ANALYSIS AND COMMENTARY

Increasing the person-centered care of patients and their families living with rare diseases. An Analysis and Commentary on 'Home-based service for enzyme replacement therapy in lysosomal storage disorders: patient reported outcomes'. Tirelli, P., Giona, F., Di Rocco, M., Cassinerio, E., Pieruzzi, F., Pisani, A., Veroux, M., on behalf of the Tutor Working Group & Giudici, G. A. & Cipriani, F. (2018). *European Journal for Person Centered Healthcare* 6 (4) 669-674

Andrew Miles BMedSci MSc MPhil PhD DSc (*hc*)[a] and Jonathan Elliott Asbridge Kt DSc (*hc*) DHSc (*hc*)[b]

a Professor of Person Centred Health and Social Care & Co-Director, European Institute for Person Centred Health and Social Care, University of West London; Honorary Professor of Person Centred Care, St, George's University Hospital Campus, University of London & Senior Vice President/Secretary General, European Society for Person Centered Healthcare/Editor-in-Chief, *European Journal for Person Centered Healthcare*

b President & Chairman of Council, European Society for Person Centered Healthcare; Chief Clinical Officer, Healthcare At Home/Deputy Chairman, Oxford Healthcare NHS Trust, England, UK; Chairman of the Editorial Board of the *European Journal for Person Centered Healthcare* & Visiting Senior Clinical Professor, European Institute for Person Centred Health and Social Care, University of West London, UK

Keywords

Accompaniment, clinical options, constellation of symptoms, diagnosis, economic benefits, enzyme replacement therapy, epidemiology, equity of access, freedom to choose, home-based care, hospital-based therapy, humanistic framework, lysosomal storage diseases (LSDs), multimorbidity, patient-reported outcomes, patient advocacy organisations, patient satisfaction, patient support groups, person-centered healthcare, quality of life, shared decision-making, specialist nursing services, stepped-up care, supportive care

Correspondence address

Professor Andrew Miles / Professor Sir Jonathan Asbridge. E-mail: andrew.miles@pchealthcare.org.uk

Accepted for publication: 29 June 2019

Introduction

The lysosome, so named from the Greek *lysis* (meaning dissolve/destroy) and *soma* (meaning body), was discovered some 65 years ago by Christian René Marie Joseph (Viscount) de Duve (1917-2013) [1-3]. It has aptly been described as the 'sanitation department' within mammalian cells. The normative function of the lysosome is pivotal for the degradation of macromolecules and in the maintenance of cellular homeostasis, including the digesting, recycling and disposing of exhausted organelles and, depending on the cell type, viruses and bacteria that have been intracellularly engulfed *via* phagocytosis. Ongoing study of lysosomal function has demonstrated the pivotal role of the lysosome-endosomal system in the regulation of autophagy, apoptosis and cell death, these processes being effected through signal transduction and exocytosis [4-10]. When executing its function, the lysosome compartmentalises its actions, thus preventing enzymatic lysis from damaging normative cell structure and function. One of these lysosomal enzymes, acid phosphatase, provided de Duve with the pivotal clue that led to the discovery of the lysosome, earning this investigator the Nobel Prize for Physiology or Medicine in 1974, an honour shared with his close colleagues Albert Claude (1899-1983) and George Palade (1912-2008) [11].

All cellular and subcellular organelle and molecular systems are subject to dysfunction, with the concept of lysosomal storage disease (LSD) being first developed in 1963 following the discovery that α-glucosidase deficiency resulted in a clinical manifestation now known as Pompe disease [12]. The description of further defects in lysosomal metabolism subsequently followed, with current classifications recognising the LSDs as a group of seventy

monogenic disorders of lysosomal catabolism, most inherited in an autosomal recessive manner, though some (three) are X-linked. Aetiologically, the disorders arise from mutations in the genetic encoding of lysosomal proteins (such as proteases, glycosidases, membrane proteins, transport proteins, enzyme activators/modifiers), where the consequent lysosomal dysfunction results in the incremental 'storage' (accumulation) of redundant substrates, leading inexorably, through cellular malfunction, to cell death. These genetically and clinically heterogeneous diseases frequently present as paediatric neurodegenerative disorders, associated not infrequently with visceromegaly, the involvement of other organ symptoms, multiple deficits in central nervous system functioning and, as a function of the specific genetic defect, sometimes skeletal dysmorphia and delays in childhood development [13].

