and surgery.

Traditionally, establishment of molecular diagnosis was made by serial testing guided by differential diagnosis. Serial testing employs tests including newborn screening panels, metabolic testing, cytogenetics, single gene sequencing and panel sequencing. Conventional molecular testing of patients with genetic disorders has earlier relied primarily on single gene or panel testing or microarrays. However, it was estimated that up to 50% of patients fail to receive a molecular diagnosis after such testing and embark on a diagnostic odyssey which is both slow and costly for health-care providers. Traditional sequential gene sequencing is not expedient in neonates owing to high cost, turnaround time and heterogeneity of phenotype at this young age.

WGS and WES have gained interest as they permit comprehensive and timely diagnosis of genetic diseases by allowing concomitant examination of all of most genes in the differential diagnosis. Exome sequencing has increasingly available following improvements in massively parallel sequencing and bioinformatics tools for data analysis, which have lowered the cost and decreased the turnaround time. Approximately 95% of the exome can be sequenced with currently available techniques. WES which is the targeted sequencing of the subset of the human genome that codes for proteins, helps to resolve undiagnosed genetic conditions, improves the diagnostic yield, guide treatment decision and the management of patients. Genome sequencing identified and analysed the sequence of all coding and

non-coding nuclear DNA, thus is costlier than exome sequencing due to high cost of data analysis. However, the diagnostic utility (20% to 30%) is almost similar with WES. Besides, although genome sequencing can identify variants outside of the coding regions, determination of pathogenicity of these variants is often not possible.

According to the requestor, to date there are more than 9,000 RD; which often comprise of serious multisystem disease that assume a disproportionate amount of healthcare resources. Genetic conditions incur higher direct heal-care costs (3.5 to 8.3 times higher per patient) and resource use. WES could transform the field of genetic disease diagnostics with rapid, high-throughput, which is needed to end the diagnostic odyssey and improve disease management in these patients. However, currently WES is not available in the MOH facilities. Hence, this necessitates the review which is conducted following the request by Clinical Geneticist from the Genetic Unit, Hospital Pulau Pinang to assess the evidence on WES to be used in diagnosing children with suspected genetic disease

Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of WES to be used in diagnosing children with suspected genetic disease.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to April 2024), EBM Reviews-Cochrane Central Register of Controlled Trials (April 2024), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2024), EBM Reviews-Health Technology Assessment 1st Quarter 2024), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2024). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 31 March 2024. Additional articles were identified from reviewing the references of retrieved articles. Among the tools used to assess the risk of bias and methodological quality of the articles retrieved is the Cochrane ROBIS risk of bias tool, ROB-2 tool and CASP checklist. All full text articles were then graded based on guidelines from the US/Canadian Preventive Services Task Force.

Results and conclusion

A total of 21 studies were included in this review. There were fourteen studies retrieved on the effectiveness of WES as diagnostic option for children with suspected genetic disease, of which five studies were on infant. The fourteen studies were comprised of two SR, one scoping review, one RCT, nine cohort studies and one case series. Two studies retrieved were on safety (qualitative studies) and another five studies were on cost-effectiveness, as well as one HTA report on WES as diagnostic option for children with suspected genetic disease. The studies were originated from US, Australia, Taiwan, Hong Kong, France, Brazil, Germany and UK. The included SR reviewed evidences from multiple countries, mainly from US and Europe. Total participants

enrolled in this review were 21,937. Study sample size varied from 29 to 500 patients.

The 21 included studies investigated the use of WES or rapid WES in children with a variety of suspected genetic conditions, the most common being developmental abnormality or delay, or neurodevelopmental disorders, with six studies investigating WES or rapid WES exclusively in newborns, and two studies investigating impact of WES among caregivers. The WES conducted varies from proband to trio in the included studies. The longest follow up reported was up to 33 months.

Effectiveness

Based on the above review, there was fair level of evidences on WES to be used in diagnosing children including infant with suspected genetic disease.

WES including rapid WES showed beneficial effect in diagnostic yield and clinical utility (change in clinical management) in diagnosing children including infant with suspected genetic disorder. WES appeared better in terms of providing diagnosis rate to patients and relatives; and the benefit of diagnosis, namely impact on clinical management to patients and relatives, than standard care.

The WES was carried out as standard WES or rapid WES, either singleton (proband) or trio; in a variety of genetic conditions in clinical practice; from children with neurodevelopmental disorders, congenital anomalies, developmental delay, intellectual disability, undiagnosed developmental abnormality, medical condition requiring rapid diagnosis, cases with suspected monogenic disease, symptomatic patients with rare disease or ill infants; commonly being neurological or neurodevelopmental disorder.

Diagnostic yield ranged from 31.6% to 52.0%, and from 36.7% to 57.5% following WES in children and infants with suspected genetic disease, respectively. Mean turn around time was 40 days (range 25 to 100 days).

Following the use of rapid WES, diagnostic yield ranged from 20% to 52.5% in critically ill infants. Time to report ranged from 5.3 to 16 days.

Impact on clinical management ranged from 26% to 52% for children or infant with suspected genetic disease following use of WES, and ranged from 57% to 88% following rapid WES in critically ill infant or patients beyond infancy.

