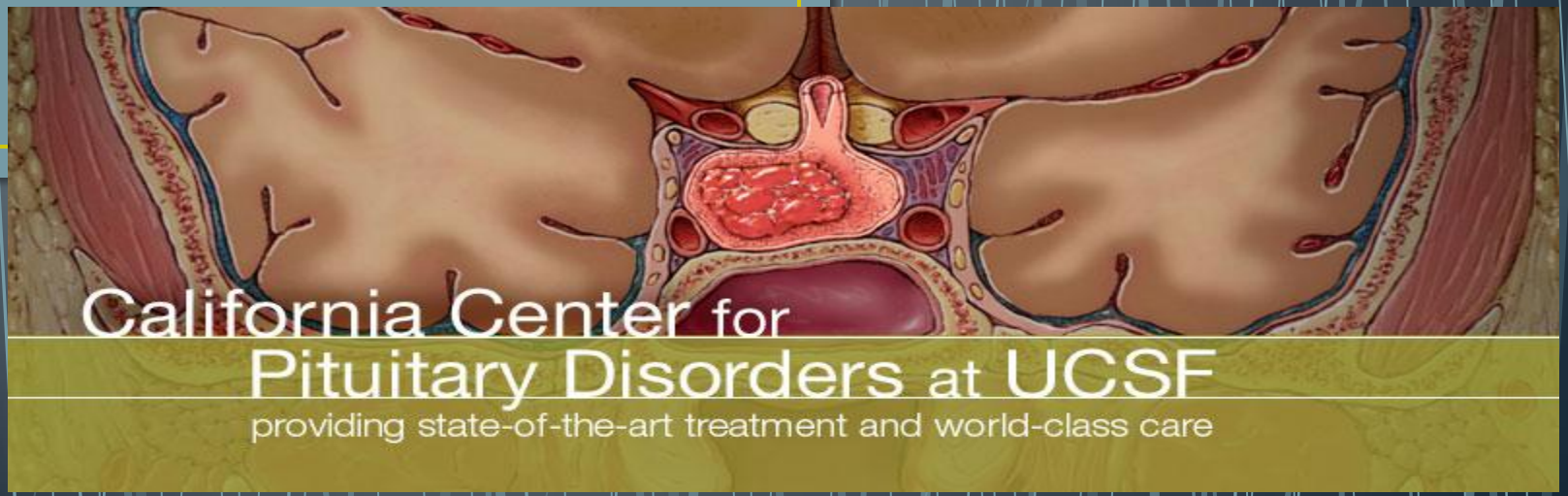
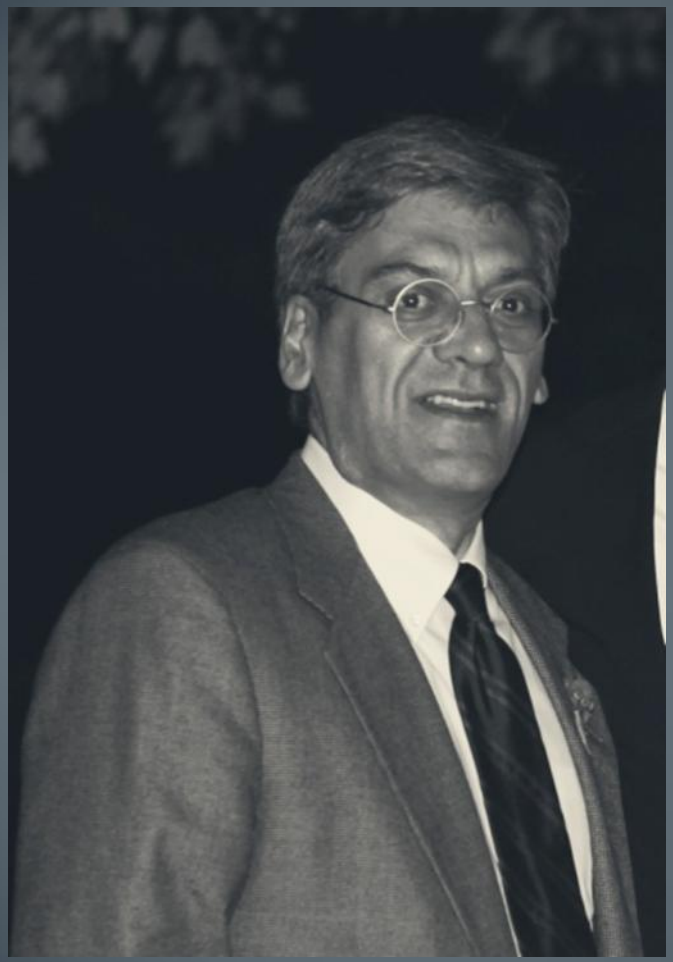
Acromegaly: 25 years of Growth

Lewis S. Blevins Jr., M.D.



Acromegaly: 25 years of Growth



Onset of Acromegaly ~ 25 yrs ago
- Profound changes in appearance
- Medical problems

My first patient with GH excess ~ 25 yrs ago
- oGTT
  - oGTT cutoffs evolved
  - IGF-1 assays
- Computed Tomography
  - dynamic enhanced MRI
- Conventional XRT
  - Stereotactic
- Bromocriptine
  - Sandostatin sc 1992
  - Cabergoline 1996-1997
  - Sandostatin LAR 1999
  - Pegvisomant 2003
  - Lanreotide 2008
  - Pasireotide ?
- Molecular pathogenesis
- Mortality data defining remission

We are witnessing an evolution in the treated natural history of the disease!

Cushing's monsters

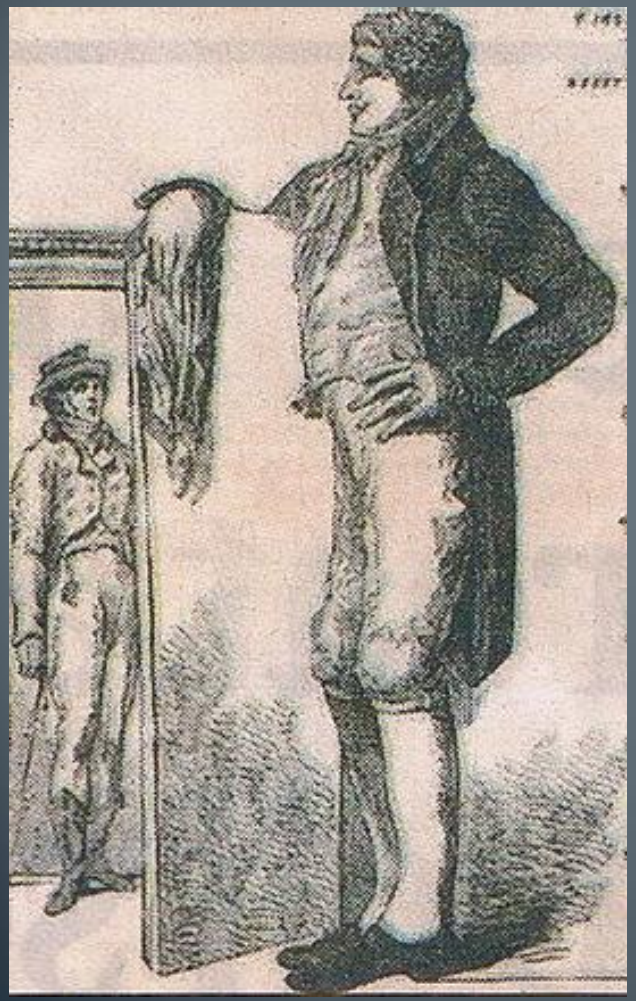
James H. Buchanan, PhD

'Nature knows no differences but rather believes that all is beautiful, all is sublime and precious that is its own. It is we humans who speak of gods and monsters, of mis-formed and well-formed, of beauty and ugliness. Nature knows nothing of this.'

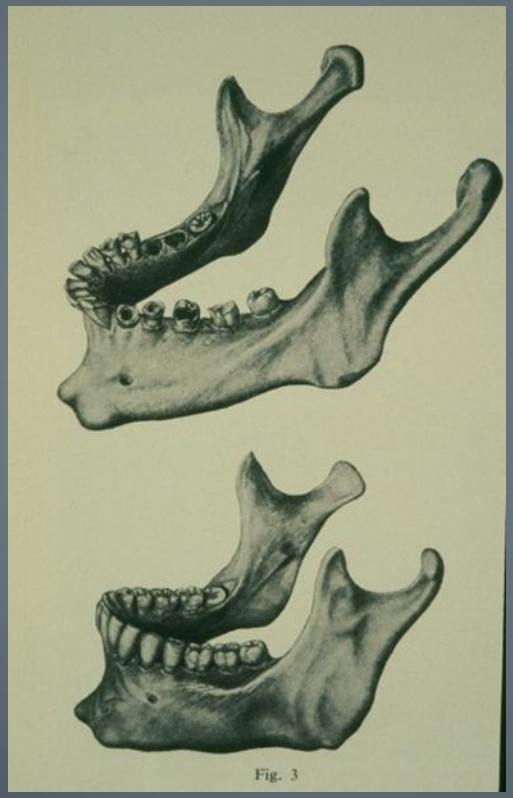
Rondo Hatton starred in "The Pearl of Death" And "The House of Horrors."