Epidemiologically, the LSDs are individually rare, but collectively common. Individually, the LSDs demonstrate estimated incidences ranging between 1:50,000 to 1:250,000 live births. Collectively, the incidence has been estimated at 1:5,000 to 1:5,500 [14]. From a therapeutic perspective, enzyme replacement therapy (ERT) remains the central focus of current therapeutic approaches for some of the LSDs, but other modalities, such as small molecule therapies (that decrease the storage process through inhibiting the production of substrates) are also of pivotal significance and are a rapidly expanding focus of drug development programmes. Additionally, nucleic acid-based therapies, including gene editing, gene replacement, and the use of antisense oligonucleotide agents, are also demonstrating considerable potential [13,15-18].

Tremendous progress has been made, then, in understanding the biological basis of the LSDs and in the development of associated treatment modalities. For those LSDs where effective therapies are available, patients have benefitted enormously in consequence. But to what extent is the treatment of the LSDs *holistic* in its nature? Do current models of care take an adequately person-centered approach in helping patients and their families manage these debilitating conditions? In order to answer these questions, we turn first to some wider considerations in terms of the lived experience of LSDs by patients and their families, and then to a paper recently published within the *Journal* by Tirelli and his colleagues [19] which analysed patient-reported outcomes within the context of a home-based service for LSD enzyme replacement therapy.

The person-centered care of the LSDs

Person-centered care typically begins not with the definitive diagnosis itself, but rather on the basis of an intuitive/presumptive diagnosis(es), where subjective fear and anxiety about what may prove objectively to be the case indicates the need for 'pre-diagnostic' care, support and counselling. While the need for such 'pre-diagnostic' care is indicated for all potentially serious conditions during the course of clinical investigation, it is of particular relevance for the LSDs, where the interval between the time of symptom onset, to definitive diagnosis, is often lengthy [13]. In the case of the early onset/paediatric LSDs, many studies have documented the development of significant, and sometimes substantial, parental anxiety and depression during the period of diagnostic uncertainty [20-22]. In the case of the late/adult onset LSDs, many of these diseases are characterised by progressive neurodegeneration, resulting in difficulties in everyday living and coping, together with ambulatory deficits/loss, cognitive decline and progressive dementia, psychosis, depression, fear, neuropathic pain, hopelessness, existential anxieties and significant decreases in quality of life. Moreover, many studies report the experience by parents of a stigma associated with the LSDs, with a sense of social isolation and a general dysfunction in ordinary family life [23-31]. These wider impacts of the primary biological dysfunction should not be ignored or accidentally unattended to - on the contrary, they call for a direct and person-centered attention [32-34].

When investigations are complete, and conclusions established, the *sensitive* communication of a confirmed diagnosis, with empathy and compassion, (which does not always characterise the breaking of bad news by practitioners [35-38]) should be followed by the early, and preferentially rapid, referral of the patient and family/carers to the nearest local branch of a national patient advocacy and support group for the LSDs. This action, person-centered by its very nature, is of pivotal clinical significance. Indeed, access to advocacy and support groups has been shown, across a wide variety of conditions and over sustained periods of study, to represent a major factor in the maintenance and improvement of patient (and caregiver) quality of life (QoL) [39-45]. Given their typical function of providing comprehensive information on the LSDs in forms and formats that are readily understood by patients, advocacy organisations and support groups can assist clinical discussions and the process of shared decision-making, working closely with patients and taking fully into account the expert knowledge provided by clinicians [32-34]. Their role in highlighting the range of options for medical equipment, and the nature of the supportive therapies that are so central to the care of the LSDs, is of great value to patients and their carers in the navigation of complex healthcare systems and in accessing services which might otherwise prove daunting and dispiriting if attempted alone. Additionally, such organisations help patients address the often high level of uncertainty about 'what will happen next' as part of the trajectory of disease progression, thereby providing an empowering assistance which helps maintain quality of life and general wellbeing [39-45].

The identification of expert practitioners for the investigation and person-centered management of the LSDs (with which advocacy organisations can greatly assist) is clearly foundational to the provision - and patient/family experience - of excellent care. Academic medical centres, or tertiary care treatment facilities, remain the obvious source of such care. Some such organisations will offer a purely biomedical approach to management, whereas others may combine the use of powerful scientific therapies with a holistic, person-centered approach. A properly person-centered and supportive care of the LSDs

