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ARTICLE

Whole-exome sequencing in intellectual disability; cost before and after a diagnosis

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Abstract

Clinical application of whole-exome and whole-genome sequencing (WES and WGS) has led to an increasing interest in how it could drive healthcare decisions. As with any healthcare innovation, implementation of next-generation sequencing in the clinic raises questions on affordability and costing impact for society as a whole. We retrospectively analyzed medical records of 370 patients with ID who had undergone WES at various stages of their diagnostic trajectory. We collected all medical interventions performed on these patients at the University Medical Center Utrecht (UMCU), Utrecht, the Netherlands. We categorized the patients according to their WES-based preliminary diagnosis ("yes", "no", and "uncertain"), and assessed the per-patient healthcare activities and corresponding costs before (pre) and after (post) genetic diagnosis. The WES-specific diagnostic yield among the 370 patients was 35% (128 patients). Pre-WES costs were €7.225 on average. Highest average costs were observed for laboratory-based tests, including genetics, followed by consults. Compared to pre-WES costs, the post-WES costs were on average 80% lower per patient, irrespective of the WES-based diagnostic outcome. Application of WES results in a considerable reduction of healthcare costs, not just in current settings, but even more so when applied earlier in the diagnostic trajectory (genetics-first). In such context, WES may replace less cost-effective traditional technologies without compromising the diagnostic yield. Moreover, WES appears to harbor an intrinsic "end-of-trajectory" effect; regardless of the diagnosis, downstream medical interventions decrease substantially in both number and costs.

Introduction

Clinical implementation of next-generation sequencing (NGS) technologies has greatly impacted the field of medical genetics. In particular, whole-exome sequencing (WES) has increased diagnostic yield across patient groups, decreased the time-to-diagnosis, and provided more comprehensive diagnoses than traditional technologies [1–4]. As a result, many patients have benefited from the use of WES as a diagnostic tool [5–8].

Despite these successes, there is a considerable number of elements that prohibit WES—or its successor, whole-genome sequencing (WGS)—from being implemented as the standard primary genetic diagnostic tool. Some cite the technical limitations of WES, e.g., its inability to detect copy number variation (CNV) routinely, although solutions have been provided [9]. Also, it has been largely debated if and how clinical genetic centers should deal with the return of (incidental) findings, as well as results from research [10]. Furthermore, the management, accessibility, and security of the resulting information have been extensively debated [11]. While these are all genuine challenges for applying WES in the clinic, it is unlikely that they will remain unresolved, especially since the framework is in place for assessing the analytical and clinical validity, clinical utility, and ethical, legal and societal issues (ACCE) [12]. Therefore, it is now important to consider how genetic testing using NGS impacts

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the rest of the healthcare trajectory. Intuitively, diagnostic yield would be a good representation of the clinical utility component in the ACCE framework—the more patients that receive a diagnosis, the better a genetic test would be. The value of having a diagnosis for an individual patient is unquestionable. However, diagnostic yield in itself cannot be used as the only justification to introduce a new technology. Assessing the quality of genome care entails more than the technology's diagnostic yield. In addition, we should therefore also focus on total costs for the entire patients medical trajectory.

Here, we consider the impact of WES on the entire healthcare trajectory by a detailed measurement of costs before WES and changes in these costs following WES. Cost-effective studies on the implementation of WES and WGS are beginning to emerge, with a total of 34 such studies to date, 29 of which utilized WES [13]. The majority of these studies concluded within the context of specific country or institution that WES could be cost-effective compared to traditional technologies [13]. Recently, two cost-effectiveness studies for WES have been performed in the Netherlands, one of which by us [14, 15]. These studies considered patients with (syndromal forms of) neurological disorders, for whom it was demonstrated that the diagnostic application of WES results in a higher diagnostic yield and could result in considerable savings (up to €5000 per patient) [14, 15]. However, these studies are hard to generalize and the few studies that have performed comprehensive economic evaluation have focused upon small, selected patient populations, and importantly did not include post-WES health care consumption.

Therefore, we performed a study to: (1) validate the results from previous studies in a larger cohort of patients with ID; (2) assess the total costs of the diagnostic trajectory; and (3) evaluate the post-test costs for medical interventions.

