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ORIGINAL ARTICLE

The impact of real practice inappropriateness and devices' inefficiency to variability in growth hormone consumption

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Abstract
Introduction Growth hormone (GH) consumption is the object of a particular attention by regulatory bodies, due to its financial impact; nevertheless, GH treatment has been demonstrated to be cost-effective and is, therefore, usually reimbursed by public health service systems. In Italy, significant differences in GH consumption between regions have been recorded. Different appropriateness in real practice is a possible explanation, but the proportion of drug wasted due to different combinations of therapeutic regimes and types of devices used in drug administration is a complementary explanation. Aim of the study is, therefore, to determine how much of the variability in GH consumption is actually due to differences in clinical practice, and how much to waste.
Materials and methods A model was settled to estimate the population with indication for GH administration, separately for children, transition subjects and adults, based on both the scientific evidence available and directly collected clinical evaluations. A systematic literature search was conducted using Cochrane Library (HTA and NHSEE) databases, Medline via Ovid, Econlit via Ovid, Embase.
Conclusion The model applied to the Italian population showed that there was apparently unexplainable over-prescription and potential under-prescription in various regions, ranging from 20 to 40 % less than the estimated theoretical consumption to over 200 %. Wastage, at level of single device, could amount to as much as 15 % of the consumption, demonstrating that price per mg is not in general a good proxy of the cost per mg of therapy. Our estimates of the wastage shows a significant potential gap in the model assessment of the HTA bodies, as far as they do not explicitly take into account the issue of wastage and, consequently, the actual variability in local clinical practice.

Keywords Growth hormone deficiency (GHD) · Epidemiology · Somatropin · Device · Efficiency

Abbreviations

AIFA	Agenzia Italiana del Farmaco (Italian Drugs Agency)
AOGHD	*Adult onset* growth hormone deficiency
CRI	Chronic renal insufficiency
GHD	Growth hormone deficiency
HAS	Haute Autorité de Santé (French National Health Authority)

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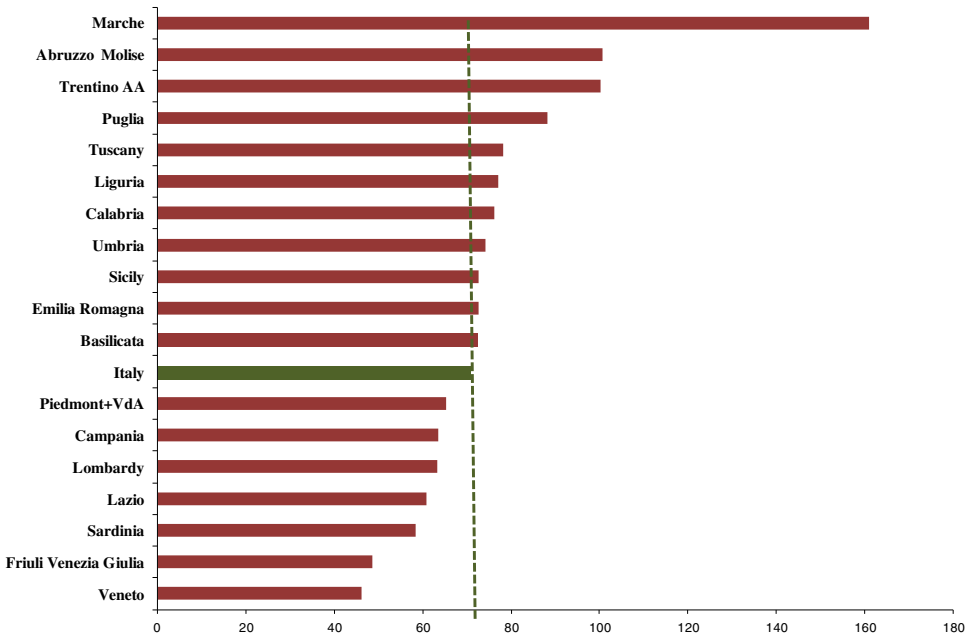

Fig. 1 Annual per capita consumption (in mg) of growth hormone in the regions of Italy (year 2011). *Source*: IMS (Market survey)

Istat	Italian National Institute of Statistics
NICE	National Institute for Health and Care Excellence
OSMED	Osservatorio nazionale sull'impiego dei Medicinali
PWS	Prader–Willi syndrome
SHOX	Short stature HOmeoboX containing

Introduction

Treatment with growth hormone (GH, somatropin) is effective in six different children pathological conditions: growth hormone deficiency (GHD), Turner's syndrome (TS), growth retardation in babies born small for gestational age (SGA), Prader–Willi syndrome (PWS), delayed growth due to chronic renal insufficiency (CRI), and growth retardation associated with a defect in the *Short Stature HOmeoboX Containing* (SHOX) gene [1, 2].[1] This treatment has also been shown to be effective in adults with GHD acquired in either adulthood or childhood [3, 4].[2]

GH treatment has been demonstrated to be cost-effective and is, therefore, usually reimbursed by public health service systems [1, 5–7], even if the results of the models are sensitive to various factors, in particular dose and duration of treatment. Models are less sensitive to price differences, although these are relevant. It should be added that GH consumption is the object of a particular attention by regulatory bodies, due to its financial impact.[3]

According to the OSMED Report [8], among the systemic preparations of hormones distributed by public structures, excluding the sex hormones, in Italy GH ranks first for cost, for an amount of about €88 million per year, which is an increase of 12.7 % from 2009. This fact was confirmed in 2012: with expenditure at €1.44/per capita, GH is the leading cost for public structures for this class of drugs.