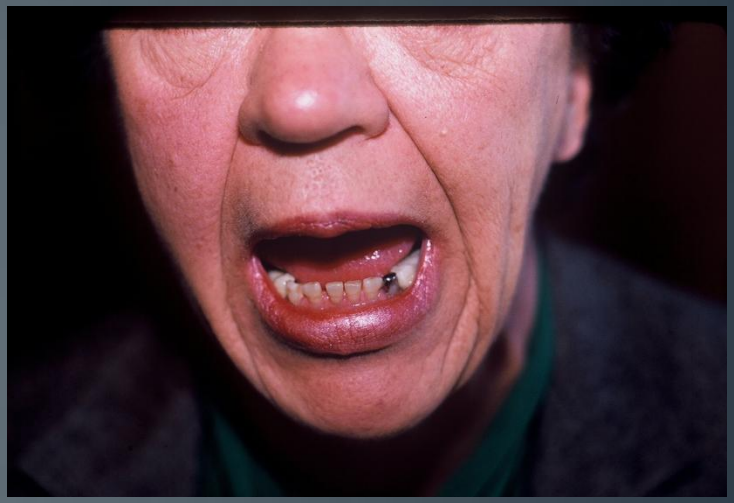
Charles Byrne
The Irish Giant 8’4”

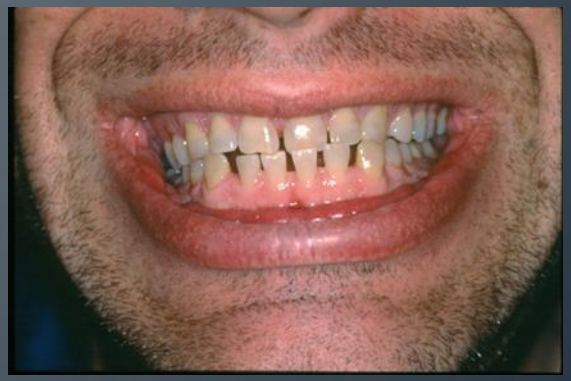
AIP mutation



Acromegaly

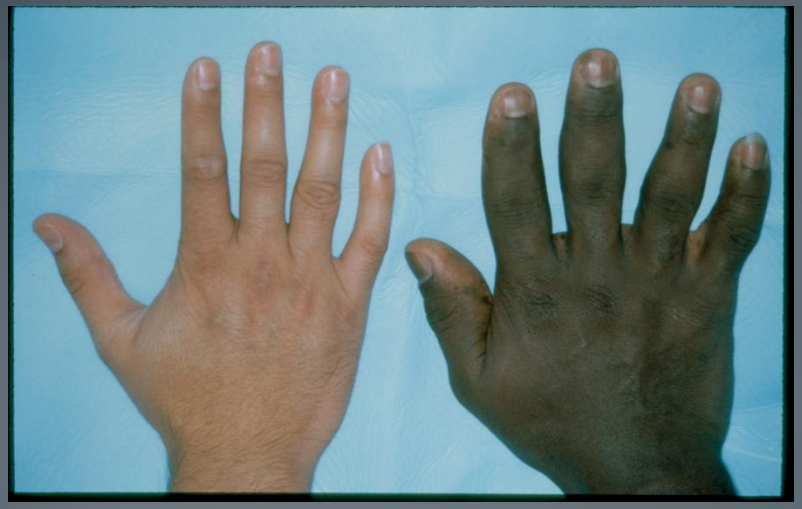


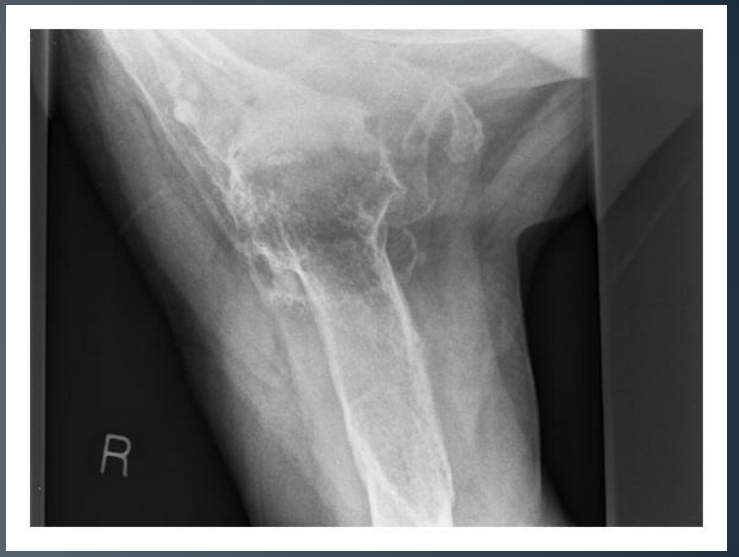


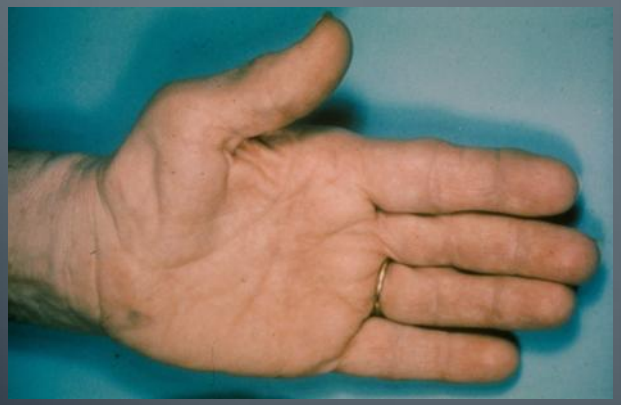


Prognathism and separation of the mandibular teeth

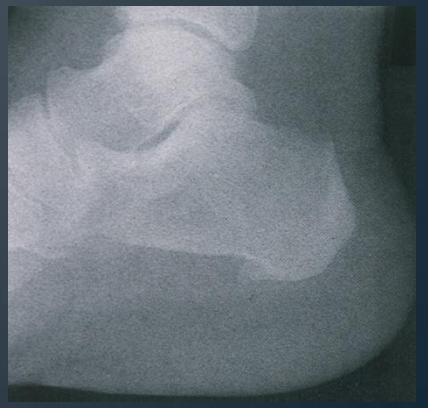
Acromegaly



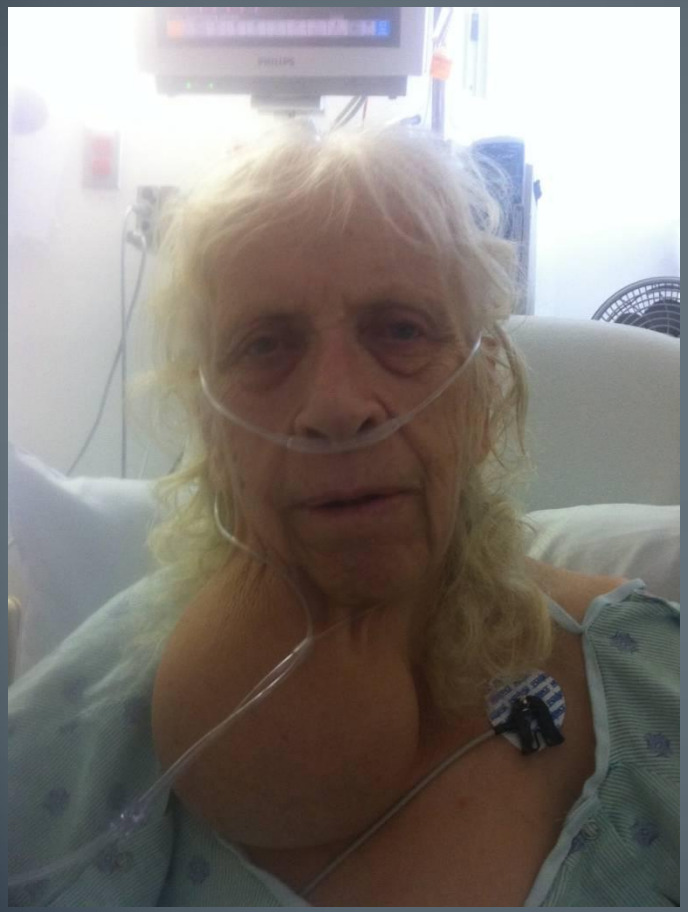




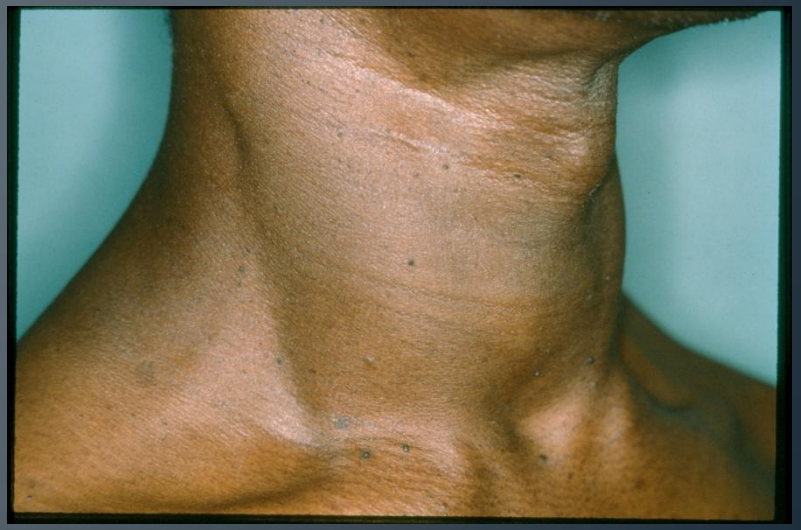
Acral enlargement
CTS with thenar wasting
Arthropathy



Acromegaly

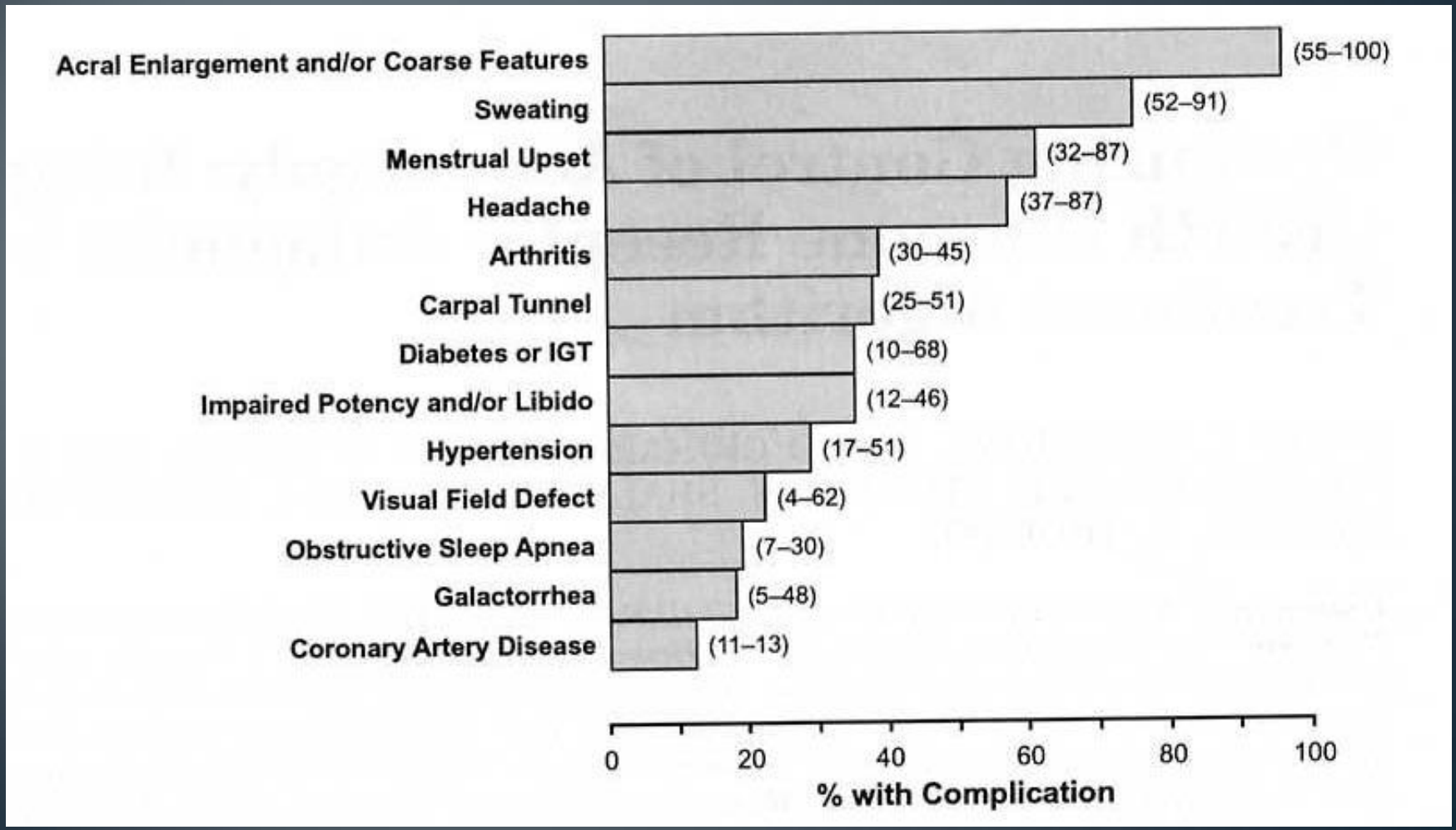


Toxic MNG due to Acromegaly and a 2 cm GH secreting adenoma



Diffuse goiter due to a combined GH and TSH-secreting adenoma

Acromegaly: Clinical Features



Acromegaly: Mode of Presentation

MODE OF PRESENTATION OF ACROMEGALY

Presenting Chief Complaint	Frequency (%)*
