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ORIGINAL COMMUNICATION

Swiss national guideline for reimbursement of enzyme replacement therapy in late-onset Pompe disease

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Abstract Glycogen storage disease type II is a rare multisystemic disorder characterised by an intracellular accumulation of glycogen due a mutation in the acid alpha glucosidase (GAA) gene. The level of residual enzyme activity, the genotype and other yet unknown factors account for the broad variation of the clinical phenotype. The classical infantile form is characterised by severe muscle hypotonia and cardiomyopathy leading to early death. The late-onset form presents as a limb girdle myopathy with or without pulmonary dysfunction. Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA) in infants is life saving. In contrast, therapeutic efficacy of rhGAA in the late-onset form is modest. High expenses of rhGAA, on-going infusions and poor pharmacokinetic efficacy raised a discussion of the cost effectiveness of ERT in late-onset Pompe disease in Switzerland. This discussion was triggered by a Swiss federal court ruling which confirmed the reluctance of a health care insurer not to reimburse treatment costs in a 67-year-old female suffering from Pompe disease. As a consequence of this judgement ERT was stopped by all insurance companies in late-onset Pompe patients in Switzerland regardless of their clinical condition. Subsequent negotiations lead to the release of a national guideline of the management of late-onset Pompe disease. Initiation and limitation of ERT is outlined in a national Pompe registry. Reimbursement criteria are defined and individual efficacy of ERT with rhGAA is continuously monitored.

Keywords Glycogen storage disease type II · Pompe disease · Enzyme replacement therapy · Reimbursement · Guideline · Registry

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Introduction

Pompe disease (glycogen storage disease type II, GSD II) is a rare multisystemic disorder characterised by lysosomal accumulation of glycogen. GSD II is caused by various mutations of the acid alpha-glucosidase (GAA) gene located on chromosome 17. The pattern of inheritance is autosomal-recessive and the incidence is estimated of 1 in 40,000 people [23]. Impaired degradation of glycogen causes a harmful deposit of lysosomal glycogen leading to cellular dysfunction, lysosomal rupture and cell death [33, 41, 42]. Moreover, impaired autophagy and further, yet unknown mechanisms, also contribute to the pathogenesis of Pompe disease [29].

The classic infantile form is characterised by muscle weakness, pulmonary dysfunction and cardiomyopathy [4, 21]. Untreated, infants die in their first year of life [16]. Enzyme replacement therapy (ERT) with recombinant human GAA (rhGAA, Myozyme®) improves survival [2, 17, 19]. However, motor limitations, hearing and speech problems and impaired cognitive function still persist [35].

The late-onset form (LOPD, late-onset Pompe disease) is diagnosed throughout childhood to adulthood presenting with a limb girdle myopathy and pulmonary dysfunction [8]. Symptoms may arise up to the 7th decade [13]. Reimbursement of ERT in LOPD patients was also approved according to significant effects on forced vital capacity (FVC) and on performance in the 6 min walking test (6-MWT) [41]. However, ERT is less effective than in the classical form and one-third of patients do not respond to therapy [32, 37]. Progressive muscle degeneration in the usually long time span from first symptoms to a definite diagnosis, low expression of the cation-independent mannose-6-phosphatase receptor (CI-MPR) leading to minor rhGAA uptake in the skeletal muscles and resistance of type IIB muscle fibres to ERT account for limited ERT efficacy among other factors [28, 33, 37]. Modification of rhGAA to increase CI-MPR dependent muscle uptake (neo-GAA) and ligation with the insulin like growth factor 2 (BMN701) as well as the use of small molecule chaperones may improve ERT effectiveness in the future [26, 33, 37, 47].

However, translation of statistically significant study results to an individual meaningful benefit is controversial. Accordingly, some governmental founded health care systems developed national reimbursement guidelines (Canada, Great Britain).

In Switzerland, up to November 2011, reimbursement of rhGAA was approved by the respective private health care insurer. The rarity of the disease, unrealistic therapeutic expectations and high cost of ERT resulted in ambiguous reimbursement decisions. In this context, the federal supreme court of Switzerland confirmed the cessation of reimbursement for ERT in a 67-year-old LOPD patient in December 2010. The court judged that treatment costs were so much out of proportion that payment to a single individual was a violation of the principle of "equality before the law". Moreover, the federal judges considered that the high costs of ERT contradicted the principle of commensurability, since for any treatment, annual expenses of 100′000 Swiss francs (approx. 85′000 Euro) were the maximal accepted upper limit.