It is known that the costs can be even notably higher in some other countries; for example, in France, with approximately the same amount of population, the total annual reimbursement by the *Assurance Maladie,* for all indications and all age classes, exceeded €149 million in 2008, of which 92 % were for children [7].

Furthermore, as the Italian National Institute of Health [9] recently reported there is also a significant difference in GH consumption between regions. This variability was confirmed, by the consumption for resident recorded in 2011 (Fig. 1). It should be noted that, although this was not a sophisticated analysis, it did not show the "north–south gradient" usually present in healthcare analyses in Italy [8], but a rather patchy pattern throughout the country.

[1] SHOX has not been included in following analysis because till 2011, in Italy, GH wasn't authorized for the specific indication.

[2] Adult onset: patients who have growth hormone deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; childhood onset: patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

[3] It's worth noting that since 2006 a biosimilar GH formulation is available (EMEA/H/C/000607).

Since, as explicitly indicated in Agenzia Italiana del Farmaco (AIFA) Note 39, "the cohort of subjects affected by the main disorders for which GH treatment is indicated should be considered essentially stable in time and distributed homogeneously in the country", a marked territorial variability in consumption can be considered a worrying signal of inappropriate over-prescription or, worse still, with regards to health, of under-treatment. Some of the variability in consumption is undoubtedly explainable by different age compositions of the population, particularly in the regions in the north of Italy (with a low birth rate), in which children (in whom the rate of treatment is higher) account for a smaller percentage of the population. Healthcare 'migration' to areas with a high density of centres of excellence for the diagnosis and treatment of the disorders under consideration, could be another factor able to affect the consumption of GH recorded in the country. The impact of this effect should, however, be at least partly mitigated by the good spread of prescribing centres in the country, as well as by the method of distributing the hormone in Italy (strictly regulated by hospital centres), which implies that obtain the therapy in areas other than the region of residence is more and more difficult. It should also be noted that GH must be stored at a low temperature, and this also hampers the provision of supplies for long periods.

Another factor that can affect variability in consumption, as demonstrated in a previous study, is the proportion of drug wasted, due to different combinations of therapeutic regimes (doses/die) and types of devices used in drug administration[4]: it has been estimated, in different scenarios, that this waste can accounts for very significative amounts [10].

It is worth noting that, to date, the models proposed by the main health technology assessment (HTA) agencies have not considered the aspect of device-related waste, although sensitivity analysis could partly take in account for that.

The aim of this study was, therefore, twofold: to determine as objectively as possible how much the variability in GH consumption is actually due to differences in clinical practice, identifying geographical areas of any under- or over-prescribing, and to determine how much any variability found is dependent on waste of the product related to the different devices available.

For these purposes, we settled a model for evaluating prevalent population, both by disease and by type of patient (child, transition patient, adult). This model, in many aspects, drew on one used by the French National Health Authority (HAS) [7], but integrating it with some of the clinical parameters used in the model proposed by Takeda for the National Institute for Health and Care Excellence (NICE) [11]. With regards to the estimates of waste, a model previously settled for Italy was used [10].

The model was tested on the Italian population overall and at regional level, in order to assess the differences between predictable consumption and real consumption in clinical practice. This geographical analysis is also justified by the substantially federal national health system in Italy, which is effectively formed of 21 different regional healthcare systems.

Materials and methods

Drug consumption is determined by the type of device used and the daily dose prescribed[5] which, in childhood, depends on the distribution of the patients by weight and pathology. In order to estimate theoretical consumptions it is, therefore, necessary to know the epidemiology of the phenomenon and the characteristics of the target population.

As far as Italy is concerned, there is a considerable lack of knowledge of the epidemiology of the disorders for which GH treatment is indicated, despite Note 39 of AIFA calls for thorough epidemiological surveillance, through the establishment of ad hoc Regional Commissions, as well as a computerized national Registry, assigning the National Institute of Health the centralized management: the risk of not conducting this surveillance being the non-reimbursement of the drug to provider by the National Health Service.

To overcome the deficit of registers, an estimate was made of the target population, separately for children, transition subjects and adults, based on both the scientific evidence available and directly collected clinical evaluations.

For what regard scientific evidence, a systematic literature search was conducted using Cochrane Library (HTA and NHSEE) databases (19 records), Medline via Ovid (350 records), Econlit via Ovid (0 record), Embase (326 records), from their inception to April 2012.

In total 695 papers (686 without duplicates) were identified and underwent to abstract review. The result has been also validated by comparing it with the bibliography in two relevant previous HTA analysis [7, 11].

[4] To date, devices available differ in technical aspects (for example, they may or not have a needle) and in capacity; the amount of device-related waste is consequent to the actual "divisibility" of the capacity to the dosage, as well as to the possibility of using all the GH before it expires. No other potential sources of inefficiency, as malfunctioning, have been considered. More details in [10].

[5] In Italy public reimbursement rely on the predisposition of a therapeutic plan by Regional specialized centres.

