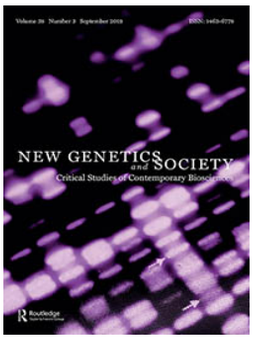

New Genetics and Society

Critical Studies of Contemporary Biosciences

ISSN: 1463-6778 (Print) 1469-9915 (Online) Journal homepage: www.tandfonline.com/journals/cngs20

Cost-effectiveness of exome sequencing: an Italian pilot study on undiagnosed patients

F. Clementina Radio, Massimiliano Ruzzeddu, Andrea Bartuli, Antonio Novelli, Marco Tartaglia & Bruno Dallapiccola

To cite this article: F. Clementina Radio, Massimiliano Ruzzeddu, Andrea Bartuli, Antonio Novelli, Marco Tartaglia & Bruno Dallapiccola (2019) Cost-effectiveness of exome sequencing: an Italian pilot study on undiagnosed patients, New Genetics and Society, 38:3, 249-263, DOI: 10.1080/14636778.2019.1601008

To link to this article: https://doi.org/10.1080/14636778.2019.1601008

Published online: 09 Apr 2019.

New Genetics and Society, 2019
Vol. 38, No. 3, 249–263, https://doi.org/10.1080/14636778.2019.1601008

Cost-effectiveness of exome sequencing: an Italian pilot study on undiagnosed patients

F. Clementina Radio [a*], Massimiliano Ruzzeddu[b], Andrea Bartuli[a], Antonio Novelli[a], Marco Tartaglia[a] and Bruno Dallapiccola[a]

[a]*Genetics and Rare diseases Research Division, Bambino Gesù Children's Hospital, Rome, Italy;* [b]*Political Science Department, University "Niccolò Cusano", Rome, Italy*

Recent advances in genomic sequencing and their implementation in clinical practice are widely recognized as diagnostic milestones, and are influencing considerably medical decision making in term of patients' management. The cost-effectiveness of genomic analysis as first-tier tests has been documented. However, only a few studies have assessed systematically the economic impact of a revised diagnostic trajectory based on exome sequencing in the health system for undiagnosed patients. We report on the assessment of diagnostic costs referred to a large cohort of patients enrolled in the Bambino Gesù Children's Hospital's "Undiagnosed Patients Program", supporting the cost-effectiveness of exome sequencing in a universalistic health care service compared to the traditional multi-step diagnostic workup. Our data provide evidence that revision of health policy to promote genomic sequencing of patients with suspected Mendelian disorders would allow reallocation of resources for rare diseases from diagnostics to patient care. At a social level, diagnosis is crucial to receive the social "sick role" and establish an effective doctor-patient relationship. The application of genomic sequencing as first-tier diagnostic test does improve this process speeding up the diagnosis and management of undiagnosed patients.

Keywords: exome sequencing; undiagnosed patients; rare diseases; diagnosis; health policy; cost-effectiveness; doctor-patient relationship

Introduction

More than 8500 disorders with proven or suspected Mendelian basis (i.e. monogenic disorders) have been reported to date (OMIM Gene Map Statistics 1996). Among these, a large fraction refers to rare diseases, which are defined as conditions having an estimated prevalence of less than 1 in 1500, 1 in 2000 and 1 in 2500 individuals in US, Europe, and Japan, respectively. About half of rare diseases

*Corresponding author. Email: fclementina.radio@opbg.net

affect children, and 80–90% are estimated to have a genetic basis, which can be investigated using genetic/genomic approaches. While rare individually, these diseases affect collectively some hundred millions of people worldwide, and 6–8% of the total European Union (EU) population.

Rare diseases have been considered a public health priority since the 1990s at both EU and Member State level (EURORDIS 2005). The "Orphan Medicinal Product Regulation" (1999) was the first of several legislative texts on rare diseases, followed by the "Communication from the Commission to the European Parliament, the Council, the European economic and social Committee, and the Committee of the Regions on Rare Diseases: Europe's challenges" in 2008, and "Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)". In Italy, the first decree on rare diseases came into force in 2001 (DM 279/2001), enabling access to treatment for these patients and the creation of a national network of expert centers. More recently, the European Commission produced a "Directive on the Application of Patient' Rights in Cross-Border Healthcare (DIRECTIVE 2011/24/EU, 2001)" that has played a key role in the development of European Reference Networks (ERNs), a net of experienced centers sharing knowledge by telehealth and coordinating the application of new technologies to improve the diagnosis and care of patients affected by rare diseases.

Subjects affected by rare diseases and their families share similar needs, suffer diagnostic delay, poorness of expert resources, uncertainty in genetic counseling, and lack of proper clinical management and care. All these issues have to be carefully considered to manage this challenge both at ethical, social, and health policy levels. Effective treatments are missing for most rare diseases, largely because of the current failure in identifying the underlying genetic defect, a prerequisite to the understanding of the underlying molecular and cellular mechanisms. Early diagnosis is also required to favor a prompt use of available treatments to prevent complications and amend the natural history of diseases (Borghesi *et al.* 2017). These difficulties could be overcome in part by the implementation of more effective public health policies directed to improve and accelerate diagnosis. At a social level, a diagnosis is crucial for these patients to receive the acknowledgement of "sick status", similarly to what is experienced by patients affected by "common" diseases (Kerr 2005; Huyard 2009).