Materials and methods

Patient selection

We included 370 patients with ID who had diagnostic trio-WES performed at the Wilhelmina Children Hospital, University Medical Centre Utrecht (UMCU), The Netherlands. Consistent with previously described ESHG recommendations [16], variant analysis and reporting are kept limited and the phenotype is focused upon by using a multistep approach and bioinformatic filtering of variants. Specifically, in-line with the ESHG recommendations, an active search for secondary findings was not performed [17]. Secondary findings that were incidentally uncovered by the filtering pipeline (unsolicited findings) were only reported if the patient chose to receive these findings.

Data collection and preparation

All available data were retrospectively collected from the hospital information systems and patient records. Data comprised all healthcare activities performed at UMC Utrecht, as registered in patient medical records. All data were pseudonymized. The start of data collection was each patient's first visit to the Wilhelmina Children Hospital, UMCU. Data collection for all patients ended on 25 November 2015. All patients underwent WES at various time points within this period.

All health care activities were eventually linked to their unit costs. Unit costs of resource use were derived from the price lists and price table issued by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZA) [18], and the cost-manual of the National Health Care Institute (Zorginstituut Nederland; ZiN) [19]. Costs for WES were excluded, except for the WES-first scenario analyses.

Volumes obtained from the data collection were multiplied with the unit costs and were expressed in mean, median, and range. Patients were thereafter subdivided into different groups according to their molecular diagnosis ("yes", "no", "uncertain") and whether healthcare activities occurred before or after WES. Costs before and after WES for patients receiving a diagnosis were labeled as "yes-pre" and "yes-post". Costs before and after WES for patients not receiving a molecular diagnosis were labeled as "no-pre" and "no-post". Costs for those patients who did not receive a diagnosis due to a variant of unknown significance (VUS) outcome were labeled as "uncertain-pre" and "uncertain-post". To obtain insight in the type of healthcare activities that would be affected by WES, we defined 12 categories (administration, imaging, cardiovascular diagnostics, daycare, genetic tests, other laboratory tests, medication, consultations, surgery, hospitalizations, emergency admissions, and other healthcare use), and performed analyses on these.

Cost analyses

All data were analyzed using the statistic software programme R [20]. For the overall cost analysis of all patients, we set up a retrospective longitudinal cost-of-illness study from a healthcare perspective, i.e., all hospital-related costs were taken into account, without a specific distinction between disease-related and disease-unrelated costs. We calculated both overall and category-specific healthcare costs per patients within the diagnostic categories ("yes", "no", "uncertain").

To assess the impact of WES on post-test healthcare activities, we assessed the costs before and after WES for each of the diagnostic groups. Since there was a substantial difference in the length of patient trajectory before and after

Table 1 Number of patients, total costs, and time before whole-exome sequencing

	$N = 370$			
	Mean	% of total	Median	Range
Time (days)	932		1019	0–1603
Diagnostic (€)	547	3%	369	0–5301
Lab (€)	2192	13%	1532	0–11,345
Daycare(€)	814	5%	211	0–10,866
Consultations (€)	2329	14%	1232	0–18,954
Genetics (€)				
Other (€)	2157	13%	1545	0–13,289
WES (€)	3600	100%	3600	3600–3600
Medication (€)	101	1%	0	0–13,904
Hospitalization (€)	7759	48%	245	0–194,381
Other (€)	447	3%	0	0–98,047
Total (€)	19,946		8734	0–316,860

WES, we corrected for time biases by calculating the costs per day for each patient. In addition, we took only costs directly related to the diagnostic trajectory into account (diagnostic procedures, laboratory investigations, daycare, consultations, and genetics). We divided the group into those patients with WES as a last diagnostic test and those patients for whom WES was used as a first-tier test.

Results

Diagnostic yield

WES-based diagnostics in the 370 patients revealed disease-causing variants in 128 of these individuals (Table 1). The diagnostic yield for WES in previously undiagnosed patients was thus 35%, not comprising diagnoses based on variant-of-unknown-significance (VUS; 41%).