Table 1 Estimate of the target population: epidemiological parameters

Pathology	Parameters	Reference value	Sources
TS	Prevalence at birth	1/2,500	Sybert and McCauley [12]
	% of girls with TS diagnosed before puberty	67 %	Sybert and McCauley [12]
PWS	Prevalence at birth	1/15,000	Average between 1/10,000—Lindgren [13] and 1/29,000—Butler [14]
	% adolescents born with PWS diagnosed and treated	85 %	Molinas et al. [15] and working group
	% males	50 %	Molinas et al. [15]
SGA	Prevalence at birth	5.4 %	Karlberg and Abertsson-Wikland [16]
	Males		
	Height at age of 4 years <−2 SDS	11 %	Albertsson-Wikland et al. [17]
	Height at age of 4 years <−2.5 SDS	3.00 %	Normal distribution
	Height at age of 4 years <−3 SDS	0.65 %	Normal distribution
	Females		
	Height at age of 4 years <−2 SDS	5 %	Albertsson-Wikland et al. [17]
	Height at age of 4 years <−2.5 SDS	1.36 %	Normal distribution
	Height at age of 4 years <−3 SDS	0.30 %	Normal distribution
CRI	Prevalence at birth	0.001 %	Ardissino [18]—and working group
	% males	67 %	Ardissino [18]

Established the our search was superimposable to that reported in the HTA analysis [7, 11], we focused on updating the review, searching for epidemiological, cost–effectiveness and health related quality of life analysis published after (2009) the cited HTA report publication, and also integrating with some analysis on childhood and transition patients not included in the cited HTA reports.

51 more studies have been identified, but 48 have been excluded because:

- regarding subjects with pathologies not of interest of our analysis, or focusing on sub-population with very specific comorbidities or sick conditions
- regarding not pertinent research fields
- review articles.

The list of excluded studies is available from the authors.

Our estimate was made using an original model inspired by that proposed in the HTA report of the French HAS, aimed at appraising the reimbursability of GH for non-GHD children in France [7]. In other terms we borrow from the HAS model the analytical approach, based on the projection of the prevalence rate (for each pathology that has an indication for GH treatment) to the newborn cohorts.

Table 1 shows the epidemiological parameters used to estimate the target population, for the pathologies non-classic-GHD in childhood, while Table 2 shows the number of subjects potentially eligible for treatment.

For patients with classic-GHD, given the lack of concordant evidence on a possible estimate of the prevalence of GHD at birth, we used the index of exposure to treatment in Piedmont, a region that since 2000 has activated a Registry. According to this Registry, the index of exposure was 9.44 subjects per 10,000 residents under the age of 18 years, of whom 70 % were males [19]. It was hypothesised that the rate of exposure to treatment was constant for age.

The recommended dose regimen of GH varies depending on the diagnosis and anthropometric characteristics of the patient (weight or body surface area). It is, therefore, necessary to define some reference standards, for each pathology, for the parameters essential in order to determine the daily therapeutic dose.

In detail, for each pathology for which treatment with GH is indicated, it is essential to know not only the therapeutic dose in mg/die per kilogram of body weight, but also:

- the distribution of weight per age (and gender);
- the mean age of starting treatment;
- the mean duration of treatment.

Table 3 shows the clinical parameters used to evaluate the population being treated in 2012.

The estimates of weight per gender, age and pathology were based on the figures used in the HTA of the NICE in the United Kingdom in 2011 [11], which are illustrated in Figs. 2 and 3.

The distribution of the mean weight for gender, age and pathology was then compared with the distribution of the age- and sex-specific Italian growth curves, in particular

Table 2 Estimate of target population

Year of birth	Age in 2012	Born[a]		TS	PWS		SGA		CRI	
		Males	Females	Females	Males	Females	Males	Females	Males	Females
1994	18	281,875	266,660	71	16	15	99	43	22	11
1995	17	274,171	258,677	69	16	15	96	42	22	11
1996	16	269,122	253,857	68	15	14	94	41	21	11
1997	15	273,472	258,096	69	16	15	96	42	22	11
1998	14	273,404	258,674	69	16	15	96	42	22	11
1999	13	270,959	255,666	69	15	15	95	41	21	11
2000	12	272,792	258,707	69	16	15	96	42	22	11
2001	11	274,518	259,054	69	16	15	96	42	22	11
2002	10	267,551	254,470	68	15	14	94	41	21	11
2003	9	273,103	260,350	70	16	15	96	42	22	11
2004	8	277,183	263,000	70	16	15	97	43	22	11
2005	7	284,472	270,479	72	16	15	100	44	23	11
2006	6	281,997	265,162	71	16	15	99	43	22	11
2007	5	285,688	269,278	72	16	15	100	44	23	11
2008	4	287,468	271,156	73	16	15	101	44	23	11
2009	3	292,421	277,462	74	17	16	103	45	23	12
2010	2	289,084	273,482	73	16	16	101	44	23	11
2011	1	285,923	269,868	72	16	15	100	44	23	11
		5,015,203	4,744,098	1,271	286	270	1,760	769	398	199

[a] Istat: Intercensual population estimates at Jan the 1st, by age and sex (http://demo.istat.it/ric/index_e.html)

with the distributions of the 3rd and 50th percentiles [20]. This comparison was carried out to verify the coherence and, therefore, the comparability of the international and national data, specific for sex, age and single disease. As an example, the distributions for GHD are shown in Fig. 4.

The weight distribution used as a reference standard was actually found to be compatible with the anthropometric evaluations of the patients receiving treatment for all the disorders under consideration.

Considering now the subjects of transitional age (18–25 years), for the subjects being treated for GHD it was assumed that 34 % of those already treated in childhood would continue treatment [21]. It was also hypothesised that the mean duration of treatment in these patients was about 7 years, with a dropout rate in the first year of 0.04 % [11] and a homogeneous distribution for age. For the transition patients, since it had been hypothesised in the proposed model that all these subjects had started treatment in childhood, a mean dose, equivalent to about half the last dose/die taken in childhood, was used for the simulations of consumption, with a minimum of 0.8 mg/die and a maximum of 1.0 mg/die [22].

Finally, the subjects over 25 years old with GHD (AOGHD/COGHD) can be divided into three main groups:

- adults with a lack of GH from birth or infancy;
- adults who develop a deficiency of GH at a later age as a result of trauma or other type of disorder of the gland that produces GH (pituitary gland);
- adults with an idiopathic lack of GH.