will, by its nature, rely on the coordinated function of multidisciplinary clinical teams. Indeed, long term and frequent follow-up is essential in this context, drawing upon the individual expertise of a range of clinicians including neurologists, psychiatrists and clinical psychologists, speech and language therapists, occupational therapists, physiotherapists, opticians, and physical medicine and rehabilitation physicians (PMRPs, commonly known as physiatrists), PMRP services, in particular, are of key significance in ensuring patient access to the assistive devices necessary for continued ambulation in those patients with progressive disease, such as adequately designed wheelchairs and even simpler aids such as walking sticks, walking/zimmer frames and rollators. Working together, clinical teams can facilitate the maintenance of activities of daily living, preventing/ameliorating the development of physical complications from disease, maintaining maximum mobility, securing and preserving communicative ability for as long as possible (and providing adaptive communication technologies when intelligible articulation fails), facilitating the resolution of visual disturbances, and monitoring and assisting swallowing when there is evidence of dysphagia. Successful accompaniment of patients and their carers in this way has the ability to deliver a level of person-centered care that translates directly into an enhanced quality of life, optimal clinical outcomes, and the minimisation of emotional/existential distress in living with the LSDs - especially in those cases where progressive deterioration is inevitable [13].

Home-based services for enzyme replacement therapy in LSDs - patient reported outcomes

Having considered in outline the general characteristics of what would constitute a person-centered care of the LSDs, we turn now to the paper 'Home-based service for enzyme replacement therapy in lysosomal storage disorders: patient reported outcomes', by Tirelli and associates [19]. The authors describe the creation, in Italy, in 2011, of the TuTor programme, a professional nursing service for the home-based delivery of specific ERTs which can be implemented, upon request, by treating physicians. Methodologically, a questionnaire-based approach was adopted in order to investigate the level of patient satisfaction with the TuTor service and to provide additional insight into patients' perceptions of the given disease. The study enabled the accumulation of patient satisfaction data from the initial 100 patients who had been enrolled into the TuTor programme, over a period of 18 months. Of key interest is the patients' own self-reported comparison and contrast of their experience of hospital-based ERT and home-based ERT.

From the study by Tirelli *et al.* [19], patients overwhelmingly described hospital-based *i.v.* ERT as disruptive, over time, to specific activities of daily living such as work and study, resulting not only in basic inconvenience, but also in a sense of stress, with a negative impact on the perception of quality of life. For example, when, at baseline, the 100 patients were asked about their hospital-based ERT, 27% of patients reported *always* needing to take leave from work to attend the hospital, with an additional 8% reporting *sometimes* or *often* having to do so. Additionally, 57% of patients reported that they *always* attended hospital with a family member or a friend, with a further 12% reporting that a companion of some type was either *sometimes* or *often* required as part of the visit. Moreover, 47% of the patients reported having to travel between 11-30 kilometers for their hospital-based ERT, with 1 in 4 patients (24%) reporting having to travel in excess of 30 km. In terms of travelling time, the average travel time was reported as being approximately 44 minutes, with 47% of patients reporting the need to travel for more than 30 minutes. If one considers that these travelling times were for one-way only, then the total travelling time for hospital-based ERT can therefore be essentially doubled.

But travelling time represents, of course, only one index of patient inconvenience. The study by Tirelli *et al.* [19] documents in addition that on arrival at hospital, ERT was not initiated immediately, but that there was, rather, an average wait of 44 minutes. Moreover, following hospital-based ERT, patients are often asked to remain in the hospital, for observation, with associated waits being, on average, 26 minutes in duration. In Tirelli *et al.*'s study [19], 42% of patients reported a wait of more than 30 minutes post-ERT infusion, with additional delays beyond this delay in the ability to leave the hospital being also recorded, based on the need to schedule the next ERT infusion appointment with the relevant hospital administrators. Hospital attendance has further implications, beyond time. Indeed, in the study, LSD patients reported an average cost to attend the hospital, *per* ERT infusion, of €18, which the authors report as equating to a total annual cost of €468 for patients with Gaucher's or Fabry disease and €936 for patients with MPS-1. To be added to these direct costs must be the attendant loss of work productivity and leisure time.

The inconveniences and costs of hospital-based LSD care constituted the principal rationale underpinning the development of the TuTor home-based nursing program described by Tirelli *et al.* [19]. For sure, their questionnaire-based study based on the alternative home-based ERT infusion model, has yielded important results of direct importance to the development of person-centered LSD care. Although the sample size of 100 patients might be considered limited for anything other than, in general terms, a pilot scientific study, we must remember the status of the LSDs as rare diseases, and that a sample of 100 patients is therefore far from unimpressive. Tirelli *et al.* [19] were able to demonstrate a high overall level of patient satisfaction, with 99% to 100% of patients rating the home-based service as *positive* or *very positive* at 6 months, 12 months and also 18 months. Interestingly, but perhaps unsurprisingly, patients rated the shorter times associated with home-based treatment to be of particular importance to them.