As of October 2010, fourteen LOPD patients were diagnosed in Switzerland. Six of them received rhGAA paid by their private health insurance. As a consequence of the federal court ruling, rhGAA reimbursement was immediately stopped in these patients regardless of their individual clinical condition. The federal court ruling triggered a broad discussion concerning the "worth of a life" and the burden of health costs in Switzerland. This discussion focussed on orphan diseases treated with high cost ERT. Comparisons with common medical treatments investigated by studies with classical designs and endpoints were done. In this context, it is important to know that patients suffering from orphan diseases are disadvantaged when their therapies are evaluated with the criteria of evidence based medicine [7]. Large scale studies, regular clinical end points and subgroup analysis cannot be performed due to the limited number of patients [34]. To balance this discussion, an interdisciplinary committee released a national guideline for indication and limitations of the reimbursement of ERT in LOPD.

Methods

We performed a comprehensive search of the Pubmed database of the US National Library of Medicine of English language literature using various combinations of the following search terms after introduction of rhGAA in 2006: Pompe disease, glycogenosis type II, glycogen storage disease type II, consensus, guideline, ERT and rhGAA. At the time of analysis (April 2012) we identified seven relevant articles which served as the basis for the guideline development (Table 1). Additionally, available English

Table 1 Academic and governmental released Pompe guidelines

Author	Year	Country/association	Assessment strategy	References
Governmental publications				
Ministry of health and long-term care	2009	Canada	No	[25]
National health service	2007	Great Britain/ NSCAG	Yes	[10]
Academic publications				
Kishnani et al.	2006	USA/ACMG	Yes	[18]
Katzin et al.	2008	n.a.	Yes	[15]
Bembi et al.	2008	n.a.	Yes	[4]
Llerena et al.	2009	Brazil/ReBrPOM	Yes	[21]
AANEM	2009	USA	Yes	[1]
Wang et al.	2011	USA/ACMG	Yes	[43]
Cupler et al.	2012	USA/AANEM	Yes	[8]

NSCAG National specialised services commissioning group, *ACMG* American college of medical genetics and genomics, *ReBrPOM* Brazilian network for studies in Pompe disease, *AANEM* American association of neuromuscular and electro diagnostic medicine, *n.a.* not applicable

written reimbursement recommendations from Canada and Great Britain (Table 1) and congress reports were also taken into account. Articles and guidelines were reviewed especially for diagnostic criteria, inclusion and exclusion criteria for ERT with rhGAA in LOPD, indication for medical therapy and baseline as well as follow-up assessment (TH, KR). Results were send by E-mail to national experts in the field of Pompe disease (neuromuscular, pulmonary and metabolic specialists). A formal consensus was developed by using a modified Nominal Group Technique within separate meetings [24]. Patients or their representatives did not participate. The results were reviewed and approved by the Swiss federal office of health.

Results

Diagnosis of LOPD

Proximal myopathy including paraspinal and respiratory muscle weakness and the pattern of inheritance are the hallmarks of LOPD [4]. On clinical suspicion blood tests should determine serum creatine kinase (CK), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) to confirm muscle destruction. Of note, 5 % of GSD II patients have CK levels in the normal range [4]. EMG studies show abnormalities like fibrillations, myotonic discharges and other myopathic features. Neurogenic patterns of impairment may be related to harmful accumulation of glycogen in anterior horn cells [33]. NCS are usually normal. All electrophysiological features are non-specific but important to exclude differential diagnoses. Muscle biopsy usually discloses a vacuolar myopathy with positive periodic acid-Schiff (PAS) stain. Asymmetrical muscle involvement in GSD II may lead to false negative biopsy results. Muscle MRI can guide muscle biopsy but is not a standard approach [27, 31].

Biochemical evaluation of GAA activity is of utmost importance to diagnose GSD II. Fibroblast cultures, blood, or muscle biopsies can be used. We recommend the dried blood spot assay (DBS) as a fast, reliable and validated method [11, 22]. Reduced GAA activity is the mainstay of diagnosis but molecular confirmation as a secondary test after genetic counselling is mandatory [1, 8, 21].