Menstrual disturbance (females)	13
Change in appearance/acral growth	11
Headaches	8
Paresthesias/carpal tunnel syndrome	6
Diabetes mellitus/impaired glucose tolerance	5
Heart disease	3
Visual impairment	3
Decreased libido/impotence (men)	3
Arthropathy	3
Thyroid disorder	2
Hypertension	1
Gigantism	1
Fatigue	0.3
Hyperhidrosis	0.3
Somnolence	0.3
Other	5
Chance (detected by physician, dentist, x-ray)	40

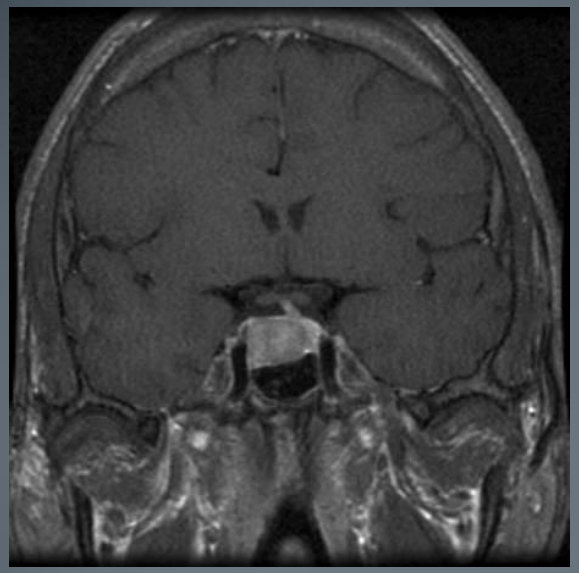
*Based on analysis of 310 patients from Klijn et al[57] and Nabarro.[82]

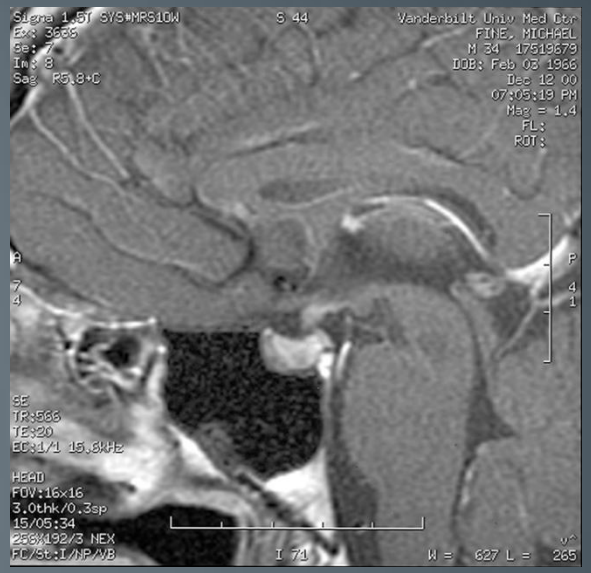
Acromegaly
Epidemiology

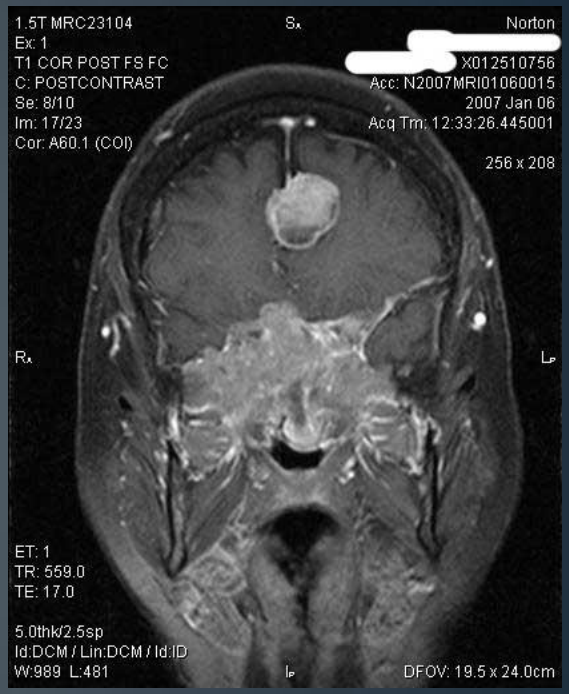
- Incidence: 3-4/million annually
- Prevalence: 40-90 cases/million
- Diagnosis delayed: ~4-10 yrs
- Primary cause: pituitary tumor
  - >75% macroadenomas
- Rare genetic syndromes
- GHRH secreting tumors (Pancreatic, Bronchial)