Safety

In terms of safety, WES Constituent Device was registered as Class II medical device by USFDA. The WES constituent device consists of reagents, instrumentation, software and instructions. There is no psychosocial impact upon receiving VUS on caregivers following WES, with most had a good understanding and the result had no impact on their perception of their child's condition. WES test results, evoked relief as well as worries, identified advantages and disadvantages,

irrespective of the type of result among parents with children whom underwent WES**.**

Cost-effectiveness

In terms of cost-effectiveness, evidence demonstrated that pathways with earlier WES testing were more likely to be cost savings compared to pathways that used WES later in the testing pathway or used WES as a last-resort strategy.Cost estimates for a single test ranged from $555 to $5,169 for WES and from $1,906 to $24,810 for WGS. Cost estimates for a trio ranged from £2,658 ($3,825) to £6,466 ($9,304).

CEA conducted in Australia from healthcare system perspective found using WES to replace most investigations (as a first line) results in a savings per additional diagnosis of AU$2,182 (US$1,702). WES as a first-line test replacing most investigations is dominant. Another CEA in Australia found if WES performed at initial tertiary presentation, the resulted incremental cost savings was A$9020 (US$6838) per additional diagnosis compared with standard diagnostic pathway. However, adding WES to the standard diagnostic pathway does not offer a cost savings, but incurs an additional cost of A$5760 (US$4371) per diagnosis.

Another CEA done in UK from NHS perspective found if WES was introduced later in the testing pathway, the ICER per additional positive genetic diagnosis was £3,171; while if the test used as a near first-line test, the ICER per additional genetic diagnosis was £2,201, compared to the usual testing approach. Sensitivity analyses showed that the largest driver of cost was the cost of the genetic testing, including cost of the exome sequencing and the associated bioinformatics analysis.

Cost analysis in a German cohort of children with NDD/epilepsy found genetic examinations had the highest cost savings potential amounting to 302,947.07€ (90.2%) out of 335,837.49€ [a total of 687,168.02€ was spent on genetic diagnostics]. This corresponds to total savable cost of 3,025.56€ per individual, compared to saving of 197.33€ for cMRI examinations and 98.98€ for metabolic testing in this cohort.

Economic implication

A cost calculation was conducted to estimate the potential cost implication should WES be integrated earlier in the diagnostic pathway for patients with suspected genetic diseases. It involves four scenario analyses which offer WES or CMA either as the first-tier or second-tier test. All patients were assumed not to undergo any prior genetic testing upon presentation at the genetic clinic, and beyond these two tests, the costs for any further testing were not considered. In a population without a clear differential diagnosis, as a first-test, the number of patients with positive results from WES was almost quadruple the number achieved with CMA, at a cost per diagnosis less than a quarter of the cost per diagnosis estimated for CMA. In all scenarios, integrating WES as the first-tier test have resulted in a lower cost per diagnosis as well as cost per patient. Even when a higher test cost for WES was applied, a similar trend was observed. This may indicate that the diagnostic yield of a genetic test plays a significant role in affecting the cost per diagnosis or the cost per patient.

Organizational

In terms of organizational, WES is conducted by laboratories that are accredited by the Clinical and Laboratory Improvement Act (CLIA) to conduct high complexity testing. This test is commonly only conducted in laboratories associated with large, tertiary medical centers or commercial genetics laboratories due to the equipment and software involved (particularly the bioinformatics platform).

Creating reasonable expectations, establishing an understanding of the value and limitations of testing, creating awareness of the potential harms, and allowing the family to make informed choices is a mainstay of informed consent. Elements of counseling should include a three-generation family pedigree; discussion of pathogenic/likely pathogenic results, benign results, and variants of uncertain significance; detection of misattributed paternity or consanguinity, and secondary findings unrelated to the reason for testing.

The ACMG 2021 guideline recommended ES and GS as a first-tier or second-tier test for patients with one or more congenital anomalies prior to one year of age, or for patients with Developmental Disorder/Intellectual Disability with onset prior to 18 years of age. The EuroGentest and the European Society of Human Genetics (2016) guidelines on the evaluation and validation of next-generation sequencing (NGS) applications for the diagnosis of genetic disorders; highlighted the importance of diagnostic utility, informed consent, information to the patient and clinician, validation and reporting.

In terms of reimbursement, several commercial payers covered WES with specific criteria have to be met by the beneficiaries. Several eligibility criteria have to be met for funding by Medicare (Australia) on WES, which are:-

- If the child is strongly suspected of having a single gene disorder and is aged 10 years or younger.
- The child has a non-informative chromosome microarray (CMA) test. Negative Fragile X testing and urine metabolic screening is also desirable.
- A clinical geneticist has been consulted about the test indications.
- The family has given informed consent using the appropriate consent forms.

The Washington State Health Authority stated that WES is a covered benefit with conditions. The test is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders in a phenotypically affected individual when all of the criteria are met (in the document). Similarly, whole exome or WGS is considered medically necessary by several commercial payers such as Kaiser Permanente, Cigna, Aetna when criteria listed (in the document) are met. Pre- and post-test genetic counseling is required for any individual undergoing whole exome or WGS.

Ethico-legal

In terms of ethico-legal, the Genetic Information Nondiscrimination Act (GINA, 2008) protects the US citizen from discrimination based on their genetic information in both health insurance and employment.