Even more neglected are undiagnosed patients. It is estimated that a significant proportion of individuals affected by rare diseases does not reach the diagnosis during life (EURORDIS 2005), and many of them receive an initial misdiagnosis (Gahl *et al.* 2012). Overall, the average diagnostic delay has been estimated as approximately 9 years (range 5–30 years) (EURORDIS 2009; Molster *et al.* 2016). These figures emphasize the time-consuming and ineffective approach of the "classic" diagnostic workup in these patients, and the need of a substantial revision of the diagnostic workflow for rare diseases to design a more successful strategy to improve clinical assessment and laboratory testing in these patients. The so-called diagnostic odyssey, including numerous clinical assessments, invasive and

sometimes harmful procedures, laboratory and instrumental evaluations and expensive and time-consuming molecular analysis, is a common experience in these fragile families. As a consequence, a growing number of undiagnosed patients are facing two main problems: the therapeutic approaches remain undetermined and the social "sick role" cannot be acquired. As Parsons (1951, 436–7) has shown, "sick people" need social acknowledgment of their condition. This is necessary to change expectations about their social performances. In fact, full social recognition of a condition of sickness grants exemption from the individual's social duties (work, family care, etc.). On the other side, the "sick role" legitimates the individual's expectation to receive assistance in a path of care. "Of course the process of recovery may be spontaneous but while the illness lasts he can't 'help it.' This element in the definition of the state of illness is obviously crucial as a bridge to the acceptance of help" (Parsons, p. 437). Said differently, patients affected by rare diseases need to face heavier problems of uncertainty than other patients, especially in the domain of doctor-patient relationship (Calnan 1984). This crucial relationship is characterized by a strong social dimension, which can affect the outcomes of the whole therapeutic process (Balint 1957; Armstrong 1982).

The completion of the "Human Genome Project" in 2001 initiated a rapid expansion of knowledge about our genome allowing accurate assessment of its sequence, topography, and extent of variation. During the last decade, the development of second generation sequencing technology, based on the use of massive parallel sequencing coupled to the implementation of bioinformatics pipelines to manage and analyze large genomic datasets, together with the progressive decrease of sequencing costs, have resulted in a wide application of genomic sequencing as a hypothesis-free, highly informative tool in exploring the molecular causes of Mendelian disorders and understanding the molecular mechanisms underlying their pathogenesis (Lu, Campeau, and Lee 2014; Sawyer *et al.* 2016). Genome and in particular exome sequencing, the latter allowing to scan the entire protein-coding portion of the genome (about 1–2% of entire genome), have shown to be highly effective strategies in the diagnostic setting, and represent useful tools for stratifying patients and improving diagnosis and care (Petrikin *et al.* 2015).

While the technological implementation has run side-by-side with the acquisition of knowledge, the "public genomics policy" has more slowly being implemented. A recent revision of the state-of-the-art has been carried out to evaluate the starting point at EU and Member States level (Mazzucco *et al.* 2017). While several European countries, including Italy, have implemented a national plan for the integration of genomics into the healthcare practice, only a few of them have implemented a structured national policy. To properly design the health policy in the areas of prevention, diagnosis and care of rare diseases, and implement available genomic tools in the National Health System, a detailed analysis has to be produced taking into account both effectiveness (evidence-based) and sustainability

(cost-effectiveness) of the systematic application of these novel technologies in the health care pathway.

The Italian Health System, founded on principles of universal coverage and non-discriminatory access to health care services can be used as a model to unbiasedly assess the cost-effectiveness of the introduction of genomics into clinical practice. The financial resources for the Italian Health System are derived from the use of general taxation, ensuring homogenous access to healthcare basket benefits (the so-called LEA) within the national territory. Due to limited resources, a fine programmatic policy has to be settled on several sides. A major issue concerns the diagnosis's costs, which have a direct impact on sustainability. In principle, the reduction of diagnostic costs could support the reallocation of resources to improve the management and treatment of rare diseases.

We report on a monocentric pilot study aiming at assessing the cost-effectiveness of exome sequencing as a first-tier diagnostic tool for undiagnosed patients compared to the traditional multi-step diagnostic workup currently existing in Italy. Our data demonstrate the effectiveness and sustainability of exome sequencing in a universalistic health care service and provide evidence that revising health policy to promote genomic sequencing of patients with suspected Mendelian disorders would allow reallocation of resources for rare diseases from diagnostics to patient care. Moreover, the application of genomic sequencing as first-tier diagnostic test is expected to improve the social acknowledgement of "sick status" and establish an effective doctor-patient relationship, speeding up the diagnosis and care of undiagnosed patients.

Materials and methods

Patients

Three hundred and twenty-four patients affected by rare and orphan diseases were consecutively enrolled in the OPBG's "Undiagnosed Patients Program", between 2014 and 2017. The program was launched in 2014 to address the needs of undiagnosed patients. Its workflow was based on a multidisciplinary evaluation to guide molecular diagnosis, and promote more effective patient management and care (Figure 1). Each patient enrolled in the program was suspected to have a Mendelian disorder (i.e. a disorder caused by mutation(s) affecting a specific gene) based on clinical presentation (e.g. model of inheritance, complexity of phenotype, and age at onset), and had been remained undiagnosed despite extensive multidisciplinary clinical, instrumental, and genetic evaluations. The clinical assessment of patients, based on criteria shared by experienced medical geneticists, dysmorphologists, and clinicians of different pediatric specialties, included family history, evaluation of craniofacial appearance, anthropometric measurements, and a detailed multidisciplinary clinical appraisal on a case-to-case basis. A web data form was used to standardize the collection of data after informed consent delivery. Before enrollment in the program, CGH/SNP-array analysis, allowing genome