Paisley A, Trainer PJ. *Expert Opin Investig Drugs.* 2006;15(3):251-256. Colao A, et al. *Endocrinol Rev*. 2004;25(1):102-152. Melmed S. *N Engl J Med*. 2006;355(24):2558-2573.Clemmons D, et al. *J Clin Endocrinol Metab*. 2003;88(10):4759-4767.

Acromegaly
Pituitary Adenomas



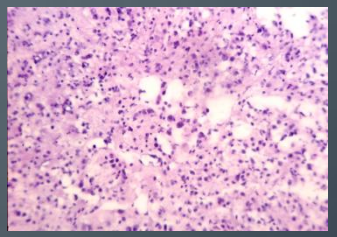


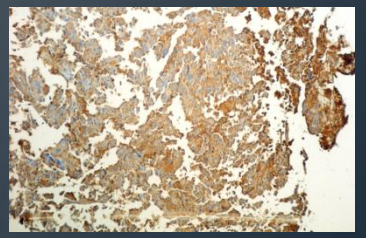


Macroadenomas 75%
Microadenomas 25%

“Micromegaly”
“Giant” adenomas

Co-secreting Tumors (PRL, TSH)
Double Adenomas





Hereditary Forms of Acromegaly

- Multiple Endocrine Neoplasia, Type 1 (MEN-1)[1]
- Carney Complex (CNC)[1]
- Isolated Familial Somatotropinomas (IFS)[2]
- Familial Isolated Pituitary Adenomas (FIPA)[3]
- McCune-Albright Syndrome

Although these syndromes are very uncommon, information learned from these hereditary syndromes provides insight into the molecular mechanisms underlying the development of sporadic GH-secreting tumors

1. Melmed S. Mechanisms for pituitary tumorigenesis: the plastic pituitary. J Clin Invest 2003;112(11):1603–18.
2. Soares BS and Frohman LA. Isolated Familial Somatotropinoma. Pituitary 2004;7:95–101.
3. Beckers A, Daly AF. The clinical, pathological, and genetic features of familial isolated pituitary adenomas. Eur J Endocrinol 2007; 157: 371–82.

MEN-1: Pituitary Tumors

Characteristics of 136 pituitary adenomas in MEN-1 patients (France/Belgium Registry)[1]

(%) Tumor Types		Macroadenomas
62%	Prolactinomas (n=85)	84%
9%	Somatotropinomas (n=12)	100%
4%	ACTH-secreting (n=6)	50%
10%	Multihormone secreting (n=13)	77%
15%	Non-functioning (n=20)	100%
	LH/FSH-secreting (n=2)	

- No genotype-phenotype correlations[1]
- Tumors tend to be larger and more aggressive[1]

1. Verges B et al. Pituitary Disease in MEN Type 1 (MEN1): Data from the France-Belgium MEN1 Multicenter Study. J Clin Endocrinol Metab 2002;87:457–65.

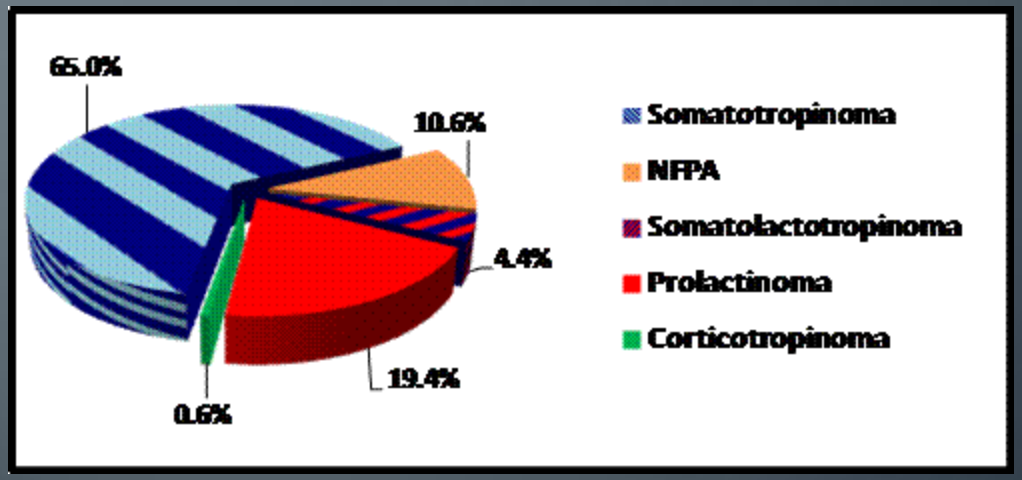
Isolated Familial Somatotropinoma

- 108 patients in 46 families[1]
- Median age at diagnosis[1] — 26 years
- Age at diagnosis <30 years[1] — 73%
  - Males[1] — 57%
- Macroadenoma frequency[1] — 88%
- Gigantism[1] — 12%
- Prolactin immunoreactivity[1] — 57%
  - Most have mild hyperprolactinemia
- Genetic locus (based on tumor deletion mapping and meiotic recombination analysis)[2]
  - 2.2 Mb interval — 11q13

1. Soares BS and Frohman LA. Isolated Familial Somatotropinoma.Pituitary 2004;7:95–101.
2. Soares BS et al. Tumor Deletion Mapping on Chromosome 11q13 in Eight Families with Isolated Familial Somatotropinomas and in 15 Sporadic Somatotropinomas. J Clin Endocrinol Metab 2003;88:4480–7.

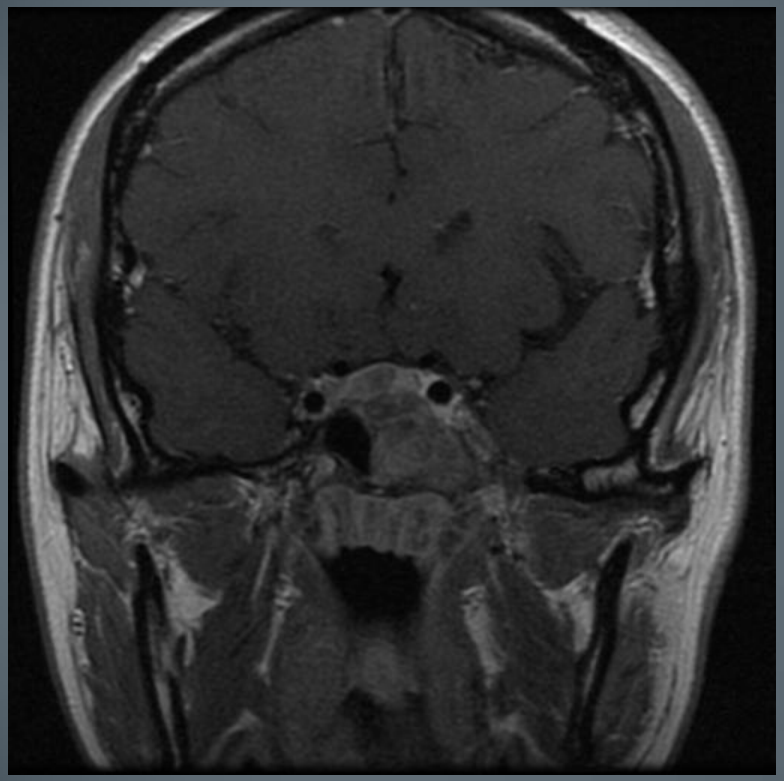
"Pituitary Adenoma Predisposition" Gene: AIP – Aryl Hydrocarbon Receptor Interacting Protein