Total costs

The average healthcare cost before WES was €16.346, and including the cost of trio-WES the total mean cost was €19.946 (Table 1). Costs per intervention category varied considerably, with hospitalization accounting for the largest portion of the costs (±48%), followed by genetic and other laboratory tests (±13%) and consultations (±14%). Costs for medication were relatively low. Around 40% of the average costs before WES were geared toward obtaining a diagnosis, i.e., interventions in the categories Diagnostics, Lab, Consultations, and Genetics, €7225.

Costs after WES

The length of follow-up after WES was on average 25% of the period before WES (240 versus 922 days), and the range was relatively wide (0–1603 days in "pre" and 41–587 days in "post"; Table 2). In order to make a valid comparison between the costs for interventions that were performed before and after WES, we subsequently calculated the average per-day-per-patient costs for each intervention category (Table 2). Also, we excluded non-diagnostic costs (Hospitalization, Daycare, Other) from further analyses and divided the total group into those patients receiving WES as first-tier test and those patients with WES at the end of the diagnostic trajectory.

Patients received WES on average after 951, 869, and 986 days for YES ($n = 116$), NO ($n = 76$), and UNCERTAIN ($n = 128$), respectively. On average, the daily healthcare costs after WES for patients receiving WES at the end of their diagnostic trajectory were around 82% lower than healthcare costs before WES (a reduction of €10.06, €8.46, and €9.16 in the "yes", "no", and "uncertain" groups, respectively); Table 2). We observed the largest decrease in the category of laboratory interventions (±90%), followed by the genetics (±86%), and diagnostics categories (±82%). A total of 76 patients did not have any medical activity up to 122 days (4 months) after WES was performed. Although we were aware of their diagnosis (due to the retrospective approach) it was not yet known for these patients at the end of the data collection. Even when we exclude these from our analyses, the reduction in costs after WES is considerable, although the size of the effect is slightly smaller (±76%) (a reduction of €9.13, €8.38, and €7.52 in the "yes", "no", and "uncertain" groups, respectively).

A small subgroup of patients have had WES as a first-tier genetic test, no other genetic test have been performed upfront. This WES was performed on average after 331, 779 and 917 days for YES (n = 12), NO (= 13) and UNCERTAIN (n = 25) respectively. On average, the daily healthcare costs for patients receiving WES as a first-tier diagnostic test were around 58% lower than those before WES (a reduction of €5.54, €9.77, and €1.11, respectively, in the "yes", "no" and "uncertain" groups; Table 2). We again observed the largest decrease in the category of laboratory interventions (±92%).

Discussion

Based on analysis of hospital records of 370 patients with (syndromal forms of) intellectual disability, we provide a first glimpse of the impact of WES on a patient's medical trajectory. We confirm results from previous cost studies,

Table 2 WES at the beginning and end of the diagnostic trajectory; cost per patient per day, pre and post, type of diagnosis

Diagnosis						
	YES_PRE ($n = 116$)	YES_POST ($n = 116$)	NO_PRE ($n = 76$)	NO_POST ($n = 76$)	UNCERTAIN_PRE ($n = 128$)	UNCERTAIN_POST ($n = 128$)
WES at the end of the diagnostic trajectory						
Diagnostic (€)	0.93	0.16	0.55	0.15	0.84	0.07
Lab (€)	4.29	0.4	3.02	0.29	3.01	0.3
Daycare (€)	0.97	0.27	0.87	0.16	1.2	0.26
Consultations (€)	2.8	1.14	2.31	0.72	2.67	0.8
Genetics (€)	3.69	0.65	3.36	0.33	3.29	0.42
Total (€)	12.68	2.62	10.11	1.65	11.01	1.85
	YES_PRE ($n = 12$)	YES_POST ($n = 12$)	NO_PRE ($n = 13$)	NO_POST ($n = 13$)	UNCERTAIN_PRE ($n = 25$)	UNCERTAIN_POST ($n = 25$)
WES as first-tier diagnostic test						
Diagnostic (€)	0.39	0.06	2.29	0.19	0.43	0.29
Lab (€)	3.94	0.3	4.83	0.01	1.21	0.15
Daycare (€)	0.98	0.21	1.97	0.57	0.5	0.54
Consultations (€)	2.82	1.73	3.27	0.9	2.1	1.73
Genetics (€)	0	0.29	0	0.92	0	0.42
Total (€)	8.13	2.59	12.36	2.59	4.24	3.13