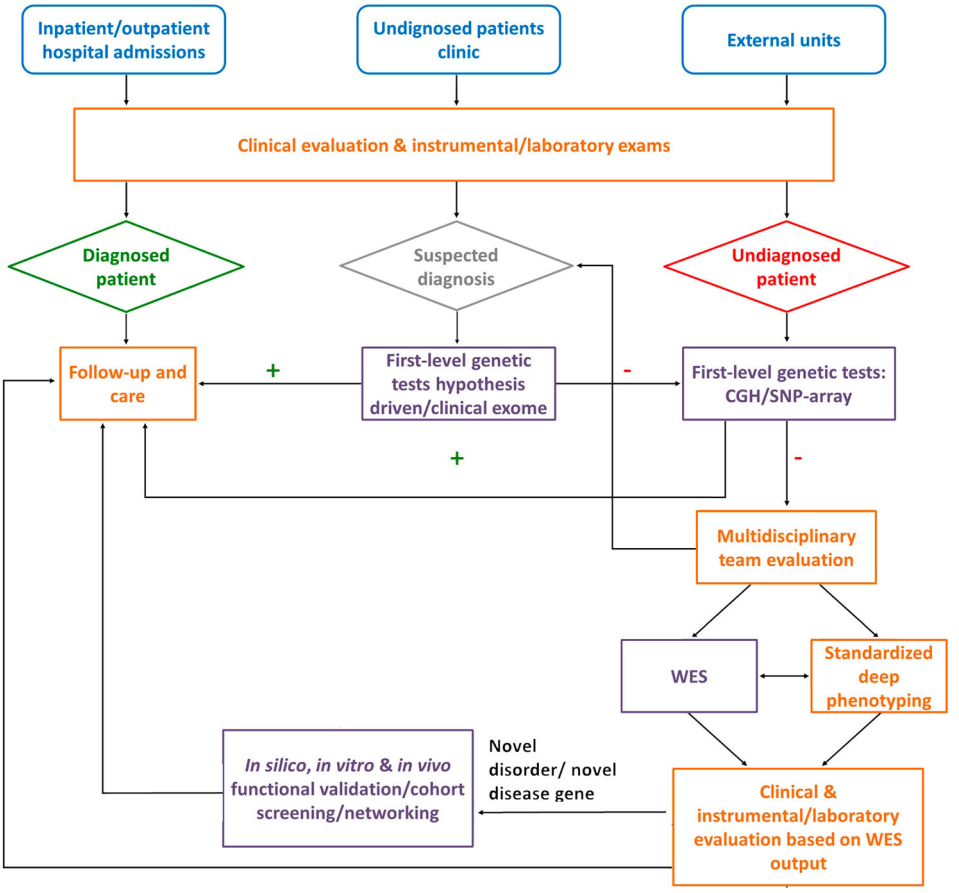

Figure 1. Workflow of the OPBG's "Undiagnosed Patients Program".

scanning of microdeletions and microduplications, had been performed to exclude disorders resulting from chromosomal structural rearrangements. Formal genetic counseling was offered to all families. Written informed consent was obtained from all analyzed cases, including family members. In the frame of multidisciplinary clinical assessment sessions, clinical exome sequencing (i.e. sequencing of the currently known genes already identified to be associated to human disease) were indicated for patients in which a known genetic disorder was suspected, while patients without any conclusive diagnostic hypothesis were considered eligible for whole exome sequencing (WES).

Molecular analyses

Clinical exome analysis was performed according to the manufacture's protocol, using the SeqCap EZ Enrichment kit – Inherited Disease Panel (Roche), and sequenced on an Illumina MiSeq or NextSeq550 platforms. The BaseSpace

pipeline (https://basespace.illumina.com/) and VariantStudio software (http://variantstudio.software.illumina.com/) were used for variant calling and annotation. WES was performed by using Sure Select XT All Exon V5 (Agilent) and Nextera Rapid Capture Exome V1.2 (Illumina) as enrichments kits, and target regions were sequenced on a Illumina HiSeq3000 and NextSeq550 platforms. WES data analysis was performed using an in-house implemented pipeline allowing reads alignments to the reference genome (hg19), and variant calling and annotation, as previously described (Kortüm *et al.* 2015; Chong *et al.* 2016; Flex *et al.* 2016; Bauer *et al.* 2018). Both approaches were performed by experienced molecular geneticists and bioinformaticians with adequate skills for analyzing and interpreting sequencing data. Continuous development and implementation of pipelines for variant annotation, filtering, and prioritization of the collected genomic data made possible to re-analyze the WES data without any need to replicate the experimental workflow. Clinical exome/WES results were reported to the referring clinicians following the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants (Richards *et al.* 2015). Similarly, incidental findings were reported, in accordance with the patient/family request, as stated in the informed consent form, accordingly with the ACMG recommendations for reporting of secondary findings (Green *et al.* 2013; Kalia *et al.* 2017).

Costs

Among the enrolled patients, the complete set of investigations, procedures, and clinical assessments had been made available on a sub-cohort of 211 patients, aged between 1 month and 43 years, with or without a conclusive diagnosis reached by clinical exome or WES analysis. All investigations, procedures and inpatient/outpatient assessments were retrospectively collected and revised by an experienced clinical geneticist (F.C.R.), using the OPBG's informative system. Based on manual curation, exclusively diagnostic evaluations/procedures were retained. Management and therapeutic admissions' costs were not included in the present study as well as the economic impact of the day-by-day management or the financial impact of travel costs place within the framework of the diagnostic odyssey. Costs of investigations were calculated based on the Italian Health System tabs (http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=3662&area=programmazioneSanitariaLea&menu=vuoto). Total costs and yearly costs of diagnostic delay, the latter resulting from the total costs divided by the number of years from the onset of symptoms to the age at the exam, were considered, and minimum, maximum and average costs were calculated for each indicator.