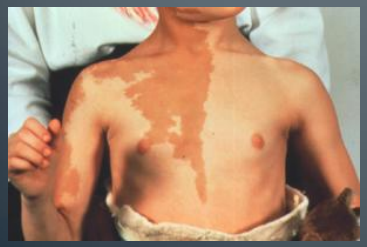
- Tumor suppressor gene 11q13
- Autosomal Dominant with incomplete penetrance
- Found in the Irish Giant and at least 4 Irish families with Familial Acromegaly
- Estimated to have occurred 1500 years ago
- 3% of sporadic Italian acromegalic patients (Eur J Endocrinol. 2010 Sep;163(3):369-76. Epub 2010))

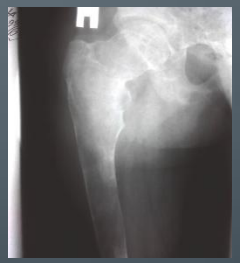


1. Yano M, Terada K, Mori M. AIP is a mitochondrial import mediator that binds to both import receptor Tom20 and preproteins. J Cell Biol. 2003;163(1):45–56.
2. Vierimaa O et al. Pituitary Adenoma Predisposition Caused by Germline Mutations in the AIP Gene. Science 2006;312:1228–1230.
3. Marlowe T, Puga A. Aryl Hydrocarbon Receptor, Cell Cycle Regulation, Toxicity, and Tumorigenesis. J Cell Biochem. 2005;96:1174–84.
4. Tuppurainen K, et al. The Role of the Aryl Hydrocarbon Receptor Interacting Protein Gene in Familial and Sporadic Pituitary Adenomas. J Clin Endocrinol Metab. 2006;91:2369–2401.

McCune Albright Syndrome
GNAS1 gene mutation







15 year-old girl
Classical features include:
-fibrous dysplasia of bone (hip, spine, sphenoid)
-"Coast of Maine" hyperpigmentation
-pituitary adenoma, hyperplasia, transitional zones

IGF-1 791 ng/mL (217-589)
GH 26.5 ng/mL

Rx'd SSA

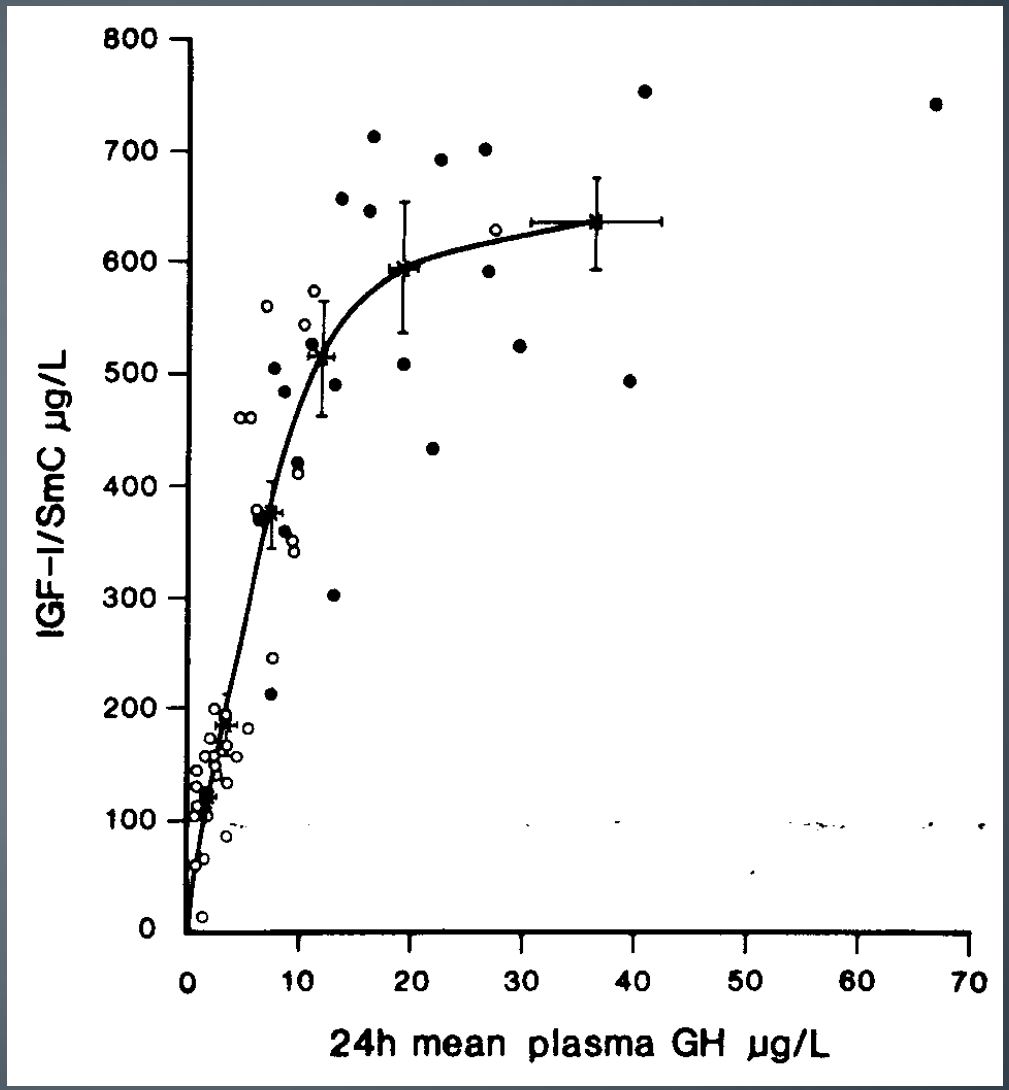
IGF-1 585 ng/mL (217-589)
GH 10 ng/mL

Diagnosis of Acromegaly
IGF-1 Assays

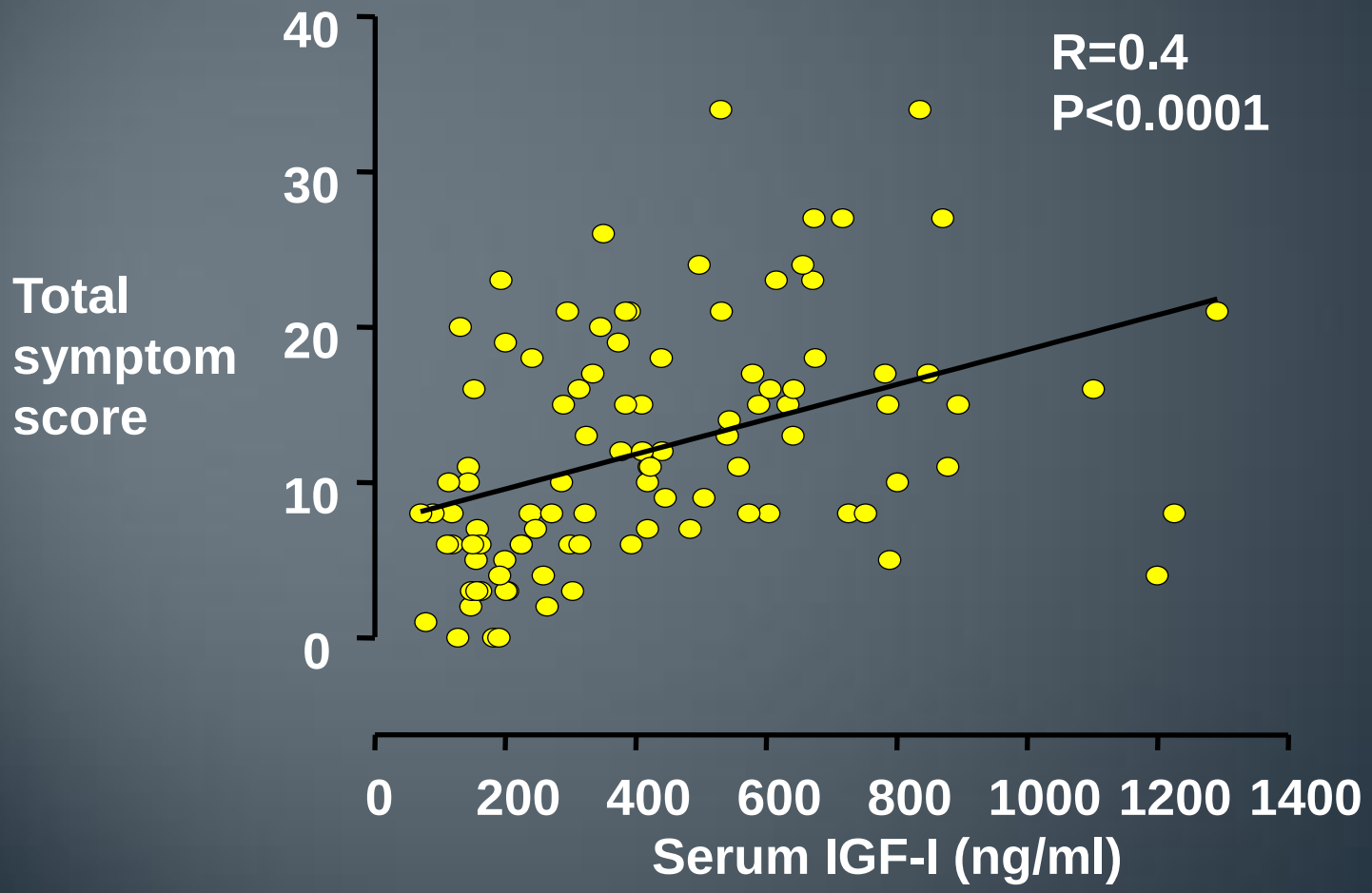
- Usually correlates well with nadir GH on OGTT in acromegaly patients[1]
  - IGF-1 should always be interpreted with reference to GH levels
- Levels are altered with age, gender and pregnancy[1]
- Considered the most sensitive and specific diagnostic test[1]
- However, there are issues with the IGF-1 assay
  - Lack of standardization[2]
  - Difficulty in comparing results between laboratories[3]
  - False negative and false positive IGF-1 levels