AOGHD is predominantly caused by pituitary and peri-pituitary tumors and their related surgical and radiation treatment.

The estimate of the subjects being treated was made starting from the sex- and age-specific rates of exposure to treatment in the region of Veneto [22], as shown in Table 4.

Consequently, the population in which the hypotheses of prevalence at birth (all childhood conditions except GHD) and prevalence among residents (for GHD in childhood, GHD in the transitional age, and subjects being treated in adulthood for all the other causes) was projected, was stratified by region, gender and age (precise age or age groups, depending on the hypothesis).

To test the precision of the model, a final comparison of our results with actual consumption has been made using the figures gathered by IMS on the 2011 Italian market.

Results

As reported in Table 5, the number of subjects diagnosed and receiving treatment in 2012 was estimate just over 11,300: of these subjects, 60 % were under 18 years old. For this group of subjects the rate of exposure to treatment was notably higher than that predicted in the already mentioned Note 39 from AIFA, which was 1:2,000. In

Table 3 Clinical parameters

Pathology	Parameter	Reference value[a]
GHD	Dose mg/kg die	0.030–0.035
	Age at start of treatment	7 years
	Duration of treatment	10 years
TS	Dose mg/kg die	0.035–0.040
	Age at start of treatment	7 years
	Duration of treatment	8 years
	% drop-out in first year	10 %
	% of non-responders at 1 year[b]	5 %
PWS	Dose mg/kg die	0.035
	Age at start of treatment	7 years
	Duration of treatment	9 years
	% drop-out in first year	10 %
	% of non-responders at 1 year[b]	5 %
SGA	Dose mg/kg die	0.035
	Age at start of treatment	7 years
	Duration of treatment	
	Females	7 years
	Males	8 years
	% drop-out in first year	15 %
	% of non-responders at 1 year[c]	10 %
CRI	Dose mg/kg die	0.045
	Age at start of treatment	7 years
	Duration of treatment	5 years
	% drop-out in first year	10 %
	% of non-responders at 1 year[b]	5 %

[a] Based on good practices as evaluated by a team of clinical experts

[b] Growth rate <1 SD or <2 cm/year

[c] No increase in stature

particular, it estimated that there is one subject in treatment for every 1,606 residents under 18 years old (1 every 1,271 male children and 1 every 2,230 female children). This is an approximately 25 % higher rate than that hypothesized by AIFA, for an increase in 1,327 subjects.

Of the whole population of patients treated with GH, paediatric subjects account for 59.5 %, transition patients with GHD account for 7.4 % and the other 33.1 % are adults.

The breakdown of the estimated, theoretical, consumption (net of waste due to devices) is different: in fact, according to the clinical parameters indicated in Table 3, the annual consumption, assuming minimum doses, is about 3.5 million mg, divided by age group as illustrated in Fig. 5, which shows that 78 % of the drug is consumed by children.

The overall estimated consumption was 78.3 % of the actual consumption in Italy in 2011, demonstrating a potential for "overprescription" and/or device-related wastage.

As already mentioned, the various devices marketed in Italy have different levels of efficiency (in terms of potential product wastage), which depends both on the dose/die of the treatment prescribed and on the stability of the products after their packaging has been opened, which conditions the maximum number of days of treatment possible, after which the product expires.

Assuming no switches among devices, Tables 7 and 8 shows the inefficiency for each of them: the index in the last column indicates as the possible wastage is in the range 5–15 % (single-dose/disposable devices assume value 1, indicating theoretically no wastage).

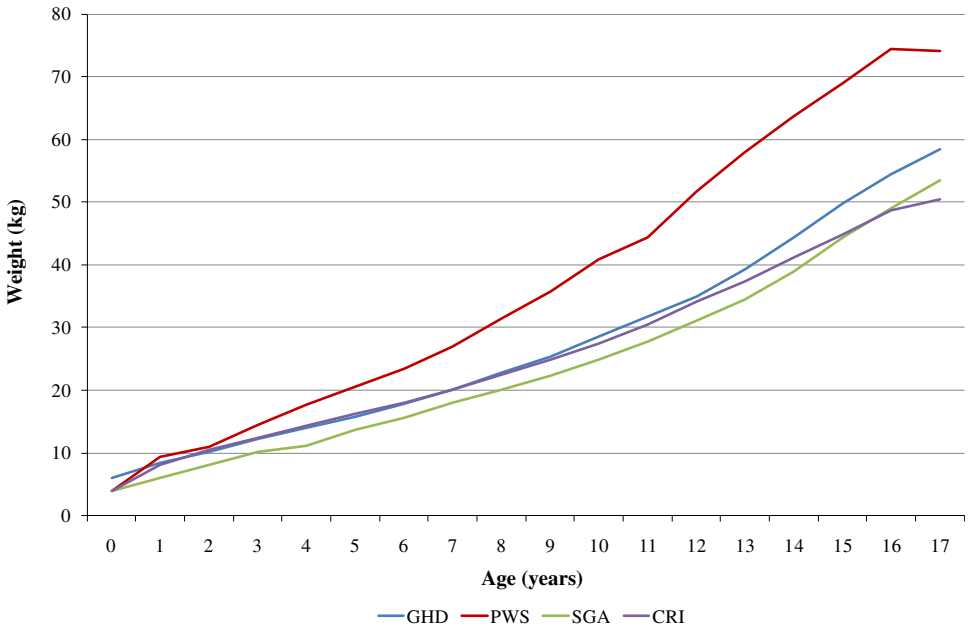

Fig. 2 Distribution of weight according to age in childhood patients divided by disorder (males). *GHD* growth hormone deficienc, *TS* Turner's syndrome, *SGA* growth retardation in babies born small for gestational age, *PWS* Prader–Willi syndrome, *CRI* chronic renal insufficiency. *Source*: Takeda 2010 [11]