showing that WES provides a considerable diagnostic yield in addition to traditional technologies [1–4]. Moreover, we show that average daily healthcare costs after WES are considerably lower than those before WES, regardless of the position in the diagnostic trajectory ("WES-first" or "WES-last") or the diagnostic outcome ("yes", "no", "uncertain"). Whereas these results have to be interpreted with caution due to the low numbers of patients (especially for "WES-first"), they facilitate a realistic assessment of the role of genetic care in future healthcare.

Our outcomes demonstrate large cost ranges when taking all cost categories into account. These ranges are mainly related to the large differences in time and number of hospitalizations for these patients. If hospitalization is excluded from the analyses, as performed when calculating the impact of WES, outcomes have less variability. Median cost outcomes are more closely together indicating the variability in results. Moreover, we have observed large differences in the BEFORE costs of the WES-first outcomes. These differences are mainly due to the low number of patients in each group ($N = 12$, 13, and 25, respectively, in the "yes", "no", and "uncertain" groups) and the relatively large individual differences in specific categories. As indicated, these results therefore need to be interpreted with caution.

More than traditional genetic diagnostic technologies, WES seems to harbor an intrinsic "end-of-trajectory" effect; healthcare costs decrease substantially, both when WES was applied as a last diagnostic test and when WES was used as first-tier test. This effect occurs largely regardless of diagnostic outcome, with one exception; an uncertain diagnosis when WES was used as a first-tier test still leads to relatively high average daily healthcare costs post WES. Still, the results indicate that using WES as a first-tier test may replace some of the traditional (non-genetic) diagnostic tests and may therefore result in a reduction of overall healthcare costs. We recognize that the effect is inflated by consideration of medical activities within UMC Utrecht only. Any medical activity that has been performed outside of UMC Utrecht (either before or after WES) was not taken into consideration. Finally, the post-WES follow-up in this study was much shorter than the pre-WES trajectory (250 versus 922 days), so the longer-term post-WES effects remain thus far not measured. Despite these limitations, the results of this study suggest that WES should be repositioned in the diagnostic trajectory of patients with ID, as it has thus far been applied as a "last resort".

Vissers et al. [21] have previously outlined that substitution of conventional genetic testing by WES in their intellectual disability cohort ($n = 150$) would result in cost saving of €774 per patient. The underlying assumptions were that WES would replace all genetic testing, and that conventional diagnostic tests would only be omitted in case of a conclusive diagnosis. The latter was assessed in interviews with pediatric neurologists who expected that the impact of WES on other diagnostic tools would remain minimal. However, based on the results of this study, one could envision a "genetics-first" scenario in which some of

the conventional costs prevail, but the "end-of-trajectory" effect impacts the downstream medical decisions to some extent. For example, under the assumption that WES replaces all traditional genotyping technologies, other diagnostic interventions, and all other laboratory investigations (€4.896 per patient), the direct effect could be an average cost reduction of €1.296 per patient in our cohort. Moreover, if we assume consistent reductions in the number of consultations, and in daycare as observed post WES in our study (50%) this would lead to a potential and total cost reduction of €2.868 (€6.468 – €3.600). Future prospective studies will likely provide a realistic estimate of the replacement rate.

We obtained a diagnostic yield of 35% among the 370 patients who had been referred for WES—those patients for whom no diagnosis was obtained with traditional technologies. In our study we did not include patients for whom a variant-of-unknown significance was identified into the diagnostic yield. This is done to prevent the over-interpretation of the "yes" and "no" group. We expect that over time the pathogenicity of an increasing number of variants will become clearer, resulting in a decrease in the number of uncertain diagnoses, which will result in a more comprehensive yield for this patient population [22].

