CRITERIA FOR FIRST-YEAR GROWTH RESPONSE TO GROWTH HORMONE TREATMENT IN PREPUBERTAL CHILDREN WITH GROWTH HORMONE DEFICIENCY: DO THEY PREDICT POOR ADULT HEIGHT OUTCOME ?

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1. Background / Aim

Several criteria for first-year growth response (FYGR) to growth hormone (GH) treatment have been proposed. We explored which FYGR criteria predicted best a poor final height outcome after GH treatment in prepubertal children with GH deficiency (GHD).

2. Subjects and methods

Height data of **129** (non acquired) GHD **children** (83 boys) who **attained adult height** and had been **treated with GH** for at least 4 consecutive years with at least 1 year before pubertal onset, were retrieved from the **Belgian GH Registry**.

First-year growth response (FYGR) parameters were: (1) increase in height (ΔHt) SDS, (2) height velocity (HV) SDS, (3) ΔHV (cm/year), (4) index of responsiveness (IoR) in KIGS prediction models[1], (5) first-year HV SDS based on the KIGS expected HV curve (HV KIGS SDS)[2], (6) near final adult height (nFAH) prediction after first-year GH treatment[3].

Poor final height outcome (PFHO) criteria were: (1) total ΔHt SDS < 1.0, (2) nFAH SDS < -2.0, (3) nFAH minus midparental height (MPH) SDS < -1.3.

ROC curve analyses were performed to define the optimal cut-off for FYGR parameters to detect PFHO. Only ROC curves with an area under the curve (AUC) of more than 70% were further analyzed.
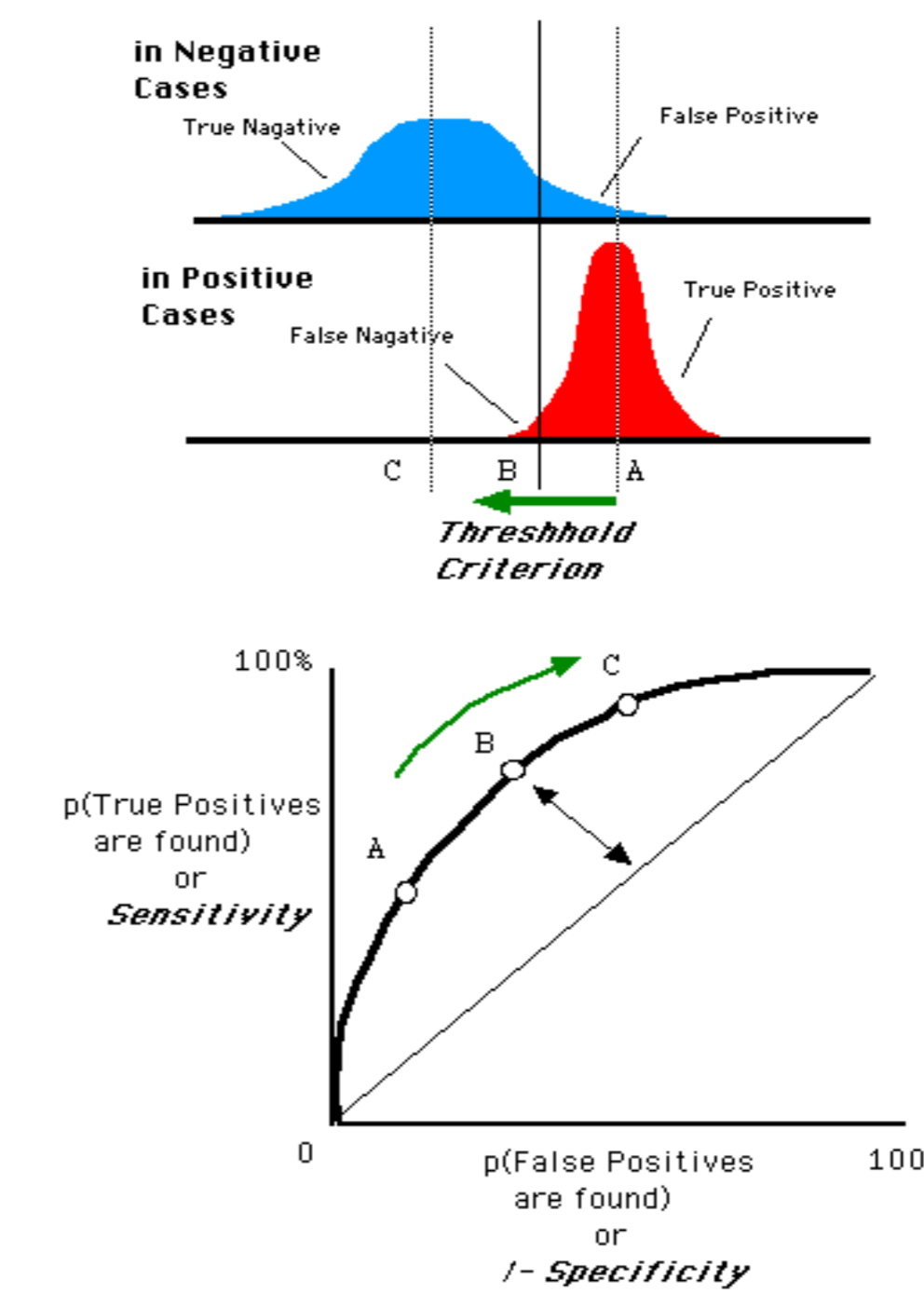

Figure: ROC is created by plotting the true positive rate (=sensitivity) against the false positive rate (=1-specificity) at various threshold settings.