One part of the philosophy of the TuTor program was that the recorded perception of patients' health could be employed as a proxy indicator of the quality of life of patients, a not unreasonable assumption. On this basis, a positive perception by patients was observed as being maintained over time and indeed across all three of the patient groups observed in the study [19]. The study was able to document, very clearly, that the opportunity to benefit from ERT at home was greatly welcomed by the greatest number of enrolled patients, with the majority confirming that they would recommend the home-based nursing service to other patients with their own condition. If we study carefully the results recorded by Tirelli and associates [19], we see clearly that they are in essential agreement with previous studies of home-based therapy for the LSDs which demonstrate that a transfer of ERT infusion from the hospital setting to the home-based care setting directly results in positive impacts on the perception of quality of life. In addition, home-based ERT has also been shown to fit more congruously with patient, carer and everyday family schedules/work commitments, and that it results in diminutions in the stress associated with hospital attendance [46,47].

Careful study of the paper by Tirelli *et al*. [19] demonstrates, in addition, that appropriately trained nursing staff delivering the TuTor program - and the TuTor call service personnel who supported them - were judged as providing a high quality service. This notable special skill set of the nursing staff improved substantially over time and was subsequently rated as 'excellent' by the majority of patients at 18 months**.** It is this observed increase, as a function of time, in the percentage of patients rating the skill of the nurses as *excellent*, that may indicate the effects of an increased comfort level of LSD patients when receiving their infusions in their own homes and feeling, in consequence, significantly more at ease with the nursing staff actively caring for them. This, too, is an important finding. Indeed, active caring is the essence of person-centered care and, as Tirelli *et al*. [19] recognize, the cultivation of a solid bond of trust between patient, carer and clinician(s), brings great benefits to the efficiency and effectiveness of clinical practice and its outcomes [48-50].

The person-centered model of care for the LSDs in the UK

In the UK, the treatment of patients with the LSDs is carried out for the most part in the patient's home. There are, of course, exceptions to this; for example, when it is more convenient for the patient to be treated at school or at his/her place of work. The organization Healthcare at Home (HaH) [51,52], expert in the provision of managed medication services, is a key provider in the UK of therapy for the LSDs. Its home-based model ensures that complex and vital care can be provided in a way which minimizes disruption to the person receiving the therapy by building the service around the person, rather than the person having to fit into a service provided for the convenience of the service provider. The LSD therapies are commissioned centrally by NHS England and the health departments of the devolved administrations, where a Framework Agreement provides for the same model for all therapies *via* the home care medicines pathway governed by the NHS in direct accordance with the recommendations of the Hackett Report [53, cf.54,55]. The pathway is flexible enough for the therapy to be provided in a way which is determined by the person receiving the treatment in terms of time of day and location, a freedom of choice which assists in the building of a bespoke person-centered experience. In terms of the precise processes through which patients are cared for following referral to the HaH service, these are described in detail within a forthcoming paper on the person-centered care of the LSDs scheduled for publication in the *Journal* at the end of the current year.

Discussion

In this *Analysis and Commentary*, we have sought to delineate some of the major aspects of what a person-centered care of the LSDs should look like, and also to analyze a specific study which has described one key component of the multi-faceted person-centered care ideal: home-based care. As Miles and Asbridge [56] emphasize, a pre-eminent characteristic of chronic illness is that patients who manifest the underlying organic pathologies develop a constellation of symptoms which extends way beyond the purely somatic, and where symptoms are typically psychological, emotional, spiritual and existential in their nature. Indeed, these authors note that patients with these conditions typically present not as "a collection of organ systems, one or more of which may be dysfunctional requiring scientifically indicated technical and pharmacological interventions, but rather as integral human beings with narratives, values, preferences, psychology and emotionality, cultural situation, spiritual and existential concerns, possible difficulties with sexual, relational, social and work functioning, possible alcohol and substance abuses and addictions, worries, anxieties, fears, hopes and ambitions - and more" [32-34,56-61].

In terms of the LSDs, and as we have discussed previously above, a plethora of studies document the development of significant, and sometimes substantial, parental anxiety and depression during the period of diagnostic uncertainty. Moreover, where progressive neurodegeneration occurs, studies describe multiple difficulties in the ability of patients to maintain the activities of daily living, failure in coping, ambulatory deficits/loss, cognitive decline, progressive dementia, psychosis, depression, neuropathic pain, hopelessness, fear, existential anxieties and significant decreases in quality of life. Stigma, a sense of social isolation, and problems in family life in consequence, act to complicate further an already highly testing situation [20-31]. In this context, it is surely clear that a reductive approach to the management of LSDs focussed solely on the science of clinical management - one which is rich in technical skill, but perhaps poor in humanity - would risk a form of abandonment of the patient, rather than an attentive accompaniment, with fully predictable effects on patients' quality of life. These wider impacts of the primary

biological dysfunction would be unwisely downplayed or accidentally unattended to - on the contrary, they call for direct and person-centered sets of clinical and social care interventions [32-34].