Initiation of ERT with rhGAA in LOPD

The modified ranking scale (mRS) is introduced to estimate global disease severity [30]. Categorisation of mRS includes key symptoms of respiratory dysfunction, muscle weakness and gait disturbances. ERT is recommended in patients with slight (two points) to moderate severe disability (four points) on the mRS (Fig. 1). Severe disability or other life-limiting diseases must not be present [8, 10, 25]. Patients fulfilling these prerequisites should receive at least a minimum of 12 months of ERT to assess individual efficacy.

Baseline evaluation

Regular clinical follow-up is mandatory throughout the course of therapy (Fig. 1). Functional assessment includes exercise capacity (6-MWT), muscle strength [Medical research council (MRC) grading scale] and pulmonary function (FVC upright and supine) [41]. The 6-MWT, MRC scale (maximum 180 points/36 muscle function tested) and predicted FVC in upright position are the baseline criteria (level 1). If the 6-MWT and the FVC are not applicable (i.e., wheel chair bound person) secondary tests are used instead (level 2). These are the 10 m walk test (10-MWT) for gait and maximal inspiratory pressure (MIP) and sniff nasal inspiratory pressure (SNIP) for pulmonary function. Cumulative MRC can be used at any level. If secondary tests cannot be performed, alternatively the Walton-Gardner Medwin scale [36], the Rotterdam 9-item handicap scale and the fatigue severity scale are used as tertiary tests (level 3) (Fig. 1).

Corresponding tests from the primary level are the benchmarking for assessment of individual benefit from ERT. If only the tertiary test can be performed, initiation of ERT should be discussed with the health insurance. In case of controversy, a second opinion can be initiated. After ethical approval and written informed consent, demographics, diagnosis, baseline and follow-up evaluations must be documented in the "Swiss Pompe registry" (www.swisspomperegistry.ch) to gain ERT reimbursement.

Follow-up assessment and ERT continuation

IgG antibodies against rhGAA should be measured before ERT-initiation and every six months thereafter. Clinical reassessment is mandatory every six months once ERT was started. Follow up data serve as surrogates of individual response. More than a 10 % decline in two of three functional tests (6-MWT, cumulative MRC sum score or predicted FVC in upright position) after 12 months compared to the baseline leads to cessation of ERT. The same cut off value of 10 % is also applicable for secondary tests (10-MWT, SNIP and MIP). If primary and secondary level tests cannot be performed, data are obtained from tertiary evaluations (Walton-Gardner Medwin Scale, Rotterdam 9-item handicap scale and Fatigue severity scale) (Fig. 1).

Cessation of ERT

Adherence and regular assessments are prerequisites for therapy continuation. Life threatening side effects of