1. Brooke AM & Drake WM. Serum IGF-I levels in the diagnosis and monitoring of acromegaly. Pituitary 2007;10:173–9.
2. GHRS (Growth Hormone Research Society; Pituitary Society). Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. J Clin Endocrinol Metab. 2004; 89:3099–102.
3. Lim EC, Pullan P. Consensus Statement Review. Biochemical Assessment and Long-Term Monitoring in Patients with Acromegaly: Statement from a Joint Consensus Conference of The Growth Hormone Research Society and The Pituitary Society. (J Clin Endocrinol Metab. 2004;89:3099–102) Clin Biochem Rev 2005;26:41–3.

Relation of IGF-1 to GH levels

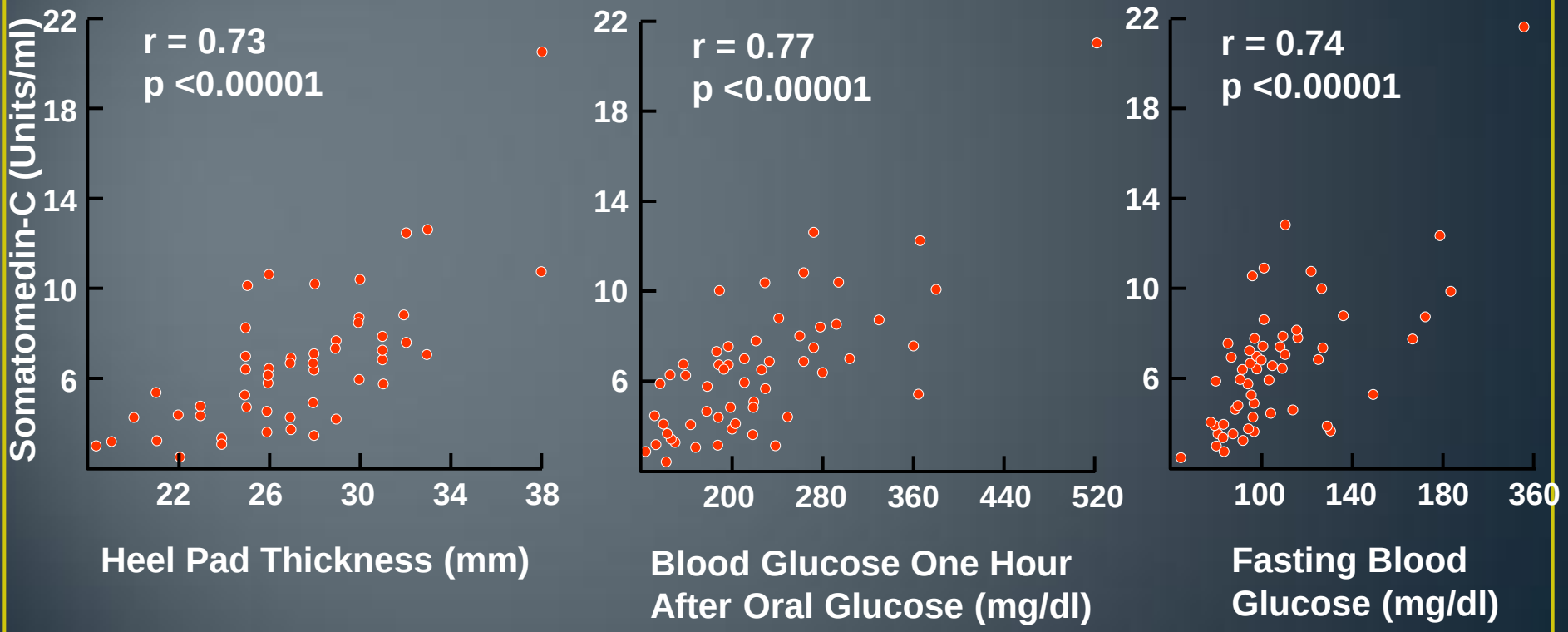


Correlation between total symptoms score and serum IGF-I in patients on medical therapy



Parkinson et al British Endocrine Society, Belfast 2001

Correlation b/w IGF-I and Clinical Findings



Clemmons, D. et al. N Engl J Med 1979;301:1138-42

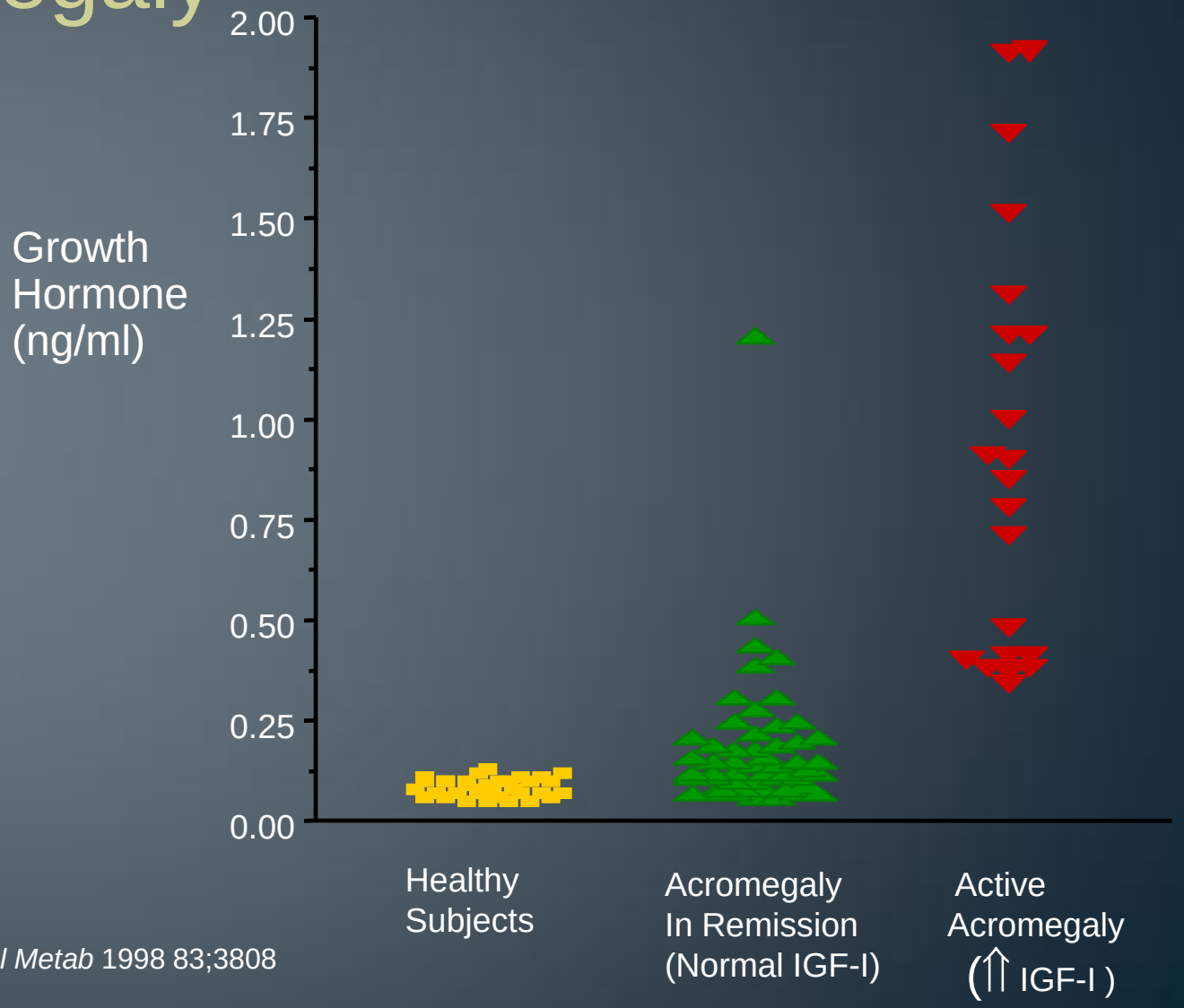
Diagnosis of Acromegaly
Use of GH Measurements