Our costing study has a few limitations. At first, in our study, we only considered medical interventions in UMC Utrecht. Our results would benefit from the possibility to take medical interventions in other hospitals into account. However, privacy regulations make it currently impossible to obtain nation-wide data from individuals. Notably, we excluded all patients with no post-WES follow-up from our scenario analyses. Another limitation is the inclusion of patients from only one hospital. Although differences between hospitals in the Netherlands could occur, we believe treatment and diagnostic pathway of these patients are relatively the same between hospitals. A last limitation of this study is the fact that we can only hypothetically demonstrate the possible cost savings. The impact of WGS on health care consumption should be validated in prospective studies.

Finally, outcomes of this research indicate again that collaboration between all different specialists is needed to ensure and improve the cost-efficient implementation of genetics first in the hospital.

Conclusion

Our study confirms that replacing traditional genetic technologies with WES results in cost-effective diagnostics for patients with ID. Moreover, the results indicate that applying WES earlier in the diagnostic trajectory of these patients could decrease overall healthcare costs, not only because of replacement of traditional technologies, but also because of an "end-of-trajectory" effect. Our study thus confirms what was hypothesized in other studies; WES can be a cost-effective diagnostic tool for patients with ID [23–25]. To our knowledge, our study encompasses the largest patient group for which healthcare cost information is available that has been reported thus far.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. Sci Transl Med. 2012;4:138ra78.
2. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. JAMA. 2014;312:1880–7.
3. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. Ann Neurol. 2014;76:473–83.
4. Dillon OJ, Lunke S, Stark Z, et al. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. Eur J Hum Genet. 2018;26:644–51.
5. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. Genet Med. 2015;17:578–86.
6. Wright CF, Fitzgerald TW, Jones WD, et al. Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. Lancet. 2015;385:1305–14.
7. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014;312:1870–9.
8. Fernandez-Marmiesse A, Gouveia S, Couce ML. NGS technologies as a turning point in rare disease research, diagnosis and treatment. Curr Med Chem. 2018;25:404–32.
9. Tan R, Wang Y, Kleinstein SE, et al. An evaluation of copy number variation detection tools from whole-exome sequencing data. Hum Mutat. 2014;35:899–907.
10. Vos S, van Delden JJM, van Diest PJ, Bredenoord AL. Moral duties of genomics researchers: why personalized medicine requires a collective approach. Trends Genet. 2017;33:118–28.
11. Frebourg T. The challenge for the next generation of medical geneticists. Hum Mutat. 2014;35:909–11.
12. Khoury MJ. Genetics and genomics in practice: the continuum from genetic disease to genetic information in health and disease. Genet Med. 2003;5:261–8.

13. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. Genet Med. 2018. Feb 15. doi: 10.1038/gim.2017.247
14. Monroe GR, Frederix GW, Savelberg SM, et al. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. Genet Med. 2016;18:949–56.
15. van Nimwegen KJ, Schieving JH, Willemsen MA, et al. The diagnostic pathway in complex paediatric neurology: a cost analysis. Eur J Paediatr Neurol. 2015;19:233–9.
16. van El CG, Cornel MC, Borry P, et al. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;21(Suppl 1): S1–5.
17. Matthijs G, Souche E, Alders M, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016;24:2–5.
18. https://www.nza.nl/regelgeving/bijlagen/Tarieventabel_DBC_zorgproducten_en_overige_producten_per_1_januari_2016_bijlage_bij_TB_CU_2066_01.
19. Zorgkostenhandleiding ZN https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/overige-publicaties/1602-richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg-bijlagen/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+(verdiepingsmodules).pdf.
20. R Core Team. The R Project for Statistical Computing. Vienna, Austria: R foundation for Statistical Computing. http://www.R-project.org.
21. LELM Vissers, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. Genet Med. 2017;19:1055–63.
22. Posey JE, Harel T, Liu P, et al. Resolution of disease phenotypes resulting from multilocus genomic variation. New Engl J Med. 2017;376:21–31.
23. Sawyer SL, Hartley T, Dyment DA, et al. Utility of whole-exome sequencing for those near the end of the diagnostic odyssey: time to address gaps in care. Clin Genet. 2016;89:275–84.
24. Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. Genet Med. 2016;18:1090–6.
25. Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. Front Pediatr. 2015;3:67.