Results

Total average cost of diagnostic procedures for each undiagnosed patient enrolled in the program was calculated to be € 11,572 (range € 160–75,840). As expected,

the total cost showed a direct correlation with the patients' age at enrollment and clinical complexity. The estimated average cost of each year of diagnostic delay (i.e. total cost divided by the number of years from the onset of symptoms to the age at the clinical exome/WES analysis) was € 2146 (range € 48–18,320). Costs were calculated both in patients who underwent clinical exome sequencing or WES analysis, regardless of the patient obtained a definite diagnosis or remained undiagnosed after testing. A schematic representation of cost distribution is shown in Figure 2. No significant difference was observed between patients who reached a diagnosis or remained unsolved after exome analysis, indicating a homogeneous selection of patients and absence of any bias in selecting known nosologic disorders. Differently, total costs and yearly cost of diagnostic delay were found to be reduced in patients analyzed by clinical exome analysis, indicating a more pertinent "traditional" clinical, instrumental and laboratory workup in patients with a diagnostic hypothesis. This finding suggests that the presence of diagnostic handles addresses more precisely both the genetic test and the diagnostic workup (i.e. clinical, instrumental and laboratory assessment). On the contrary, the absence of pathognomonic features does not allow to direct the diagnostic workup accurately, resulting in unnecessary and sometimes harmful assessments and procedures. Remarkably, despite the relatively short period of this pilot study, costs showed an appreciable decreasing temporal trend as a result of the application of this coordinated multidisciplinary workflow (Figure 2, panel f).

Dissection of costs related to clinical assessment (i.e. inpatient/outpatient hospital admissions), instrumental investigations, biochemical/metabolic measurements, and genetic testing documented that genetic analyses accounted for 58% of the total costs (Figure 2, panel g), indicating that a significant reduction of diagnostic costs could be obtained in principle, favoring a more efficient reallocation of resources to improve patients' management.

Discussion

While genetic disorders are individually rare, collectively they affect some hundred millions people worldwide. The burden of genetic diseases in children's hospital admissions document a significant impact of these conditions on pediatric mortality, as it has been estimated that 23% of infant deaths are due to genetically determined disorders (Hoyert *et al.* 2001). Estimates also indicate the relevant contribution of genetic diseases on admission to pediatric intensive care unit, with 70% of these children reported to have partly or wholly genetically determined disorders (FitzPatrick, Skeoch, and Tolmie 1991; Feldkamp *et al.* 2017). Overall, genetic diseases represent the first cause of hospital access for children with life-threatening/complex diseases (McCandless, Brunger, and Cassidy 2004). Among genetic diseases, a significant proportion is represented by rare and undiagnosed disorders. While a subset of patients receives a diagnosis at first evaluation based exclusively on clinical assessment, undiagnosed patients often exhibit non-