- Random GH levels are not generally useful
  - lacks specificity: overlaps with upper range in healthy subjects, and is elevated in patients with poorly controlled diabetes mellitus, renal failure and malnutrition2
- Measuring GH during a 75g OGTT is the standard technique for the diagnosis of acromegaly[1]
- False-positives may occur with diabetes mellitus, liver disease, renal disease, adolescence and anorexia nervosa

I tend to employ oGTT in the following scenarios:
- elevated IGF-1 in absence of clinical findings of Acromegaly or pituitary tumor
- post operative patients with high normal IGF-1, possible tumor, GH > 1 ng/mL

1. AACE Acromegaly Guidelines Task Force. AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract 2004;10:213–25.
2. Freda PU. Pitfalls in the biochemical assessment of acromegaly. Pituitary 2003;6:135–40.
3. Pulc' A S et al. Guidelines for the diagnosis and treatment of acromegaly: a Canadian perspective. Clin Invest Med 2005;28:172–187.

Nadir GH during OGTT by IRMA in Acromegaly

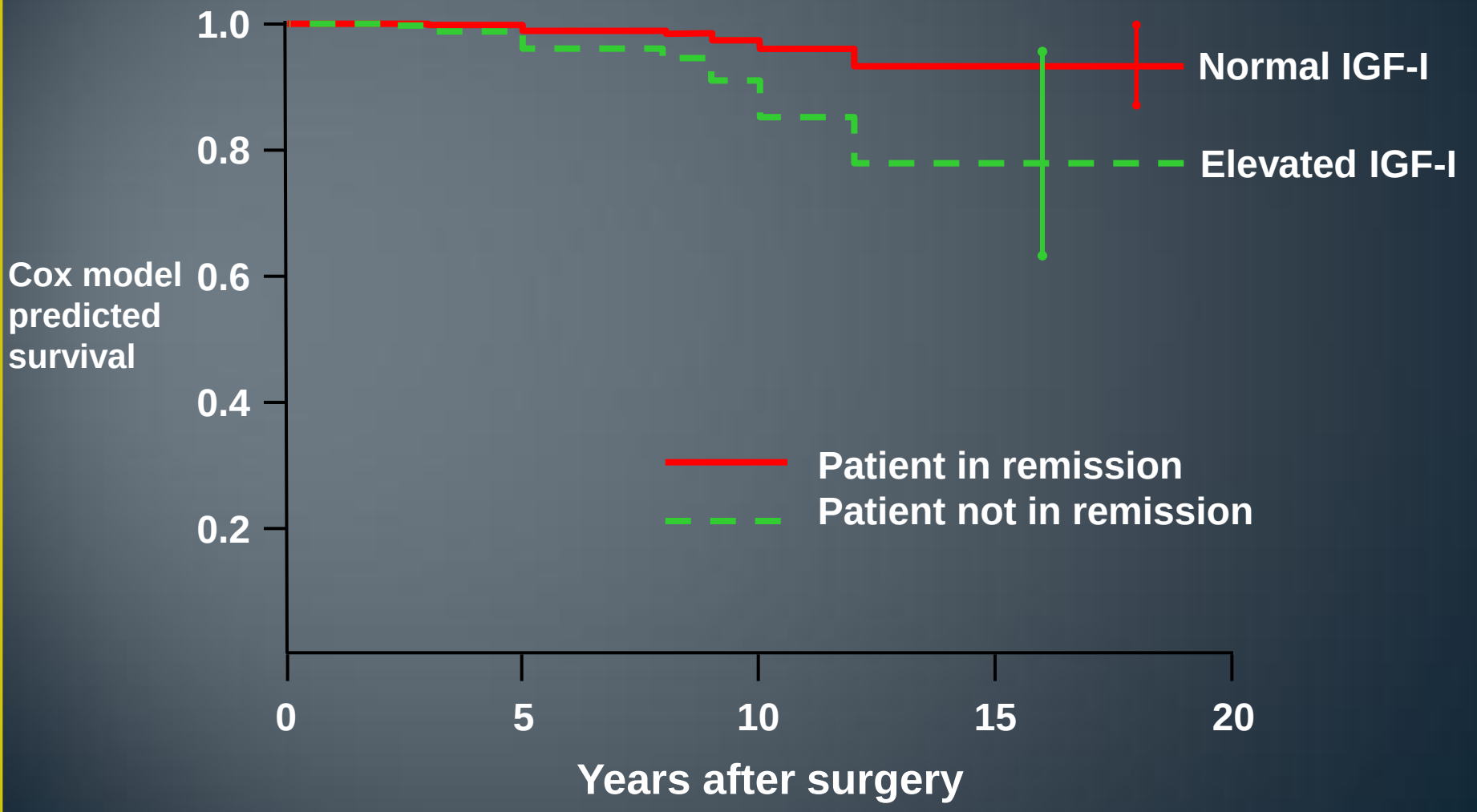


Freda P et al., *J Clin Endocrinol Metab* 1998 83;3808

Acromegaly
Goals of Therapy

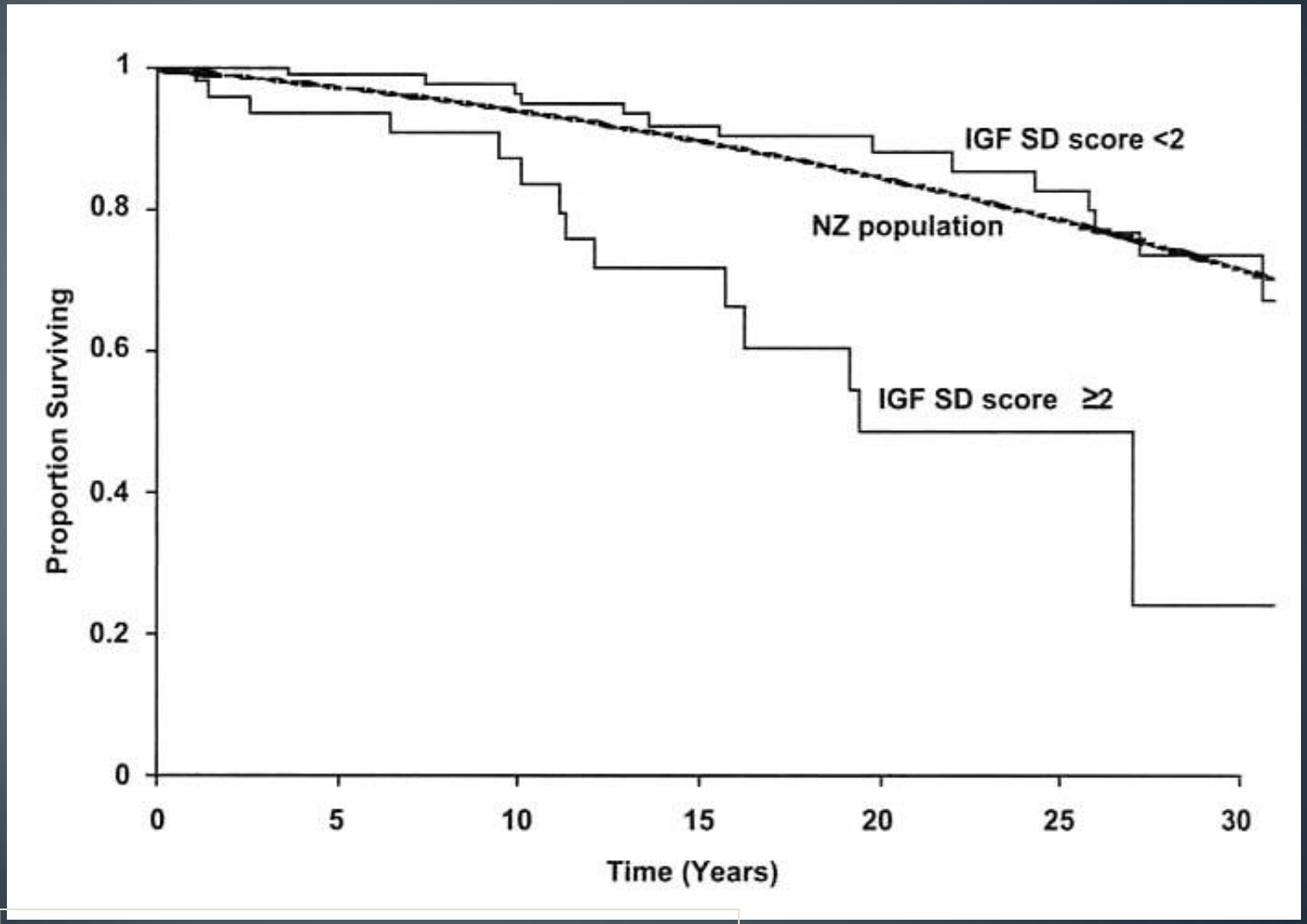
- "It's nearly impossible to cure a patient with Acromegaly these days"
- Resect or remove tumor
  - Resolution of mass effects
  - Prevention of progression
- Preserve or improve pituitary function
- Improvement in symptoms and signs
- Improve survival
  - Normalize IGF-1 and GH