An advocacy for a fuller, person-centered approach to the care of the LSDs has, we believe, the very real potential to drive important changes in the way clinical services are delivered to people living with these debilitating conditions. Indeed, a stepped-up, person-centered model of care for the LSDs, would represent a solidly 'fit for purpose' way forward, raising the bar of clinical professionalism from what is often a lower common denominator of legally acceptable, basic technoscientific competence, to the higher numerator of person-centered excellence [cf. 32-34,56-61]. Insofar as the scientific evidence for person-centered care is concerned, and in terms of how this could be applied in developing the current standards of care in the management of the LSDs, a rapidly developing empirical research base exists which demonstrates that person-centered care can improve clinical outcomes and contain or decrease clinical costs. Moreover, it increases both patient and clinician satisfaction with care. Far from being an abstract concept, therefore, person-centered care is in fact a new and essentially radical proposition, resting firmly on an ethical justification, a scientific evidence-based justification and an economic justification [33]. For these reasons, we commend this model of practice to all those colleagues with an interest in, or responsibility for, the care of patients and families living with the LSDs.

Conclusion

Enormous progress has been made in LSD research and therapeutic development over the past two decades, with many successful clinical trials resulting in EMA and FDA-approved therapies. While these interventions have greatly improved patient quality of life and survival, the majority of the LSDs remain without an effective therapy, particularly those with CNS involvement. While rightly celebrating ongoing biomedical and technological advance in healthcare, we must remember that science is not an end in itself - its ultimate destination is the person of the patient, without whom science in medicine has no context [62,63]. If the management of the LSDs is to become optimal, then a science-*plus* approach is required which recognises the importance of placing modern LSD science within a solidly humanistic framework of care. We refer here to the need not only to address the primary biological dysfunction through ERT (and other pending advances), but to carefully attend to the whole constellation of 'patient factor' morbidities which arise from it.

Home-based care of the LSDs, discussed above, is a principal example of a responsive system which is both patient and person-centered. From the perspective of the individual patient, it is a safe clinical approach associated with a variety of direct benefits. One immediate such benefit is its substantial reduction of the multiple personal inconveniences to patients and their carers of the hospital-based alternative. But there are also other benefits which must be taken fully into account. Indeed, home-based LSD care is associated with major cost benefits when compared to the costs of treatment within the acute hospital setting, an important consideration indeed with reference to increasingly constrained healthcare budgets. Significantly, it thus provides yet a further empirical example of how person-centered approaches to care can increase quality of life, patient satisfaction, maximize clinical outcomes, and also reduce healthcare costs [cf.33].

Finally, when talking of home-based models of care *versus* hospital-situated alternatives, it is of considerable importance that patients and carers should be given *both* options from which to choose, since freedom to choose, equity of access, and shared decision-making, are all pre-requisites for an authentically person-centered model of care. The approaches described by Tirelli et al. [19], and undertaken routinely for the NHS by Healthcare at Home [cf.51-55], represent major quality improvements as part of the ongoing shift away from *institution-focussed* models of care in the direction of far more *person-centered* clinical services.

Conflicts of Interest

We declare no conflicts of interest.

References

[1] de Duve, C., Pressman, B.C., Gianetto, R., Wattiaux, R. & Appelmans, F. (1955). Tissue fractionation studies - 6. Intracellular distribution patterns of enzymes in rat-liver tissue. *The Biochemical Journal* 60 (4) 604-617.

[2] de Duve, C. (2005). The lysosome turns fifty. *Nature Cell Biology* 7, 847-849.

[3] Bainton, D.F. (1981). The discovery of lysosomes. *Journal of Cell Biology* 91 (3) 66S-76S.

[4] Settembre, C., Fraldi, A., Medina, D.L. & Ballabio, A. (2013). Signals from the lysosome: a control centre for cellular clearance and energy metabolism. *Nature Reviews Molecular Cell Biology* 14, 283-296.

[5] Medina, D.L. & Ballabio, A. (2015). Lysosomal calcium regulates autophagy. *Autophagy* 11, 970-971.

[6] Perera, R.M. & Zoncu, R. (2016). The lysosome as a regulatory hub. *Annual Review of Cell and Developmental Biology* 32, 223-253.