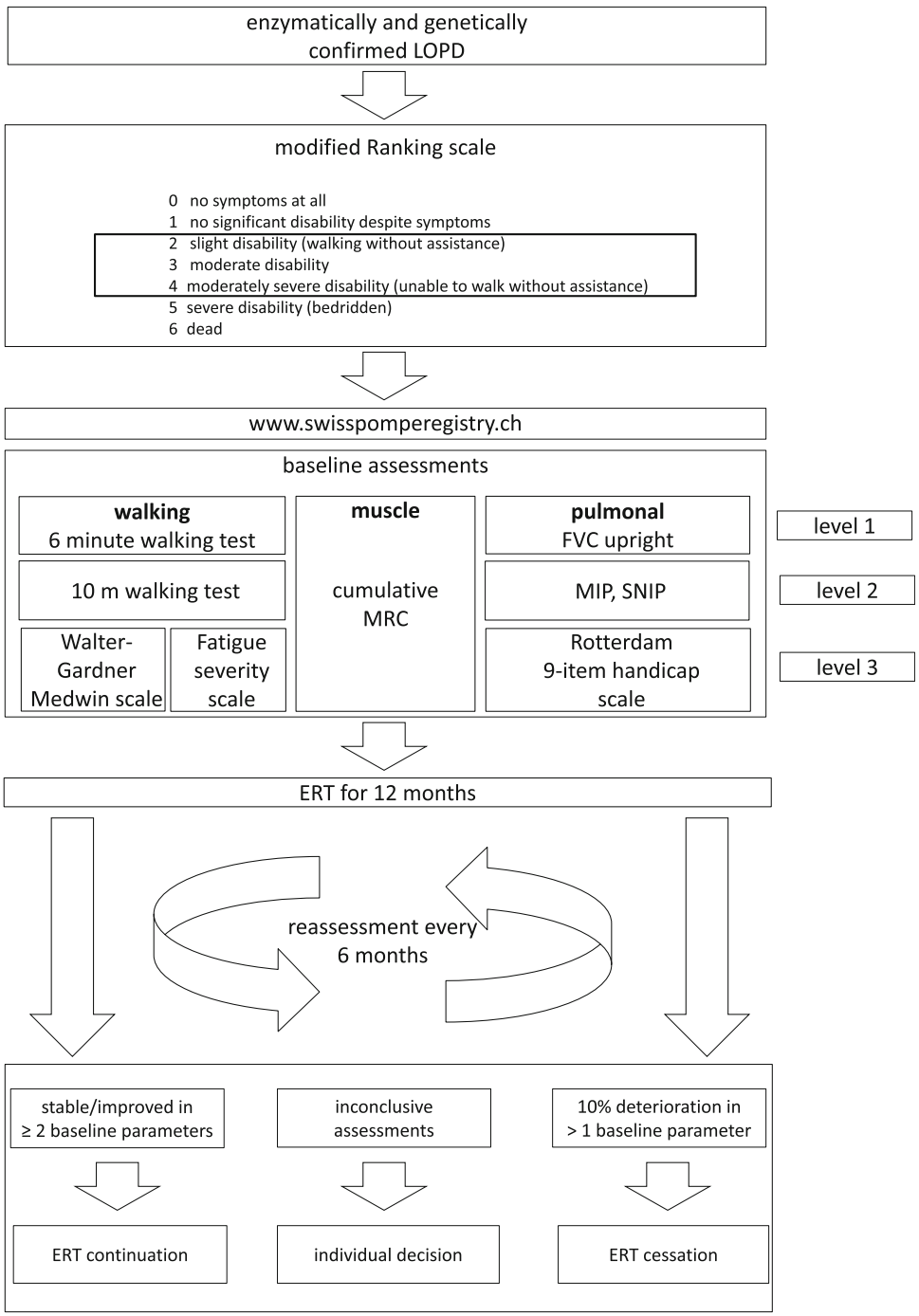

Fig. 1 Diagnostic pathway of the Swiss Pompe registry. Patients enter the registry with a confirmed diagnosis, a modified ranking scale (mRS) between two and four points and baseline assessments. ERT with rhGAA is than prescribed for 12 months. Re-evaluation has to be performed every six months. After every 12 months interval of ERT, continuation of therapy depends on individual efficacy

rhGAA leads to abrogation unless supportive (i.e., immunosuppressive) strategies are available. Relevant clinical decline and the need for mechanical ventilation, severe progression of co-morbidities or development of other severe diseases interfering with the treatment or reduce life expectancy lead to discontinuation of ERT (Table 2).

Table 2 Criteria of rhGAA cessation

- Decline of >10 % in two out of three level 1 tests after 12 months of ERT.
- Decline of >10 % in one level 1 test and in one level 2 test, only if other level 1 tests are not applicable.
- Decline of >10 % in one level 2 test and deterioration in level 3 assessments after discussion with the medical consultant of the health care insurer.

Discussion

Ambiguous reimbursement decisions of ERT were the driving force to setup a national guideline for the diagnosis, treatment and assessment for patients with late-onset Pompe disease in Switzerland. The recommendations are based on an interdisciplinary consensus approved by the Swiss national institute of health. Five principle criteria for ERT with rhGAA were defined (Table 3). They aim to treat every qualifying LOPD patient at least for 12 months to test for individual response and to justify the high costs of continuous ERT.

The typical clinical picture in combination with GAA enzyme deficiency and genetic analyses are necessary to diagnose LOPD [1, 8, 21, 43, 45]. This sufficiently rules out relevant differential diagnoses. Various mutations in the GAA gene are non-pathogenic or of unknown clinical significance [8]. Therefore, diagnosis of LOPD could not solely rely on mutation analysis like in other guidelines [25].