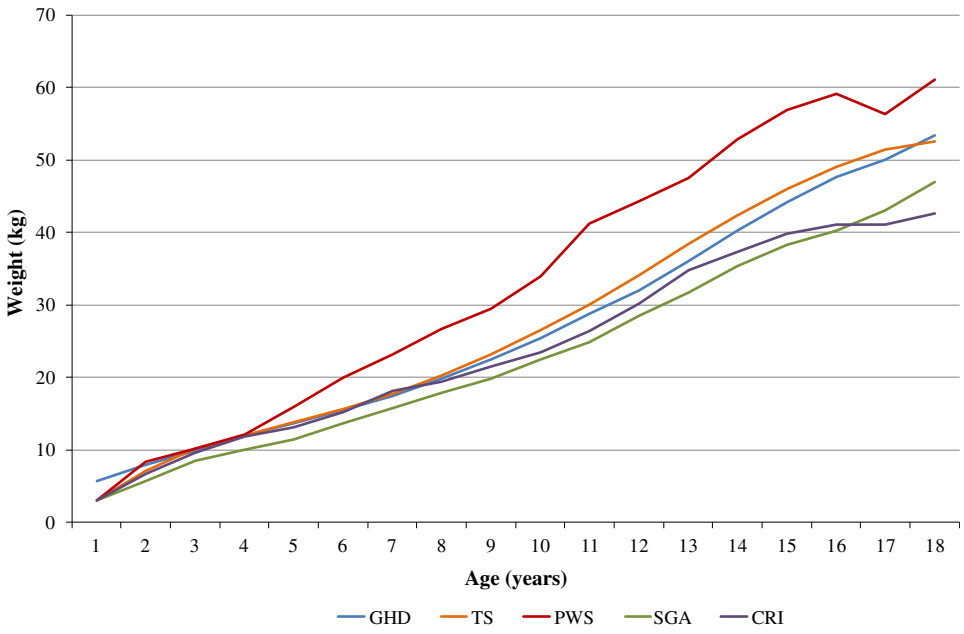

Fig. 3 Distribution of weight according to age in childhood patients divided by disorder (females). *GHD* growth hormone deficienc, *TS* Turner's syndrome, *SGA* growth retardation in babies born small for gestational age, *PWS* Prader–Willi syndrome, *CRI* chronic renal insufficiency. *Source*: Takeda 2010 [11]

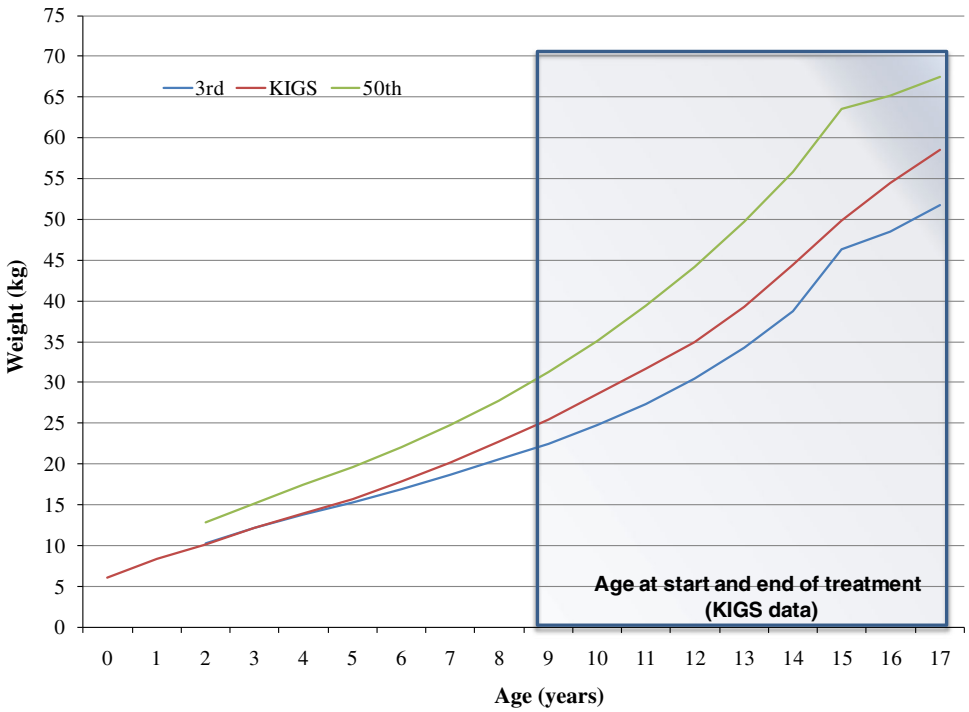

Fig. 4 Distribution of weight according to age in patients with GHD receiving treatment (males). *KIGS* data Kabi International Growth Study database da Takeda 2010 [11]. 3rd e 50th third and fiftieth percentile in the Italian cross-sectional growth charts [20]

Table 4 AOGHD/COGHD: rate of exposure to treatment in the Region of Veneto in patients divided by age class and average dose

Age class	19–40		41–50		51–60		61–70		71–85	
Gender	M	F	M	F	M	F	M	F	M	F
Prevalence per 100,000 residents	9.4	6.3	8.8	5.4	11.7	9.1	13.8	3.5	6.8	3.0
Mean dose (mg/die)	0.48	0.63	0.36	0.44	0.24	0.34	0.27	0.34	0.28	0.36