[7] Todkar, K., Ilamathi, H.S. & Germain, M. (2017). Mitochondria and lysosomes: discovering bonds. *Frontiers in Cell and Developmental Biology* 5, 106. doi:10.3389/fcell.2017.00106.

[8] Kilpatrick, B.S., Eden, E.R., Hockey, L.N., Yates, E., Futter, C.E. & Patel, S. (2017). An Endosomal NAADP-Sensitive Two-Pore Ca^{2+} Channel Regulates ER-Endosome Membrane Contact Sites to Control Growth Factor Signalling. *Cell Reports* 18 (7) 1636-1645.

[9] Annunziata, I., Sano, R. & d'Azzo, A. (2018). Mitochondria-associated ER membranes (MAMs) and

lysosomal storage diseases. *Cell Death & Disease* 9 (3) 328.
[10] Lawrence, R.E. & Zoncu, R. (2019). The lysosome as a cellular centre for signalling, metabolism and quality control. *Nature Cell Biology* 21, 133-142.
[11] Nobel Prize Committee for Physiology or Medicine - Press Release (1974). Nobel Prize awarded jointly to Albert Claude, Christian de Duve and George E. Palade "for their discoveries concerning the structural and functional organization of the cell". Available at: https://www.nobelprize.org/prizes/medicine/1974/summary/.
[12] Hers, H.G. (1965). Inborn lysosomal diseases. *Gastroenterology* 48, 625-633.
[13] Platt, F.M., d'Azzo, A., Davidson, B.L., Neufeld, E.F. & Tifft, C.J. (2018). Lysosomal storage disease. *Nature Reviews Disease Primers* 4 (1) [Article Number: 28 pp 1 - 25].
[14] Meikle, P.J., Hopwood, J.J., Clague, A.E. & Carey, W.F. (1999). Prevalence of lysosomal storage disorders. *Journal of the American Medical Association* 281, 249-254.
[15] Lachmann, R.H. (2019). Treating lysosomal storage disorders: what have we learnt? *Journal of Inherited Metabolic Disease* Epub ahead of print: https://doi.org/10.1002/jimd.12131.
[16] Freedman, R., Sahhar, M., Curnow, L., Lee, J. & Peters, H. (2013). Receiving enzyme replacement therapy for a lysosomal storage disorder: a preliminary exploration of the experiences of young patients and their families. *Journal of Genetic Counseling* 22 (4) 517-532.
[17] Ortolano, S., Vieitez, I., Navarro, C. & Spuch, C. (2014). Treatment of lysosomal storage diseases: recent patents and future strategies. *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* 8 (1) 9-25.
[18] Jameson, E., Jones, S. & Remmington, T. (2019). Enzyme replacement therapy with laronidase (Aldurazyme(®) for treating mucopolysaccharidosis type I. *Cochrane Database of Systematic Reviews* 6:CD009354.
[19] Tirelli, P., Giona, F., Di Rocco, M., Cassinerio, E., Pieruzzi, F., Pisani, A., Veroux, M., Alberto, G., Guidici, G.A. & Cipriani, F. (2018). Home-based service for enzyme replacement therapy in lysosomal storage disorders: patient reported outcomes. *European Journal for Person Centered Healthcare* 6 (4) 669-674.
[20] McConkie-Rosell, A., Hooper, S.R., Pena, L.D.M., Schoch, K., Spillmann, R.C., Jiang, Y.H., Cope, H. & the Undiagnosed Diseases Network. (2018). Psychosocial profiles of parents of children with undiagnosed diseases: managing well or just managing? *Journal of Genetic Counseling* 27 (4) 935-946.
[21] Baumbusch, J., Mayer, S. & Sloan-Yip, I. (2018) Alone in a Crowd? Parents of Children with Rare Diseases' Experiences of Navigating the Healthcare System, *Journal of Genetic Counseling* 28 (1) 80-90.