Initiation and continuation of ERT in LOPD is a controversial issue regarding patients individual efficacy, cost effectiveness and therapeutic burden [34]. Progressive and serious deterioration in untreated patients has already been reported in larger series [13, 14, 38, 46]. Long-term follow-up data showed that half of 16 patients became wheelchair bound and three became ventilator dependent [39]. Rapid clinical decline was also observed. The degree of disability has already been identified as a negative prognostic factor for survival [12]. In contrast, patients can be clinically stable for years without therapy [20], others further decline even with ERT [37].

Beneficial effects after 12–48 months of ERT have been demonstrated in controlled and uncontrolled trials [3, 6, 36, 41]. In a systematic review two-thirds of 368 LOPD patients stabilized or improved [37]. In another study, an increase in muscle strength and stabilization of upright FVC was reported in 49 patients compared to the pre-treatment period [9]. Early initiation of ERT has been advocated to prevent disease progression and may lead to better outcome [9, 15]. Longer disease duration (>15 years) and pulmonary involvement are risk factors for rapid clinical decline and may serve as surrogates for ERT initiation [38].

Muscle weakness, respiratory dysfunction and gait disturbances serve as surrogates for ERT in most [5, 8, 10, 21], but not all LOPD guidelines [44]. Accordingly, ERT initiation is only recommended in patients with relevant clinical symptoms as treatment benefit in pre-symptomatic patients has not been demonstrated [15, 20, 40]. The mRS is used to assess the global health status (Fig. 1). It is more suitable in a neurological disease than an oncological scale like the ECOG performance status used in other guidelines [25]. However, validation of both scores in LOPD is lacking.

Like the LOTS trial, severely disabled (mRS $\geq$5) and invasively ventilated patients are excluded from ERT [41]. ERT has to be withdrawn at the occurrence of other life-threatening diseases, severe anaphylactic reactions and the need for invasive ventilation [8, 10, 21, 25].

Individual efficacy of ERT is monitored by regular follow-up examinations (Fig. 1). Other guidelines use qualitative estimates to assess clinical changes, but the Swiss authorities demanded comparable numerical follow-up data to exclude subjective confounders. However, numerical measurements may also be influenced by uncontrollable factors, such as motivation of the patient, pain, or the general well-being. Moreover, in a progressive muscle disease, it is not clear how efficacy can be defined in a quantitative way. Is an increase in the 6-MWT or vital capacity required to demonstrate treatment efficiency, and, if so, how much of an increase is relevant? Or is a disease stabilisation enough to demonstrate treatment efficiency? After initial improvement, the latter has been demonstrated in long-term follow up studies in LOPD patients [32, 36, 41].

The 6-MWT and FVC in the sitting position are the main baseline and follow-up examinations [41]. Additionally, we calculate a cumulative MRC scale covering "overall" muscle weakness [38]. If one or more of these tests are not applicable, second and third line measurements are used (Fig. 1). To account for non-specific interferences in functional tests and questionnaires, two assessments with six months intervals are considered to document a positive or negative trend. This serves as a control of data consistency. Only if two subsequent six - months assessments are concordant (decline or increase), a definite decision about ERT continuation can be made [8, 21]. A decline of less than 10 % of any assessment parameter after 12 months of treatment was judged sufficient to prove individual ERT efficacy, accounting for the

Table 3 The five principle criteria of ERT in LOPD

1. Positive proof of the diagnosis is mandatory.
2. Patients with minor symptoms should not receive ERT, because additional gain of functionality could not be expected.
3. Patients with severely disabling symptoms and, thus, unfavourable prognosis should not receive ERT.
4. Patients with additional disabling diseases or with diseases hampering the success of ERT should not receive ERT.
5. Treatment should be continued if it is effective; it should be discontinued if it is not effective. Efficacy of the treatment should be demonstrated by standardized and unequivocal measurement parameters.

possibility of mild disease progression and expected errors of assessment. However, this value is arbitrarily chosen.

Our national consensus is subject to diverse limitations. It fits to the Swiss health care system and cannot be transferred without modifications to any other country. No international experts were involved in the consensus process. The reimbursement proposal was approved by the Swiss national health care authorities and, hence, non-academic influence is present. However, our national LOPD proposal expands the number of available guidelines (Table 1) and contributes to the European discussion of cost effectiveness of orphan drugs in rare diseases [34]. As the scientific knowledge about LOPD will increase and ERT will improve regular updates are planned in two-year intervals.