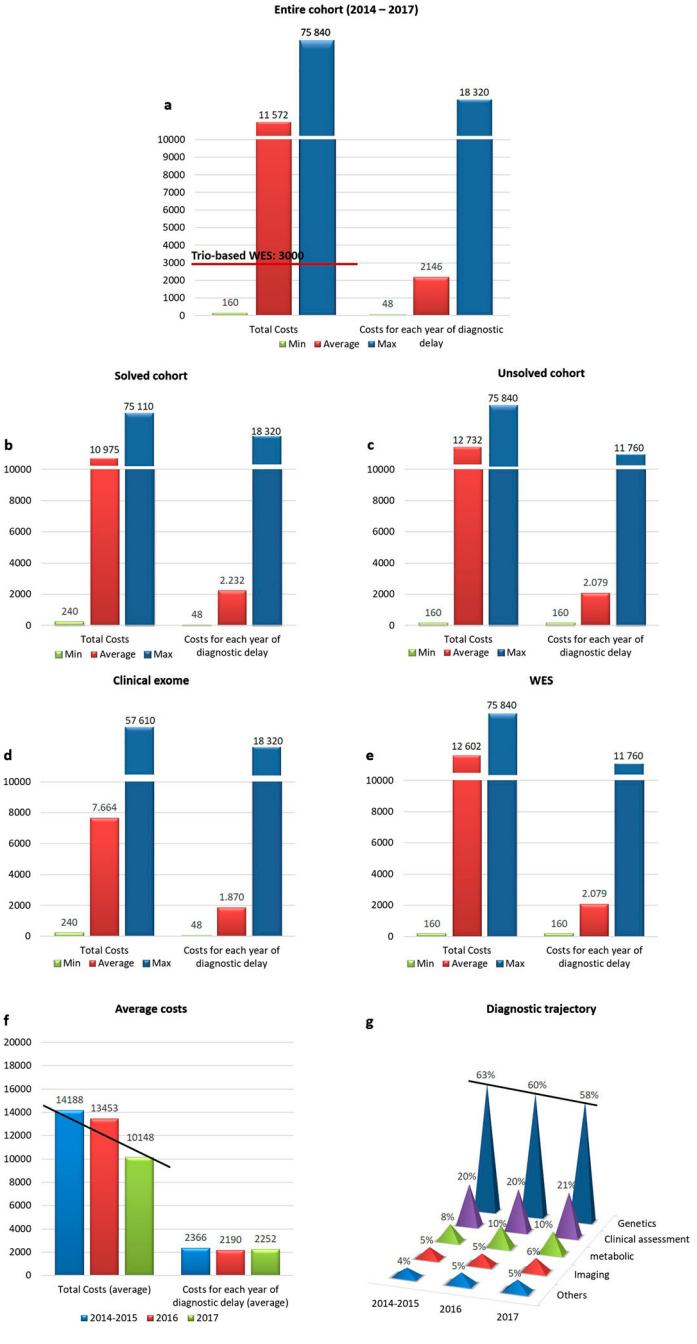

Figure 2. A schematic representation of cost distribution. (a) Costs evaluation in the entire cohort. (b) Costs evaluation in post-exome solved cohort. (c) Costs evaluation in post-exome unsolved cohort. (d) Costs evaluation in patients undergoing clinical exome scan. (e) Costs evaluation in patients undergoing WES analysis. (f) Declining trend during time of total costs in the entire cohort, the cost for each year of diagnostic delay appears stable. (g) Declining trend during time of the impact of genetic analysis on the total amount of diagnostic cost.

specific/non-pathognomonic features or are too young to reach the full expression of the disorder or even are affected by ultra-rare/unique/previously unrecognized conditions. In a subset of these subjects a complex clinical phenotype resulting from the concomitant presence of two diseases due to mutations in two known disease genes may occur. Reassessment during the follow-up might provide insight for diagnosis, even though an overall reduction of the diagnostic rate based exclusively on clinical appraisal at each follow-up has been documented (Shashi *et al.* 2014; Douzgou *et al.* 2016).

During the last decade, new cytogenetic and molecular testing approaches have made available efficient and cost-effective diagnostic tools. In particular, clinical exome and WES have been validated as high-throughput strategies for rare genetically heterogeneous disorders, and are increasingly used in the diagnostic workflow for undiagnosed patients, presenting with a condition of suspected mendelian origin, resulting in a success rates of 25–50% (Petrikin *et al.* 2015; Sawyer *et al.* 2016). Consistently, a diagnostic yield close to 50% has been reached in the ongoing OPBG's "Undiagnosed Patients Program" (manuscript in preparation). Of note, by coupling the power of clinical exome analysis (i.e. *in silico* scan of genes known to be involved in human disease) with the informativeness resulting from clinical/functional validation of genomic variants in candidate disease-genes and the unique opportunity to re-analyze the originally collected sequencing data with an overall considerable reduction of analytic costs, WES is a particular effective and economically sound diagnostic tool. Importantly, data re-analysis of WES originally providing negative results in terms of identification of putative disease causative variant(s) has been documented to provide additional success rate of 10–30% (Nambot *et al.* 2018).

While the implementation of exome sequencing in clinical practice is widely recognized as a diagnostic milestone and its cost-effectiveness as a first-tier test has been documented (Lu, Campeau, and Lee 2014; Valencia *et al.* 2015), only a few studies have systematically assessed the economic impact of its use on the health system. Monroe *et al.* (2016) estimated an average total cost of USD 16,409 per patient, compared with the cost of a trio-based WES at USD 3972 in a cohort of 17 patients. Stark *et al.* (2017) evaluated the diagnostic costs in 40 undiagnosed infants, highlighting an average cost of USD 21,099 per patient. Vissers *et al.* (2017) analyzed 150 children affected by complex neurological disorders and calculated the total cost for the diagnostic workup in € 10,685 (range € 9544–11,909) per patient, compared with the cost of trio-based WES of € 3500.

The OPBG's "Undiagnosed Patients Program" has been launched in 2014 to address the needs of undiagnosed patients. The program workflow is based on a multidisciplinary team evaluation to guide molecular diagnosis, and promote more effective patient management and care (Figure 1). The clinical re-evaluation of enrolled patients directs the laboratory workup towards a first-level hypothesis-driven genetic test (i.e. target re-sequencing or clinical exome, in presence of a suspected diagnosis) or a hypothesis-free genomic scan (i.e. WES, in the absence of

any diagnostic hypothesis). This approach has resulted in a significant increase in the diagnostic yield (first-level genetic tests hypothesis-driven: 70%; WES: 40%, not including an additional 15% of cases with novel disease/candidate genes pending functional/clinical validation) with a reduction of diagnostic delay (average turning back time: 1–6 months). A retrospective cost analysis performed on 211 undiagnosed patients showed an average cost of € 11,572 to reach a diagnosis, compared with the cost of trio-based clinical exome/WES of about € 3000. A similar average cost was calculated for both post-exome solved and unsolved cases, suggesting unbiased patients' enrollment. Of note, a significant declining trend of total cost and cost of genetic analysis was observed throughout the period of the patients' enrollment. This likely reflects the positive impact on costs of the progressive translational use of clinical exome sequencing/WES analysis as an early diagnostic tool (Lu, Campeau, and Lee 2014), even in absence of specific health policy.

The use of WES as first-tier approach in patients with undetermined diseases is predicted to reduce the number of genetic/metabolic testing with consequent cost saving. This analysis has the benefit of assessing all known disease genes, while simultaneously providing a substrate for future reanalysis without a relevant difference in costs compared with clinical exome sequencing approach nonetheless making possible novel disease-gene discovery through clinical/functional validation of candidate disease-genes and speeding up the diagnostic workflow. The sole genetic investigation to be considered preceding WES is CGH/SNP-array to exclude structural rearrangements, which is diagnostic in a substantial proportion of individuals affected by complex disorders. The diagnostic workflow of patients that remain undiagnosed after WES should take into account additional omics approaches (e.g. whole genome sequencing, transcriptome, and methylome analysis), with additional costs to be considered and evaluated during next years in order to define their diagnostic effectiveness and sustainability.