Source: Veneto Regional commission for the prescription of growth hormone [23]

Table 5 Estimate of subjects diagnosed and receiving treatment in 2012

Age	Pathology	M	F	Total
<18 years	GHD	3,680	1,477	5,157
	SGA	478	211	689
	TS		503	503
	PWS	115	111	226
	CRI	113	58	171
	Total in childhood	4,386	2,360	6,746
	Resident population on 1 January 2011	5,574,710	5,263,144	10,837,854
	Rate of exposure to treatment	1:1,271	1:2,230	1:1,606
≥18 years	Transitional age	461	377	838
	AOGHD/ COGHD	2,333	1,412	3,745
	Overall total	7,180	4,149	11,329

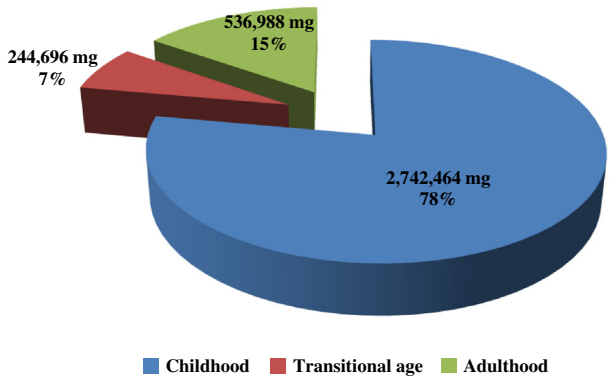

Fig. 5 Theoretical annual consumption (mg) by age group

Table 6 Estimate of the effects of device-related product wastage on growth hormone consumption for pathology

Disorder	Efficiency index					
	HAS			NICE		
	Min.	Mean	Max.	Min.	Mean	Max.
GHD	Not analyzed			1.02	1.05	1.13
TS	1.02	1.05	1.10	1.06	1.14	1.22
PWS	1.04	1.09	1.19	1.05	1.11	1.22
SGA	1.01	1.03	1.10	1.03	1.05	1.13
CRI	1.01	1.04	1.12	1.04	1.07	1.14

It is worth noting that inefficiency reflects in an analogous gap between price per mg and effective cost per mg of therapy.

We also evaluated the impact of waste, implicit in the inefficiency of the different devices available, on the results of the model applied by the French HAS and that used by Takeda for the NICE. As far as concerns the HAS, the distribution of weight per age and gender of the subjects eligible for treatment for each pathology analyzed, was determined starting from the data of the budget impact, which supplied the distribution of the age and gender of the subjects eligible for treatment. In the simulation involving Takeda's model, besides the distribution of weight by pathology, age and gender drawn from the KIGS, also applied in the Italian analysis, we also used the baseline data employed by the authors in the sensitivity analysis, for both dose per kilogram/die and for age at the start and end of treatment. The results are presented in Table 6.

In other terms, Table 6 shows our estimate of the potential gap existing between consumption predicted in the different scenarios produced by HAS and Takeda, and effective (i.e. considering devices inefficiency) consumption.

Table 7 shows both the estimated theoretical consumption and the effective consumption—i.e. theoretical plus the potential device-related wastage estimated following the model proposed in [10]—by type of device, referred to the prevalent population in Italy described above, assuming the minimum dose in mg/die, while Table 8 shows the same data, for the same patients, but assuming the maximum dose in mg/die.

As far as concerns the single-dose/disposable devices, the estimates of consumption in childhood should be decreased by those relative to patients who, because of their age and, therefore, mean body weight, exceed the dose of 2 mg/die, which is not available in this formulation. But in the proposed epidemiological model, very few patients require this dose: in fact, the estimate is 40 subjects, for an annual total consumption of 35,000 mg which is accounts for less than 1 % of the total GH consumption.

For an overall evaluation, as faithful as possible to the Italian scenario, it should also be considered that only Genotropin and Omnitrope are currently indicated for PWS.

For this syndrome, for which a unique dose (0.035 mg/kg per day) is assumed in both the scenarios hypothesized, the theoretical annual consumption of GH is 131,947 mg, which is equivalent to about 5 % of the estimated total: this consumption should be subtracted from the other brands which could, therefore, cover at most 95 % of the needs.

Overall, the data on the actual national consumption of GH actually lie between those for the minimum hypothesis (all subjects treated with the minimum dose/die and no wastage), and those for the maximum hypothesis (all subjects treated with the maximum dose/die and maximum wastage): more precisely, the actual consumption was 21.7 % higher than the theoretical minimum and 9.4 % lower than the theoretical maximum. Thus, apart from a proportion of variability in both the population being treated and in the therapeutic regimens adopted, it can be

Table 7 Theoretical and effective annual consumption by type of device (minimum dose in mg/die)