In conclusion, we here present a Swiss national guideline to standardize ERT reimbursement in LOPD patients. The recommendation overlaps with other guidelines and introduces new features. Our proposal may contribute to health economic considerations on the management of patients with LOPD and other lysosomal storage diseases in other countries.

Conflicts of interest TH and KR received travel expenses, speaking honorary and served as medical consultants for Genzyme, Switzerland.

Appendix: Participants of the guideline process

- Thomas Hundsberger, MD, Neurologist
- Lukas, Kern, MD, Pneumonologist
- Marianne Rohrbach, MD, PhD, Paediatrician and metabolic specialist
- Kai-Michael Rösler, MD, Neurologist
- Representatives of the Swiss federal office of health
- Representatives of Genzyme, Switzerland

References

1. AANEM practice topic (2009) Diagnostic criteria for late-onset (childhood and adult) Pompe disease. Muscle Nerve 40:149–160
2. Amalfitano A, Bengur AR, Morse RP, Majure JM, Case LE, Veerling DL, Mackey J, Kishnani P, Smith W, McVie-Wylie A, Sullivan JA, Hoganson GE, Phillips JA III, Schaefer GB, Charrow J, Ware RE, Bossen EH, Chen YT (2001) Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. Genet Med 3:132–138
3. Angelini C, Semplicini C, Ravaglia S, Bembi B, Servidei S, Pegoraro E, Moggio M, Filosto M, Sette E, Crescimanno G, Tonin P, Parini R, Morandi L, Marrosu G, Greco G, Musumeci O, Di IG, Siciliano G, Donati MA, Carubbi F, Ermani M, Mongini T, Toscano A (2012) Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. J Neurol 259:952–958
4. Bembi B, Cerini E, Danesino C, Donati MA, Gasperini S, Morandi L, Musumeci O, Parenti G, Ravaglia S, Seidita F, Toscano A, Vianello A (2008) Diagnosis of glycogenosis type II. Neurology 71:S4–11
5. Bembi B, Cerini E, Danesino C, Donati MA, Gasperini S, Morandi L, Musumeci O, Parenti G, Ravaglia S, Seidita F, Toscano A, Vianello A (2008) Management and treatment of glycogenosis type II. Neurology 71:S12–S36
6. Bembi B, Pisa FE, Confalonieri M, Ciana G, Fiumara A, Parini R, Rigoldi M, Moglia A, Costa A, Carlucci A, Danesino C, Pittis MG, Dardis A, Ravaglia S (2010) Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. J Inherit Metab Dis 33:727–735
7. Buckley BM (2008) Clinical trials of orphan medicines. Lancet 371:2051–2055
8. Cupler EJ, Berger KI, Leshner RT, Wolfe GI, Han JJ, Barohn RJ, Kissel JT (2012) Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve 45:319–333
9. de Vries JM, Brugma JD, Ozkan L, Steegers EA, Reuser AJ, van Doorn PA, van der Ploeg AT (2011) First experience with enzyme replacement therapy during pregnancy and lactation in Pompe disease. Mol Genet Metab 104:552–555
10. Deegan P (2007) Guidelines for the investigation and management of late onset acid maltase deficiency (type II glycogen storage disease/Pompe disease); Version 3
11. Goldstein JL, Young SP, Changela M, Dickerson GH, Zhang H, Dai J, Peterson D, Millington DS, Kishnani PS, Bali DS (2009) Screening for Pompe disease using a rapid dried blood spot method: experience of a clinical diagnostic laboratory. Muscle Nerve 40:32–36
12. Gungor D, de Vries JM, Hop WC, Reuser AJ, van Doorn PA, van der Ploeg AT, Hagemans ML (2011) Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. Orphanet J Rare Dis 6:34
13. Hagemans ML, Winkel LP, Hop WC, Reuser AJ, van Doorn PA, van der Ploeg AT (2005) Disease severity in children and adults with Pompe disease related to age and disease duration. Neurology 64:2139–2141
14. Hagemans ML, Winkel LP, Van Doorn PA, Hop WJ, Loonen MC, Reuser AJ, Van der Ploeg AT (2005) Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. Brain 128:671–677
15. Katzin LW, Amato AA (2008) Pompe disease: a review of the current diagnosis and treatment recommendations in the era of enzyme replacement therapy. J Clin Neuromuscul Dis 9:421–431
16. Kishnani PS, Corzo D, Leslie ND, Gruskin D, van der Ploeg A, Clancy JP, Parini R, Morin G, Beck M, Bauer MS, Jokic M, Tsai CE, Tsai BW, Morgan C, O'Meara T, Richards S, Tsao EC, Mandel H (2009) Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease. Pediatr Res 66:329–335
17. Kishnani PS, Nicolino M, Voit T, Rogers RC, Tsai AC, Waterson J, Herman GE, Amalfitano A, Thurberg BL, Richards S, Davison M, Corzo D, Chen YT (2006) Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase in infantile-onset Pompe disease. J Pediatr 149:89–97
18. Kishnani PS, Steiner RD, Bali D, Berger K, Byrne BJ, Case LE, Crowley JF, Downs S, Howell RR, Kravitz RM, Mackey J, Marsden D, Martins AM, Millington DS, Nicolino M, O'Grady G, Patterson MC, Rapoport DM, Slonim A, Spencer CT, Tifft CJ, Watson MS (2006) Pompe disease diagnosis and management guideline. Genet Med 8:267–288
19. Klinge L, Straub V, Neudorf U, Schaper J, Bosbach T, Gorlinger K, Wallot M, Richards S, Voit T (2005) Safety and efficacy of