Several additional non-medical costs have to be considered during the life span care of undiagnosed patients. However, a punctual economic evaluation of dedicated time and quality of life in the affected families is not feasible and have to be based on an analysis of the "social" costs. Although it is assumed that in general the cost of care is not modified by WES results, availability of diagnosis is the first step toward a more appropriate management. Even if no cure is available, diagnosis is expected to allow the family to obtain a proper genetic counseling and to engage informed reproductive choice. A recent study in Italy demonstrated that the cost of each undiagnosed patient is superimposable to the cost of a patient affected by two different chronic diseases (i.e. around € 5000) (Spandonaro *et al.* 2015). This cost is expected to increase during time, in particular with the advance in therapeutic approaches (e.g. biological drugs). Reducing diagnostic cost and interrupting the diagnostic odyssey of these patients will make available additional resources for both management and care as well as for research.

Even if the use of clinical exome sequencing/WES analysis as an early diagnostic tool has a positive impact on costs, caution must be exercised in reporting and managing secondary/incidental findings emerging by the systematic use of NGS technologies in clinical practice. In the OPBG's "Undiagnosed Patients Program" cohort, the rate of secondary/incidental findings was less than 2%. Only known pathogenic or expected pathogenic variants in the 56 genes of the ACMG guidelines were considered for reporting, after informed consent collection, even when unrelated to the primary medical reason for testing. No data are available on the possible impact on public health of incorrect management of these findings, principally related with not specialized handling of genetic tests or, more dangerous, consumer-directed testing, and dedicated studies are needed to address this issue. Similarly, a systematic evaluation of the impact of new genomic sequencing technologies on society and possible discriminatory conduct has to be carefully performed. Much of social science is concerned with uncovering sources of heterogeneity within and between populations in the processes that determine life courses. Particular attention should be devoted to psychological and social aspects related to genomic analysis. Families must be informed and make aware about the opportunities and informativeness as well as the limits of genome sequencing applications. However, the systematic application of these technologies is expected to reduce the timing and exhaustiveness of genetic analysis devoted to reach a diagnosis, reducing the uncertain in doctor-patient relationship. When a doctor and a patient meet, a reciprocal acknowledgment is necessary. The patient needs to trust in the doctor's authority and professional skills, while the doctors needs to fully accept the patient as a "sick person" which needs to be treated and care. As suggested by May *et al.* (2004), between the two actors a negotiation is taking place, which leads to a shared representation of the illness and the therapeutic path to be undertaken. Habitually this negotiation process matches the doctor's leading position – in terms of technical competences, and official decision power – with the patient's need for healings, information and availability to follow doctor's instructions. It has been stressed that "In other medical settings, where the relationship is more personalized or the contact between doctor and patient is more prolonged, the doctor-patient relationship has been portrayed as a form of negotiation". For example, "in a study on tuberculosis patients who were inmates of a sanitorium it is shown how the relationship is characterized by the lack of information given to patients by doctors and by a process of bargaining over the timetable" (Calnan 1984). When a doctor meets undiagnosed patients, this relationship reveals to be quite biased: the lack information might limit both the doctor's acknowledgment of the patient and patient's trust in doctors and his/her hope for a full recover (Ducournau *et al.* 2013). In this context, besides the symptoms that they cause, rare diseases are a powerful stress factor which can jeopardize patients' recover and/or their life quality (Gundersen 2011). The application of clinical exome sequencing/WES analysis as an early diagnostic tool is expected to have consequent positive impact in medical management and care as well as

reduce the stress due to the lack of meaning related to the "sick status" (Gundersen 2011).

In conclusion, the present study supports the cost-effectiveness of clinical exome sequencing and WES analysis as first-tier diagnostic tests in the routine diagnostic workup of patients with suspected Mendelian disorders in specialized services, proving effectiveness and sustainability of this approach in a universalistic health care system, with a direct impact on driving a "public genomics policy". The present economic evaluation is dynamic and expected to change over time, depending on technical variations and societal and economic issues. In particular, it seems possible to anticipate an additional reduction of genomic sequencing costs and no price increase. These data suggest the current need of rethinking the diagnostic strategies for undiagnosed patients, based on cost-effectiveness analysis and social/sociological value.

Acknowledgement

Authors wish to thank all colleagues that are contributing to the OPBG's "Undiagnosed Patients Program", and all participating undiagnosed patients and their families.

Funding

This study was supported in part by grants from Fondazione Bambino Gesù (Vite Coraggiose, to M.T. and B.D.), and Italian Ministry of Health (Ricerca Corrente 2016, 2017 and 2018, to A.N. and M.T.).

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

F. Clementina Radio http://orcid.org/0000-0003-1993-8018

References

Armstrong, D. 1982. "The Doctor-Patient Relationship: 1930–80." In *The Problem of Medical Knowledge*, edited by A. Wright, and A. Treacher. Edinburgh: Edinburgh University Press.

Balint, M. 1957. *The Doctor, his Patient, and the Illness*. London: Pitman.

Bauer, C. K., P. Calligari, F. C. Radio, V. Caputo, M. L. Dentici, N. Falah, F. High, et al. 2018. "Mutations in KCNK4 that Affect Gating Cause a Recognizable Neurodevelopmental Syndrome." *The American Journal of Human Genetics* 103 (4): 621–630. doi:10.1016/j.ajhg.2018.09.001.

Borghesi, A., M. A. Mencarelli, L. Memo, G. B. Ferrero, A. Bartuli, M. Genuardi, M. Stronati, et al. 2017. "Intersociety Policy Statement on the use of Whole-Exome Sequencing in the Critically ill Newborn Infant." *Italian Journal of Pediatrics* 43 (1): 100. doi:10.1186/s13052-017-0418-0.