[22] Inglese, C.N., Elliott, A.M., Lehman, A., Adam, S., du Souich, C., Mwenifumbo, J., Nelson, T.N., van Karnebeek, C. & Friedman, J.M. (2019). New developmental syndromes: Understanding the family experience, *Journal of Genetic Counseling* 28 (2) 202-212.
[23] Bolsover, F.E., Murphy, E., Cipolotti, L., Werring, D.J. & Lachmann, R.H. (2014). Cognitive dysfunction and depression in Fabry disease: a systematic review. *Journal of Inherited Metabolic Disease* 37 (2) 177-187.
[24] Grisold, W., Struhal, W. & Grisold, T. (2019). What is advocacy? In: Advocacy in Neurology, pp. 3-20. (Grisold, W., Struhal, W. & Grisold, T. Eds.). Oxford: Oxford University Press.
[25] Maione M. (2008). The Lived Experience of Parents with Children Diagnosed with Mucopolysaccharidosis waiting for Enzyme Replacement Therapy. Available from: https://www.researchgate.net/publication/45512728_The_lived_experience_of_parents_with_children_diagnosed_with_mucopolysaccharidosis_waiting_for_enzyme_replacement_therapy.
[26] Grant, S., Cross, E., Wraith, E.J., Jones, S., Mahon, L., Lomax, M, Brigger, B. & Hare, D. (2013). Parental social support, coping strategies, resilience factors, stress, anxiety and depression levels in parents of children with MPS III (Sanfilippo syndrome) or children with intellectual disabilities (ID). *Journal of Inherited Metabolic Diseases* 36, 281-291.
[27] Somanadhan, S. & Larkin, P.J. (2016). Parents' experiences of living with, and caring for children, adolescents and young adults with Mucopolysaccharidosis (MPS). *Orphanet Journal of Rare Disease* 11, 138.
[28] Besier, T., Born, A., Henrich, G., Hinz, A', Quittner, A. L., Goldbeck, L. & the TIDES Study Group (2011). Anxiety, depression, and life satisfaction in parents caring for children with cystic fibrosis. *Pediatric Pulmonology* 46, 672-682.
[29] Weng, H.J., Niu, D.M., Turale, S., Tsao, L.I., Shih, F.J., Yamamoto-Mitani, N., Chang, C.C. & Shih, F.J. (2012). Family caregiver distress with children having rare genetic disorders: a qualitative study involving Russell-Silver Syndrome in Taiwan. *Journal of Clinical Nursing* 21 (1-2) 160-169.
[30] Anderson, M., Elliott, E. & Zurynski, Y. (2013). Australian families living with rare disease: experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet Journal of Rare Disease* 8, 22.
[31] Pelentsov, L.J., Laws, T.A. & Esterman, A.J. (2015). The supportive care needs of parents caring for a child with a rare disease: a scoping review. *Disability and Health Journal* 8 (4) 475-491.
[32] Miles, A. & Asbridge, J.E. (2016). The chronic illness problem. The person-centered solution. *European Journal for Person Centered Healthcare* 4 (1) 1-5.
[33] Miles, A. & Asbridge, J.E. (2017). Person-Centered Healthcare – moving from rhetoric to methods, through implementation to outcomes. *European Journal for Person Centered Healthcare* 5 (1) 1-9.
[34] Miles, A. & Asbridge, J.E. (2018). Person-centeredness in health and social care – what exactly is it that patients and their carers want? *European Journal for Person Centered Healthcare* 6 (1) 1-4.
[35] Hanratty, B., Lowson, E., Holmes, L., Grande, G., Jacoby, A., Payne, S., Seymour, J. & Whitehead, M. (2012). Breaking bad news sensitively: what is important to patients in their last year of life? *BMJ Supportive & Palliative Care* 2 (1) 24-28.
[36] Parry, R., Land, V. & Seymour, J. (2014). How to communicate with patients about future illness progression