recombinant acid alpha-glucosidase (rhGAA) in patients with classical infantile Pompe disease: results of a phase II clinical trial. Neuromuscul Disord 15:24–31
20. Laloui K, Wary C, Carlier RY, Hogrel JY, Caillaud C, Laforet P (2011) Making diagnosis of Pompe disease at a presymptomatic stage: to treat or not to treat? Neurology 77:594–595
21. Llerena JC Jr, Horovitz DM, Marie SK, Porta G, Giugliani R, Rojas MV, Martins AM (2009) The Brazilian consensus on the management of Pompe disease. J Pediatr 155:S47–S56
22. Lukacs Z, Nieves CP, Mengel E, Hartung R, Beck M, Deschauer M, Keil A, Santer R (2010) Diagnostic efficacy of the fluorometric determination of enzyme activity for Pompe disease from dried blood specimens compared with lymphocytes-possibility for newborn screening. J Inherit Metab Dis 33:43–50
23. Martiniuk F, Chen A, Mack A, Arvanitopoulos E, Chen Y, Rom WN, Codd WJ, Hanna B, Alcabes P, Raben N, Plotz P (1998) Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. Am J Med Genet 79:69–72
24. Nair R, Aggarwal R, Khanna D (2011) Methods of formal consensus in classification/diagnostic criteria and guideline development. Semin Arthritis Rheum 41:95–105
25. Ontario Ministry of health and long-term care (2009) Ontario public drug programs, exceptional access program, Myozyme (alglucosidase-alfa)-adult/late onset Pompe disease reimbursement guideline; Version 1
26. Parenti G, Andria G (2011) Pompe disease: from new views on pathophysiology to innovative therapeutic strategies. Curr Pharm Biotechnol 12:902–915
27. Pichiecchio A, Poloni GU, Ravaglia S, Ponzio M, Germani G, Maranzana D, Costa A, Repetto A, Tavazzi E, Danesino C, Moglia A, Bastianello S (2009) Enzyme replacement therapy in adult-onset glycogenosis II: is quantitative muscle MRI helpful? Muscle Nerve 40:122–125
28. Raben N, Lu N, Nagaraju K, Rivera Y, Lee A, Yan B, Byrne B, Meikle PJ, Umapathysivam K, Hopwood JJ, Plotz PH (2001) Conditional tissue-specific expression of the acid alpha-glucosidase (GAA) gene in the GAA knockout mice: implications for therapy. Hum Mol Genet 10:2039–2047
29. Raben N, Wong A, Ralston E, Myerowitz R (2012) Autophagy and mitochondria in Pompe disease: nothing is so new as what has long been forgotten. Am J Med Genet C Semin Med Genet 160:13–21
30. Rankin J (1957) Cerebral vascular accidents in patients over the age of 60. I. General considerations. Scott Med J 2:127–136
31. Ravaglia S, Pichiecchio A, Ponzio M, Danesino C, Saeidi GK, Poloni GU, Toscano A, Moglia A, Carlucci A, Bini P, Ceroni M, Bastianello S (2010) Changes in skeletal muscle qualities during enzyme replacement therapy in late-onset type II glycogenosis: temporal and spatial pattern of mass vs. strength response. J Inherit Metab Dis 33:737–745
32. Regnery C, Kornblum C, Hanisch F, Vielhaber S, Strigl-Pill N, Grunert B, Muller-Felber W, Glocker FX, Spranger M, Deschauer M (2012) 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J Inherit Metab Dis 35:837–845