Annual theoretical consumption (mg)		Child hood	Transitional age		Adulthood	Total	Efficiency index
		2,742,464	244,696		536,988	3,524,148	
Brand[a]	Package	mg/pack	Childhood	Transitional age	Adulthood	Total	
Effective annual consumption (mg)							
Genotropin	7 syr 0.6 IU/0.2 mg	1.4	2,742,464	244,696	536,988	3,524,148	1.00
	7 syr 1.2 IU/0.4 mg	2.8					
	7 syr 1.8 IU/0.6 mg	4.2					
	7 syr 2.4 IU/0.8 mg	5.6					
	7 syr 3 IU/1 mg	7.0					
	4 syr 3.6 IU/1.2 mg	4.8					
	4 syr 4.2 IU/1.4 mg	5.6					
	4 syr 4.8 IU/1.6 mg	6.4					
	4 syr 5.4 IU/1.8 mg	7.2					
	4 syr 6 IU/2 mg	8.0					
	1vial 16 IU/5.3 mg	5.3	3,145,962	270,185	566,120	3,982,267	1.13
	1 vial 32 IU/12 mg	12.0	2,828,042	244,696	640,596	3,713,333	1.05
Humatrope	1 cart 6 mg	6.0	2,975,209	262,174	539,298	3,776,681	1.07
	1 cart 12 mg	12.0	2,828,042	244,696	640,596	3,713,333	1.05
Norditropin	"simplexx" 1 cart 15 IU/5 mg	5.0	2,885,214	254,892	551,840	3,733,850	1.05
	"simplexx" 1 cart 15 mg	15.0	2,831,442	254,892	744,882	3,831,216	1.09
Nutropin	AQ 1 cart 30 IU/10 mg	10.0	2,885,214	254,892	593,744	3,733,850	1.06
Saizen	1 vial 24 IU/8 mg	8.0	3,074,651	244,696	557,423	3,876,771	1.10
Omnitrope	1 cart 3.3 mg/ml 1.5 ml	5.0	2,889,536	254,892	551,840	3,696,268	1.05
	6.7 mg/ml 1.5 ml	10.0	2,885,214	254,892	593,744	3,733,850	1.06

[a] Only devices reimbursed by the Italian NHS has been considered; beside Zomacton 4 mg bottle has not been included because no accurate estimate of the waste was possible, due to the fact that could be re-established at different concentrations

stated the likelihood of the proposed model for estimating GH consumption.

Besides, we can note as at national level consumption, after considering device-related wastage, appears compatible with appropriate prescribing behavior and with the guarantee of full coverage of the specific therapeutic needs. But, in contrast, the comparison of the estimates and the actual consumption at regional level shows a very heterogeneous picture.

Figure 6 shows the percentage differences between consumption of GH recorded in the regions in 2011 and that of the two extreme hypothesised scenarios.

Overall, three groups of regions with reasonably homogeneous consumption can be identified (Table 8). A first group (Veneto, Campania and Friuli-Venezia-Giulia), in which the potential proportion of subjects in treatment is between 20 and 22 % of the national total, but the real consumption of GH is only 15 %; a second group, accounting for 50 % of the population, that actually consumes approximately the same proportion of the total national GH; while the third group, comprising 30 % of subjects eligible for treatment, consumes 39 % of the hormone (Table 9).

Discussion

Before 1985, the only treatment for some of the pathologies under consideration was natural GH, available in small quantities. Nowadays the availability of biosynthetic GH has overcome the problem of shortage of treatment, but raised issues of appropriateness of prescriptions.

As proof of this, the economic assessment models [7, 11], although concluding that treatment with GH is cost-effective, describe that the results are strongly influenced by the assumptions made regarding the dose and duration of the treatment.

The proposed analysis shows that other variables must also be considered in clinical practice, such as local under- or over-prescribing, as well as different degrees of drug wastage due to the use of the various devices available for the administration of GH.

Integrating the models proposed in the literature, with one that enables an evaluation of the impact of drug wastage, we aimed to check whether the levels of consumption were compatible with appropriate prescribing behaviors at a local level, a factor which could remain hidden in an analysis conducted only on a national basis.

Table 8 Theoretical and effective annual consumption by type of device (maximum dose in mg/die)

Theoretical annual consumption (mg)		Childhood	Transitional age		Adulthood	Total	Efficiency index
		3,098,960	305,870		536,988	3,941,818	
Brand	Package	mg/pack	Childhood	Transitional age	Adulthood	Total	
Effective annual consumption (mg)							
Genotropin	7 syr 0.6 IU/0.2 mg	1.4	3,098,960	305,870	536,988	3,941,818	1.00
	7 syr 1.2 IU/0.4 mg	2.8					
	7 syr 1.8 IU/0.6 mg	4.2					
	7 syr 2.4 IU/0.8 mg	5.6					
	7 syr 3 IU/1 mg	7.0					
	4 syr 3.6 IU/1.2 mg	4.8					
	4 syr 4.2 IU/1.4 mg	5.6					
	4 syr 4.8 IU/1.6 mg	6.4					
	4 syr 5.4 IU/1.8 mg	7.2					
	4 syr 6 IU/2 mg	8.0					
	1vial 16 IU/5.3 mg	5.3	3,653,690	324,222	566,120	4,544,032	1.15
	1 vial 32 IU/12 mg	12.0	3,197,045	305,870	640,596	4,143,511	1.05
Humatrope	1 cart 6 mg	6.0	3,363,488	305,870	539,298	4,208,656	1.07
	1 cart 12 mg	12.0	3,197,045	305,870	640,596	4,143,511	1.05
Norditropin	"simplexx" 1 cart 15 IU/5 mg	5.0	3,679,109	305,870	551,840	4,536,819	1.15
	"simplexx" 1 cart 15 mg	15.0	3,285,512	305,870	744,882	4,336,264	1.10
Nutropin	AQ 1 cart 30 IU/10 mg	10.0	3,258,873	305,870	593,744	4,158,487	1.05
Saizen	1 vial 24 IU/8 mg	8.0	3,314,808	305,870	557,423	4,178,101	1.06
Omnitrope	1 cart 3.3 mg/ml 1.5 ml	5.0	3,679,109	305,870	551,840	4,536,819	1.15
	6.7 mg/ml 1.5 ml	10.0	3,258,873	305,870	593,744	4,158,487	1.05