Calnan, M. 1984. "Clinical Uncertainty: Is it a Problem in the Doctor-Patient Relationship?." *Sociology of Health and Illness* 6 (1): 74–85. doi.org/10.1111/1467-9566.ep10777367.

Chong, J. X., V. Caputo, I. G. Phelps, L. Stella, L. Worgan, J. C. Dempsey, A. Nguyen, et al. 2016. "Recessive Inactivating Mutations in TBCK, Encoding a Rab GTPase-Activating Protein, Cause Severe Infantile Syndromic Encephalopathy." *The American Journal of Human Genetics* 98 (4): 772–781. doi:10.1016/j.ajhg.2016.01.016.

Communication from the commission to the European Parliament, the council, the European economic and social Committee and the Committee of the regions on Rare Diseases: Europe's challenges. 2008. https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf.

Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). 2009. http://ec.europa.eu/chafea/documents/health/prague-rd-council-recommendation_en.pdf.

Decreto ministeriale recante "Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie" ai sensi dell'articolo 5, comma 1, lettera b) del decreto legislativo 29 aprile 1998, n. 124. (DM 279/2001). 2001. http://www.salute.gov.it/imgs/C_17_normativa_194_allegato.pdf.

Directive on the Application of Patient' Rights in Cross-Border Healthcare (DIRECTIVE 2011/24/EU). 2001. http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1396269481289&uri=CELEX:32011L0024.

Douzgou, S., E. Chervinsky, Y. Gyftodimou, S. Kitsiou-Tzeli, S. Shalev, E. Kanavakis, D. Donnai, and J. Clayton-Smith. 2016. "Dysmorphology Services: A Snapshot of Current Practices and a Vision for the Future." *Clinical Genetics* 89 (1): 27–33. doi:10.1111/cge.12571.

Ducournau, P., P. Gourraud, E. Rial-Sebbag, A. Cambon-Thomsen, and A. Bulle. 2013. "Direct-to-consumer Health Genetic Testing Services: What Commercial Strategies for Which Socio-Ethical Issues?" *Health Sociology Review* 22 (1): 75–87. doi.org/10.5172/hesr.2013.22.1.75.

EURORDIS. 2005. Rare Diseases: Understanding this Public Health Priority.

EURORDIS. 2009. The Voice of 12,000 Patients.

Feldkamp, M. L., J. C. Carey, J. L. B. Byrne, S. Krikov, and L. D. Botto. 2017. "Etiology and Clinical Presentation of Birth Defects: Population Based Study." *BMJ* 357: j2249. doi:10.1136/bmj.j2249.

FitzPatrick, D. R., C. H. Skeoch, and J. L. Tolmie. 1991. "Genetic Aspects of Admissions to a Paediatric Intensive Care Unit." *Archives of Disease in Childhood* 66 (5): 639–641.

Flex, E., M. Niceta, S. Cecchetti, I. Thiffault, M. G. Au, A. Capuano, E. Piermarini, et al. 2016. "Biallelic Mutations in TBCD, Encoding the Tubulin Folding Cofactor D, Perturb Microtubule Dynamics and Cause Early-Onset Encephalopathy." *The American Journal of Human Genetics* 99 (4): 962–973. doi:10.1016/j.ajhg.2016.08.003.

Gahl, W. A., T. C. Markello, C. Toro, K. F. Fajardo, M. Sincan, F. Gill, H. Carlson-Donohoe, et al. 2012. "The National Institutes of Health Undiagnosed Diseases Program: Insights into Rare Diseases." *Genetics in Medicine* 14 (1): 51–59. doi:10.1038/gim.0b013e318232a005.

Green, R. C., J. S. Berg, W. W. Grody, S. S. Kalia, B. R. Korf, C. L. Martin, A. L. McGuire, et al. 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.

Gundersen, T. 2011. "'One Wants to Know What a Chromosome is': The Internet as a Coping Resource When Adjusting to Life Parenting a Child with a Rare Genetic Disorder." *Sociology of Health & Illness* 33 (1): 81–95. doi:10.1111/j.1467-9566.2010.01277.x.

Hoyert, D. L., M. A. Freedman, D. M. Strobino, and B. Guyer. 2001. "Annual Summary of Vital Statistics: 2000." *Pediatrics* 108 (6): 1241–1255.

Huyard, C. 2009. "How Did Uncommon Disorders Become 'Rare Diseases'? History of a Boundary Object." *Sociology of Health & Illness* 31 (4): 463–477. doi:10.1111/j.1467-9566.2008.01143.x.

Kalia, S. S., K. Adelman, S. J. Bale, W. K. Chung, C. Eng, J. P. Evans, G. E. Herman, et al. 2017. "Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): A Policy Statement of the American College of

Medical Genetics and Genomics." *Genetics in Medicine* 19 (2): 249–255. doi:10.1038/gim.2016.190.

Kerr, A. 2005. "Understanding Genetic Disease in a Socio- Historical Context: A Case Study of Cystic Fibrosis." *Sociology of Health & Illness* 27 (7): 873–896. doi:10.1111/j.1467-9566.2005.00462.x.

Kortüm, F., V. Caputo, C. K. Bauer, L. Stella, A. Ciolfi, M. Alawi, G. Bocchinfuso, et al. 2015. "Mutations in KCNH1 and ATP6V1B2 Cause Zimmermann-Laband Syndrome." *Nature Genetics* 47 (6): 661–667. doi:10.1038/ng.3282.