33. Schoser B, Hill V, Raben N (2008) Therapeutic approaches in glycogen storage disease type II/Pompe disease. Neurotherapeutics 5:569–578
34. Simoens S, Cassiman D, Dooms M, Picavet E (2012) Orphan drugs for rare diseases: is it time to revisit their special market access status? Drugs 72:1437–1443
35. Spiridigliozzi GA, Heller JH, Kishnani PS (2012) Cognitive and adaptive functioning of children with infantile Pompe disease treated with enzyme replacement therapy: long-term follow-up. Am J Med Genet C Semin Med Genet 160:22–29
36. Strothotte S, Strigl-Pill N, Grunert B, Kornblum C, Eger K, Wessig C, Deschauer M, Breunig F, Glocker FX, Vielhaber S, Brejova A, Hilz M, Reiners K, Muller-Felber W, Mengel E, Spranger M, Schoser B (2010) Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol 257:91–97
37. Toscano A, Schoser B (2013) Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol 260:951–959
38. van der Beek NA, de Vries JM, Hagemans ML, Hop WC, Kroos MA, Wokke JH, de Visser M, van Engelen BG, Kuks JB, van der Kooi AJ, Notermans NC, Faber KG, Verschuuren JJ, Reuser AJ, van der Ploeg AT, van Doorn PA (2012) Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis 7:88
39. van der Beek NA, Hagemans ML, Reuser AJ, Hop WC, van der Ploeg AT, van Doorn PA, Wokke JH (2009) Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. Neuromuscul Disord 19:113–117
40. van der Ploeg AT, Reuser AJ (2008) Pompe's disease. Lancet 372:1342–1353
41. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, Herson S, Kishnani PS, Laforet P, Lake SL, Lange DJ, Leshner RT, Mayhew JE, Morgan C, Nozaki K, Park DJ, Pestronk A, Rosenbloom B, Skrinar A, van Capelle CI, van der Beek NA, Wasserstein M, Zivkovic SA (2010) A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med 362:1396–1406
42. van der Ploeg AT, Reuser AJ (2008) Pompe's disease. Lancet 372:1342–1353
43. Wang RY, Bodamer OA, Watson MS, Wilcox WR (2011) Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med 13:457–484
44. Wang RY, Bodamer OA, Watson MS, Wilcox WR (2011) Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med 13:457–484
45. Winchester B, Bali D, Bodamer OA, Caillaud C, Christensen E, Cooper A, Cupler E, Deschauer M, Fumic K, Jackson M, Kishnani P, Lacerda L, Ledvinova J, Lugowska A, Lukacs Z, Maire I, Mandel H, Mengel E, Muller-Felber W, Piraud M, Reuser A, Rupar T, Sinigerska I, Szlago M, Verheijen F, van Diggelen OP, Wuyts B, Zakharova E, Keutzer J (2008) Methods for a prompt and reliable laboratory diagnosis of Pompe disease: report from an international consensus meeting. Mol Genet Metab 93:275–281
46. Winkel LP, Hagemans ML, van Doorn PA, Loonen MC, Hop WJ, Reuser AJ, van der Ploeg AT (2005) The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol 252:875–884
47. Zhu Y, Jiang JL, Gumlaw NK, Zhang J, Bercury SD, Ziegler RJ, Lee K, Kudo M, Canfield WM, Edmunds T, Jiang C, Mattaliano RJ, Cheng SH (2009) Glycoengineered acid alpha-glucosidase with improved efficacy at correcting the metabolic aberrations and motor function deficits in a mouse model of Pompe disease. Mol Ther 17:954–963