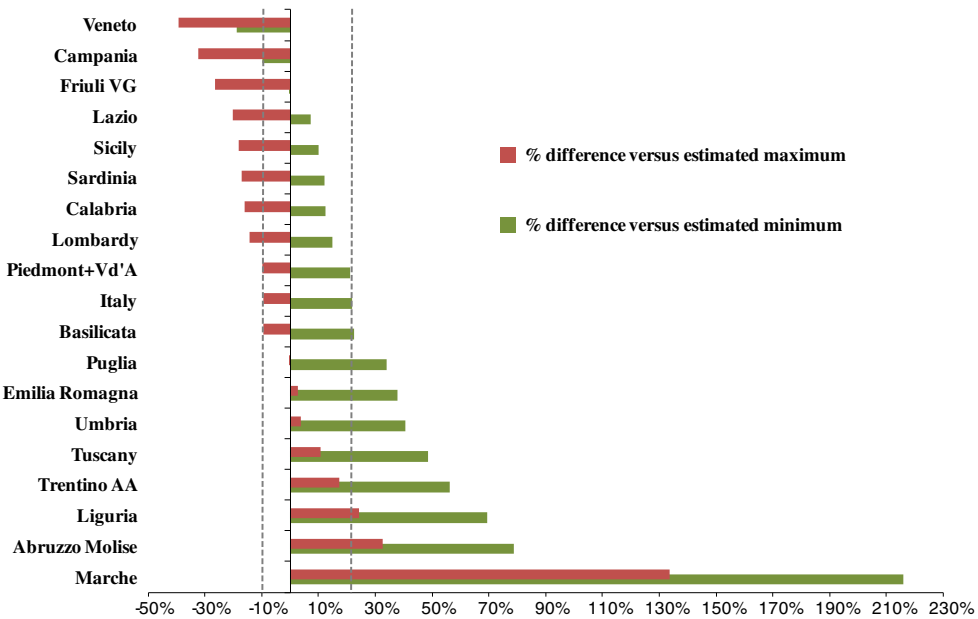

Fig. 6 Percentage difference between real and estimated minimum and maximum consumption of growth hormone per region

The model applied to the Italian population showed that there was apparently unexplainable over-prescription and potential under-prescription in various regions. The comparison of real and estimated consumption in the different regions of Italy revealed some extreme prescribing behaviors which, depending on the proposed assumptions, varied from 20 to 40 % less than the estimated theoretical consumption to over 200 %.

Table 9 Distribution by region of the subjects eligible for treatment with GH and real consumption of the product

Region	Resident population		Estimated no. of subjects to treat			GH consumption in 2011 (mg)	GH consumption pro capite[a] (mg)
	Total	5–19 years	Childhood	Transitional age	Adulthood		
Veneto	4,937,854	686,602	543	61	305	228,183	251.0
Campania	5,834,056	1,019,000	802	102	354	371,144	295.0
Friuli VG	1,235,808	152,459	112	17	78	60,038	290.0
Group 1	12,007,718	1,858,061	1,457	180	737	659,365	277.7
	20 %	22 %	22 %	21 %	20 %	15 %	
Lazio	5,728,688	797,283	619	77	354	348,579	332.0
Sicily	5,051,075	821,678	638	86	311	367,151	354.7
Sardinia	1,675,411	217,191	161	23	106	97,765	337.1
Calabria	2,011,395	310,757	254	34	126	153,135	369.9
Lombardy	9,917,714	1,352,495	1061	118	614	628,091	350.3
Piedmont + Vd'A	4,585,565	581,475	470	52	285	299,203	370.8
Basilicata	587,517	86,770	60	16	36	42,372	378.3
Group 2	29,557,365	4,167,649	3,263	406	1,832	1,936,295	352.0
	49 %	48 %	48 %	48 %	49 %	45 %	
Puglia	4,091,259	649,934	516	69	252	361,302	431.7
Emilia Romagna	4,432,418	558,835	444	52	273	321,492	418.1
Umbria	906,486	115,154	88	17	56	67,338	418.2
Tuscany	3,749,813	464,555	375	39	232	293,181	453.8
Trentino AA	1,037,114	165,301	134	17	64	103,938	483.4
Liguria	1,616,788	188,228	137	17	100	124,646	490.7
Abruzzo Molise	1,662,146	225,650	179	23	103	167,445	549.0
Marche	1,565,335	208,026	153	18	96	252,128	944.3
Group 3	19,061,359	2,575,683	2,026	252	1,176	1,691,469	489.7
	31 %	30 %	30 %	30 %	31 %	39 %	
Italy	60,626,442	8,601,393	6,746	838	3,745	4,287,129	378.4

[a] (GH 2011 actual consumption)/(Estimates of subjects to treat)

The proposed model also took into account the effect of potential hormone wastage, a variable not considered in the models so far published.

Wastage, at level of single device, for the Italian population, could amount to so much as 15 % of the consumption, demonstrating that price per mg is not in general a good proxy of the cost per mg of therapy.

Transposing our estimates of the wastage in the scenarios depicted by some of the principal HTA models published, shows a significant potential gap between predicted and possible effective consumption, that can reach 22 % for some pathologies.

In conclusion, both inappropriate prescribing (too much and too little) in real practice and waste deriving from the inefficiency of the devices available for administering GH, significantly impact on predictable consumption.

Transferability to real practice of the results obtained from the internationally published HTA's models, although appropriate sensitivity analyses have been undergone, is debatable, as far as these models do not explicitly taken into account the issue of wastage and furthermore cannot, obviously, take into account the effect of variability in local clinical practice: both factors which are considered in our model, that analyses the different regional behaviors within the national health system.

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