and end of life: a systematic review. *BMJ Supportive & Palliative Care* 4 (4) 331-341.
[37] Aoun, S. (2018). The palliative approach to caring for motor neurone disease: from diagnosis to bereavement. *European Journal for Person Centered Healthcare* 6 (4) 675-684.
[38] Aoun, S., Hogden, A. & Kho, L.K. (2018). "Until there is a cure, there is care". A person-centered approach to supporting the wellbeing of people with Motor Neurone Disease and their family carers. *European Journal for Person Centered Healthcare* 6 (2) 320-328.
[39] Lavery, C. (2006). Role of patient support groups in lysosomal storage diseases. In: Fabry Disease: Perspectives from 5 Years of FOS. (Eds: Mehta A, Beck M, Sunder-Plassmann G). Oxford PharmaGenesis [Chapter 12. Available from: https://www.ncbi.nlm.nih.gov/books/NBK11585/].
[40] Aymé, S., Kole, A. & Groft, S. (2008). Empowerment of patients: lessons from the rare diseases community. *Lancet* 371 (9629) 2048-2051.
[41] Black, P.A. & Baker, M. (2011). The impact of parent advocacy groups, the Internet, and social networking on rare diseases: The IDEA League and IDEA League United Kingdom example. *Epilepsia* 52 (s2).
[42] Embuldeniya, G., Veinot, P., Bell, E., Bell, M., Nyhof-Young, J., Sale, J.E.M. & Britten, N. (2013). The experience and impact of chronic disease peer support interventions: A qualitative synthesis. *Patient Education and Counseling* 92 (1) 3-12.
[43] Hall, J.G. (2013). The role of patient advocacy/parent support groups. *South African Medical Journal* 103 (12) 1020-1022.
[44] Rhee, M., Mui, P., Cadogan, C., Imerman, J., Lindsell, S. & Samant, T. L. (2014). The Role of Brain Tumor Advocacy Groups, *Current Neurology and Neuroscience Reports* 14 (4) 442.
[45] Mongan, D., Long, J. & Farragher, L. (2016). Models of patient advocacy. Evidence brief. Health Research Board, UK. Available at: https://health.gov.ie/wp-content/uploads/2016/12/Final-Version-Patient-Advocacy-Services.pdf.
[46] Cousins, A., Lee, P., Rorman, D., Raas-Rothschild, A., Banikazemi, M., Waldek, S. & Thompson, L. (2008). Home-based infusion therapy for patients with Fabry disease. *British Journal of Nursing* 17 (10) 653-657.
[47] Milligan, A., Hughes, D., Goodwin, S., Richfield, L. & Mehta, A. (2006). Intravenous enzyme replacement therapy: better in home or hospital? *British Journal of Nursing* 15 (6) 330-333.
[48] Huang, I.C., Kenzik, K.M., Sanjeev, T.Y., Shearer, P.D., Revicki, D.A., Nackashi, J.A. & Shenkman, E.A. (2010). Quality of life information and trust in physicians among families of children with life-limiting conditions. *Patient Related Outcome Measures* 2010 (1) 141-148.
[49] Carlström, E.D., Hansson Olofsson, E., Olsson, L.E., Nyman, J. & Koinberg, I.L. (2017). The unannounced patient in the corridor: trust, friction and person-centered care. *International Journal of Health Planning and Management* 32 (1) e1-e16.
[50] Wolf, A., Moore, L., Lydahl, D., Naldemirci, O., Elam, M. & Britten, N. (2017). The realities of partnership in person-centred care: a qualitative interview study with patients and professionals. *BMJ Open* 7, e016491.
[51] Healthcare at Home. Transforming Healthcare. Available at: www.hah.co.uk.
[52] Healthcare at Home. Available at: https://www.nhs.uk/Services/pharmacies/Overview/DefaultView.aspx?id=12522.
[53] Hackett, M. (2011). Homecare Medicines. Towards a Vision for the Future. Department of Health. Available at: http://media.dh.gov.uk/network/121/files/2011/12/111201-Homecare-Medicines-Towards-a-Vision-for-the-Future2.pdf.
[54]. Hackett, M. (2013). Homecare Medicines Towards a Vision for the Future - Taking Forward the Recommendations. Department of Health. Available at: https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Professional%20standards%20for%20Homecare%20services/towards-a-vision-for-the-future-taking-forward-the-recommendations.pdf.
[55] Royal Pharmaceutical Society (2014). Handbook for Homecare Services in England. Available at: https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Professional%20standards/Professional%20standards%20for%20Homecare%20services/homecare-services-handbook.pdf.
[56] Miles, A. & Asbridge, J.E. (2019). The NHS Long Term Plan (2019) - is it person-centered? *European Journal for Person Centered Healthcare* 7 (1) 1-11.
[57] Miles, A. & Asbridge, J.E. (2014). Modern healthcare: a technical giant, yet an ethical child? *European Journal for Person Centered Healthcare* 2, 135-139.
[58] Miles, A. (2015). From EBM to PCH: always predictable, now inexorable. *Journal of Evaluation in Clinical Practice* 21, 983-987.
[59] Miles, A. (2017). From evidence-based to evidence-informed, from patient-focussed to person-centered – the ongoing 'energetics' of health and social care discourse as we approach the Third Era of Medicine. *Journal of Evaluation in Clinical Practice* 23 (1) 3-4.
[60] Miles, A. (2018). Evidence-based medicine - 2018. Quo Vadis? *Journal of Evaluation in Clinical Practice* 24 (1) 3-6.
[61] Miles, A. & Asbridge, J.E. (2014). On the need for transformational leadership in the delivery of person-centered clinical practice within 21st Century healthcare systems. *European Journal for Person Centered Healthcare* 2, 261-264.
[62] Montgomery, K. (2006) How Doctors Think. Clinical Judgement and the Practice of Medicine. Oxford: Oxford University Press.
[63] Miles, A. (2007). Science: a limited source of knowledge and authority in the care of patients. *Journal of Evaluation in Clinical Practice*, 13, 545-563.