Lu, J. T., P. M. Campeau, and B. H. Lee. 2014. "Genotype–Phenotype Correlation — Promiscuity in the Era of Next-Generation Sequencing." *New England Journal of Medicine* 371 (7): 593–596. doi:10.1056/NEJMp1400788.

May, C., G. Allison, A. Chapple, C. Chew-Graham, C. Dixon, L. Gask, R. Graham, A. Rogers, and M. Roland. 2004. "Framing the Doctor-Patient Relationship in Chronic Illness: A Comparative Study of General Practitioners' Accounts." *Sociology of Health & Illness* 26 (2): 135–158. doi:10.1111/j.1467-9566.2004.00384.x.

Mazzucco, W., R. Pastorino, T. Lagerberg, M. Colotto, E. d'Andrea, C. Marotta, C. Marzuillo, et al. 2017. "Current State of Genomic Policies in Healthcare among EU Member States: Results of a Survey of Chief Medical Officers." *European Journal of Public Health* 27 (5): 931–937. doi:10.1093/eurpub/ckw155.

McCandless, S. E., J. W. Brunger, and S. B. Cassidy. 2004. "The Burden of Genetic Disease on Inpatient Care in a Children's Hospital." *The American Journal of Human Genetics* 74 (4): 788. doi:10.1086/381053.

Molster, C., D. Urwin, L. Di Pietro, M. Fookes, D. Petrie, S. van der Laan, and H. Dawkins. 2016. "Survey of Healthcare Experiences of Australian Adults Living with Rare Diseases." *Orphanet Journal of Rare Diseases* 11: 30. doi:10.1186/s13023-016-0409-z.

Monroe, G. R., G. W. Frederix, S. M. Savelberg, T. I. de Vries, K. J. Duran, J. J. van der Smagt, P. A. Terhal, et al. 2016. "Effectiveness of Whole-Exome Sequencing and Costs of the Traditional Diagnostic Trajectory in Children with Intellectual Disability." *Genetics in Medicine* 18 (9): 949–956. doi:10.1038/gim.2015.200.

Nambot, S., J. Thevenon, P. Kuentz, Y. Duffourd, E. Tisserant, A. L. Bruel, A. L. Mosca-Boidron, et al. 2018. "Clinical Whole-Exome Sequencing for the Diagnosis of Rare Disorders with Congenital Anomalies and/or Intellectual Disability: Substantial Interest of Prospective Annual Reanalysis." *Genetics in Medicine* 20 (6): 645–654. doi:10.1038/gim.2017.162.

OMIM (Online Mendelian inheritance in man), Gene Map Statistics. Baltimore: Johns Hopkins University, Center for Medical Genetics, 1996. www.omim.org/statistics/geneMap.

Orphan Medicinal Product Regulation. 1999. http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf.

Parsons, T. 1951. *The Social System*. Glencoe, IL: The Free Press.

Petrikin, J. E., L. K. Willig, L. D. Smith, and S. F. Kingsmore. 2015. "Rapid Whole Genome Sequencing and Precision Neonatology." *Seminars in Perinatology* 39 (8): 623–631. doi:10.1053/j.semperi.2015.09.009.

Richards, S., N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W. W. Grody, et al. 2015. "Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the America College of Medical Genetics and Genomics and the Association for Molecular Pathology." *Genetics in Medicine* 17 (5): 405–423. doi:10.1038/gim.2015.30.

Sawyer, S. L., T. Hartley, D. A. Dyment, C. L. Beaulieu, J. Schwartzentruber, A. Smith, H. M. Bedford, et al. 2016. "Utility of Whole-Exome Sequencing for Those Near the end of the Diagnostic Odyssey: Time to Address Gaps in Care." *Clinical Genetics* 89 (3): 275–284. doi:10.1111/cge.12654.

Shashi, V., A. McConkie-Rosell, B. Rosell, K. Schoch, K. Vellore, M. McDonald, Y. H. Jiang, P. Xie, A. Need, and D. B. Goldstein. 2014. "The Utility of the Traditional Medical Genetics Diagnostic Evaluation in the Context of Next-Generation Sequencing for Undiagnosed Genetic Disorders." *Genetics in Medicine* 16 (2): 176–182. doi:10.1038/gim.2013.99.

Spandonaro, F., M. Mezzanzanica, E. Daina, and C. Zocchetti. 2015. "Laboratorio Malattie Rare: epidemiologia e utilizzazione dei servizi sanitari nel contesto delle Malattie Rare." dissertation, CREA Sanità, Rome.

Stark, Z., D. Schofield, K. Alam, W. Wilson, N. Mupfeki, I. Macciocca, R. Shrestha, S. M. White, and C. Gaff. 2017. "Prospective Comparison of the Cost-Effectiveness of Clinical Whole-Exome Sequencing with That of Usual Care Overwhelmingly Supports Early Use and Reimbursement." *Genetics in Medicine* 19 (8): 867–874. doi:10.1038/gim.2016.221.

Valencia, C. A., A. Husami, J. Holle, J. A. Johnson, Y. Qian, A. Mathur, C. Wei, et al. 2015. "Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience." *Frontiers in Pediatrics* 3: 67. doi:10.3389/fped.2015.00067.

Vissers, L. E. L. M., K. J. M. van Nimwegen, J. H. Schieving, E. J. Kamsteeg, T. Kleefstra, H. G. Yntema, R. Pfundt, et al. 2017. "A Clinical Utility Study of Exome Sequencing Versus Conventional Genetic Testing in Pediatric Neurology." *Genetics in Medicine* 19 (9): 1055–1063. doi:10.1038/gim.2017.1.