Illustration: https://commons.wikimedia.org/w/index.php?curid=407628

3. Results

- Characteristics (mean): age at start 6.8 years, height SDS at start -3.31, duration of GH treatment 9.7 years, total ΔHt SDS 2.23, nFAH SDS -1.17, nFAH minus MPH SDS -0.16

- **PFHO:** total ΔHt SDS < 1: 12%, nFAH SDS < -2: 22%, nFAH minus MPH SDS < -1.3: 10%

- The currently used FYGR criteria (in bold in tables) had **low specificities and sensitivities** to detect PFHO (table 1 + 2) (no results presented for nFAH minus MPH SDS <-1.3 as all AUC's were <70%).

- To obtain a **95% specificity**, the **cut-off value (and sensitivity) of FYGR parameters** were:
  - ΔHt SDS < 0.35 (40%), HV SDS < -0.85 (43%), ΔHV < 1.3 cm/year (36%), IoR < -1.57 (17%), HV KIGS SDS < -0.83 (40%) to predict total ΔHt SDS < 1
  - predicted nFAH SDS (with GH peak) < -1.94 (25%), predicted nFAH SDS (without GH peak) < -2.02 (25%) to predict nFAH SDS < -2

- At these cut-offs, the amount of correctly diagnosed poor final responders equals the amount of false positives.

Table 1. ROC curve analysis: **cut-off values** for **first-year response and responsiveness parameters**, with its sensitivity and specificity to **predict total ΔHt SDS <1** [a] (CA)

ΔHt [b], SDS	sensitivity (%)	specificity (%)	HV, cm/yr	sensitivity (%)	specificity (%)	HV for age and sex, SDS	sensitivity (%)	specificity (%)
0.20	20	100	5.9	13	100	-1.93	14	100
0.28	33	98	6.5	33	98	-1.00	29	97
0.35	*40*	*95*	6.6	40	97	*-0.85*	*43*	*95*
0.50	**60**	**86**	*6.8*	*47*	*95*	-0.38	57	88
0.57	73	82	7.4	60	90	**1.00**	**78**	**67**
1.03	93	50	10.8	93	49	2.48	93	45
1.14	100	43	11.0	100	45	2.56	100	43
AUC: 85% (95% CI: 77 - 90%)			AUC: 85% (95% CI: 77 - 91%)			AUC: 83% (95% CI: 75 - 89%)		
ΔHV [c], cm/yr	sensitivity (%)	specificity (%)	HV for first-year GH treatment [d], SDS	sensitivity (%)	specificity (%)	IoR (without GH peak)	sensitivity (%)	specificity (%)
-2.3	27	100	-1.57	13	100	-2.24	0	100
1.2	36	97	-1.14	20	98	-1.82	8	97
1.3	*36*	*95*	**-1.00**	**33**	**97**	*-1.57*	*17*	*95*
1.6	45	92	*-0.83*	*40*	*95*	-1.28	17	92
3.2	**45**	**74**	-0.68	53	90	-0.97	58	90
4.9	82	49	1.03	93	24	0.69	92	32
5.1	100	49	1.46	100	12	1.16	100	21
AUC: 79% (95% CI: 70 - 86%)			AUC: 78% (95% CI: 70 - 85%)			AUC: 73% (95% CI: 64 - 81%)		

CA= SDS calculated at chronological age; SDS= standard deviation score; cm= centimeter; HV= height velocity; GH= growth hormone; IoR= index of responsiveness; AUC= area under the ROC curve; CI= confidence interval, [a]gain in height SDS from start of GH treatment until near final adult height; [b]gain in height SDS after first-year GH treatment; [c]HV during first-year GH treatment minus HV during pretreatment year; [d]growth targets for first-year GH response by Ranke et al.
bold= currently used FYGR criteria, italic= FYGR criteria at 95% specificity.

Table 2. ROC curve analysis: **cut-off values for predicted nFAH after first-year GH treatment**[a], with its sensitivity and specificity to **predict nFAH SDS <-2** (Prader, CA)

predicted nFAH SDS (with GH peak)[a]	sensitivity (%)	specificity (%)	predicted nFAH SDS (without GH peak)[a]	sensitivity (%)	specificity (%)
-2.62	19	100	-2.53	25	100
-1.94	*25*	*95*	*-2.02*	*25*	*95*
-1.74	44	91	-1.77	44	91
-1.65	63	90	-1.70	63	90
-1.04	88	68	-1.20	88	74
-0.87	94	55	-0.78	94	52
-0.69	100	47	-0.64	100	44
AUC: 85% (95% CI: 77 - 90%)			AUC: 84% (95% CI: 77-90%)		

nFAH= near final adult height; GH= growth hormone; SDS= standard deviation score; CA= SDS calculated at chronological age; AUC= area under the ROC-curve; CI= confidence interval; [a]prediction model for nFAH after first-year GH treatment by Ranke et al.

> **Example:** first-year ΔHt SDS <0.5 has a sensitivity of 60% and a specificity of 86% to predict total ΔHt SDS <1.
> Sens 60% = 60% of **poor** final responders (FR) has a **poor** first-year response (FYR), 40% of **poor** FR has a **good** FYR
> Spec 86% = 86% of **good** FR has a **good** FYR, 14% of **good** FR has a **poor** FYR

References: 1. Ranke MB, Lindberg A: Observed and predicted growth responses in prepubertal children with growth disorders: guidance of growth hormone treatment by empirical variables. J Clin Endocrinol Metab 2010;95:1229-1237
2. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA: Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study. J Clin Endocrinol Metab 1999;84:1174-1183.
3. Ranke et al. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr 2013;79:51-67.

4. Conclusion

First-year growth response criteria perform poorly as predictors of poor final height outcome after long-term GH treatment in prepubertal GHD children.

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