Long-term Mortality After Transsphenoidal Surgery



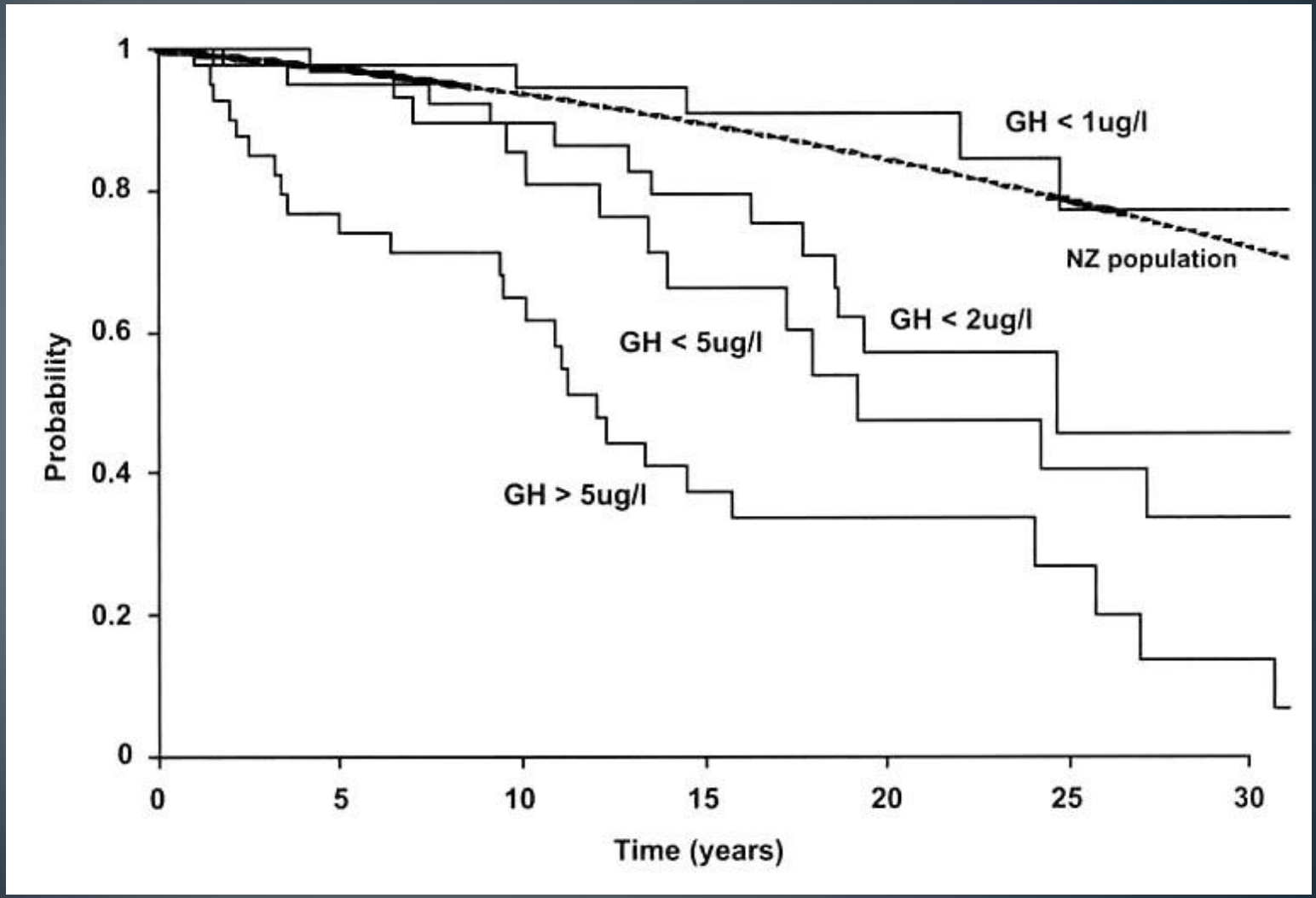
Swearingen, B. et al. *J Clin Endocrinol Metab* 1998;83:3419

Survival as a function of IGF-1 levels



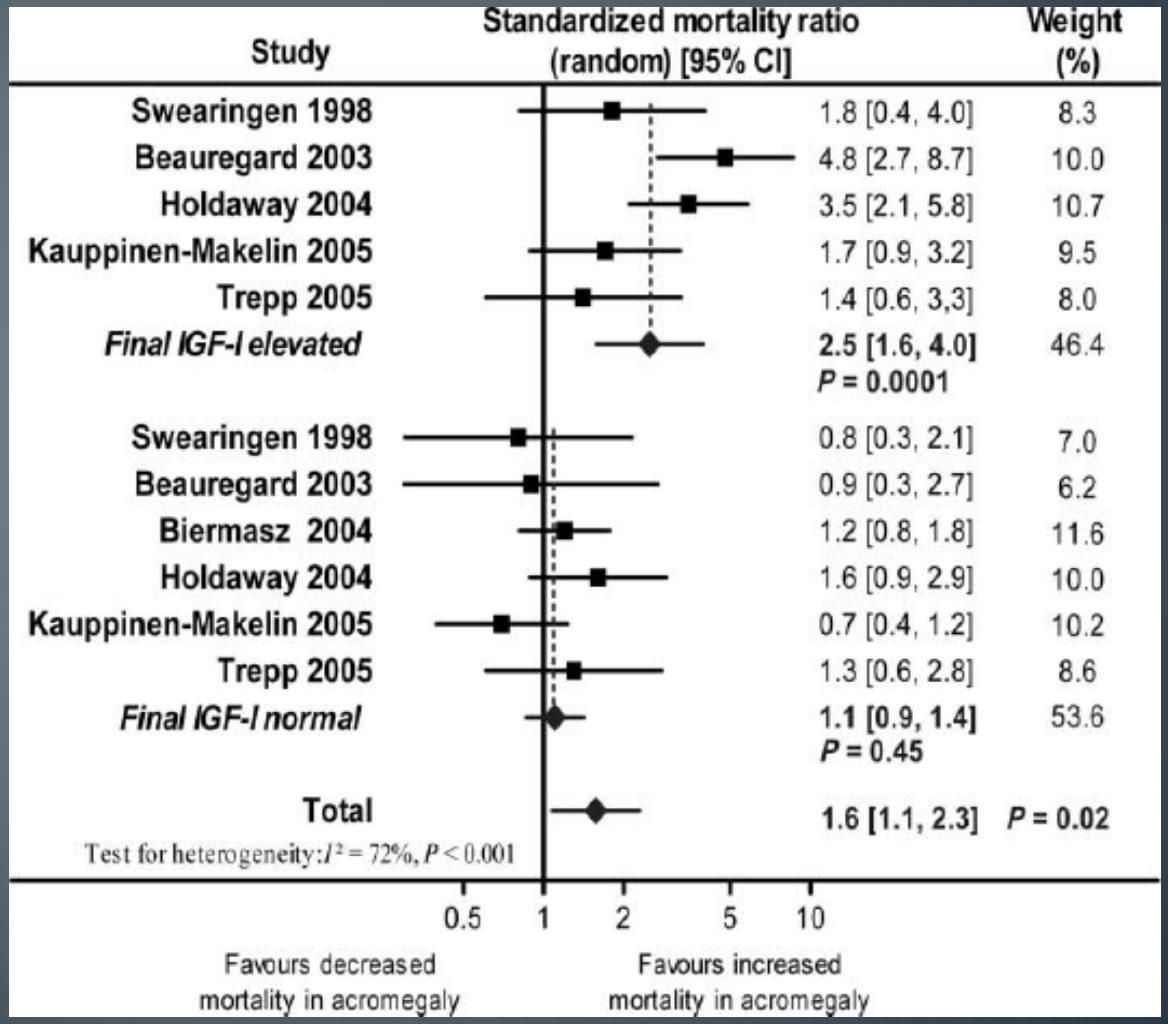
Holdaway et al. JCEM 89:667-674,2004

Survival as a function of GH levels



Holdaway et al. JCEM 89:667-674,2004

SMR in Acromegaly



Criteria for Remission in Acromegaly

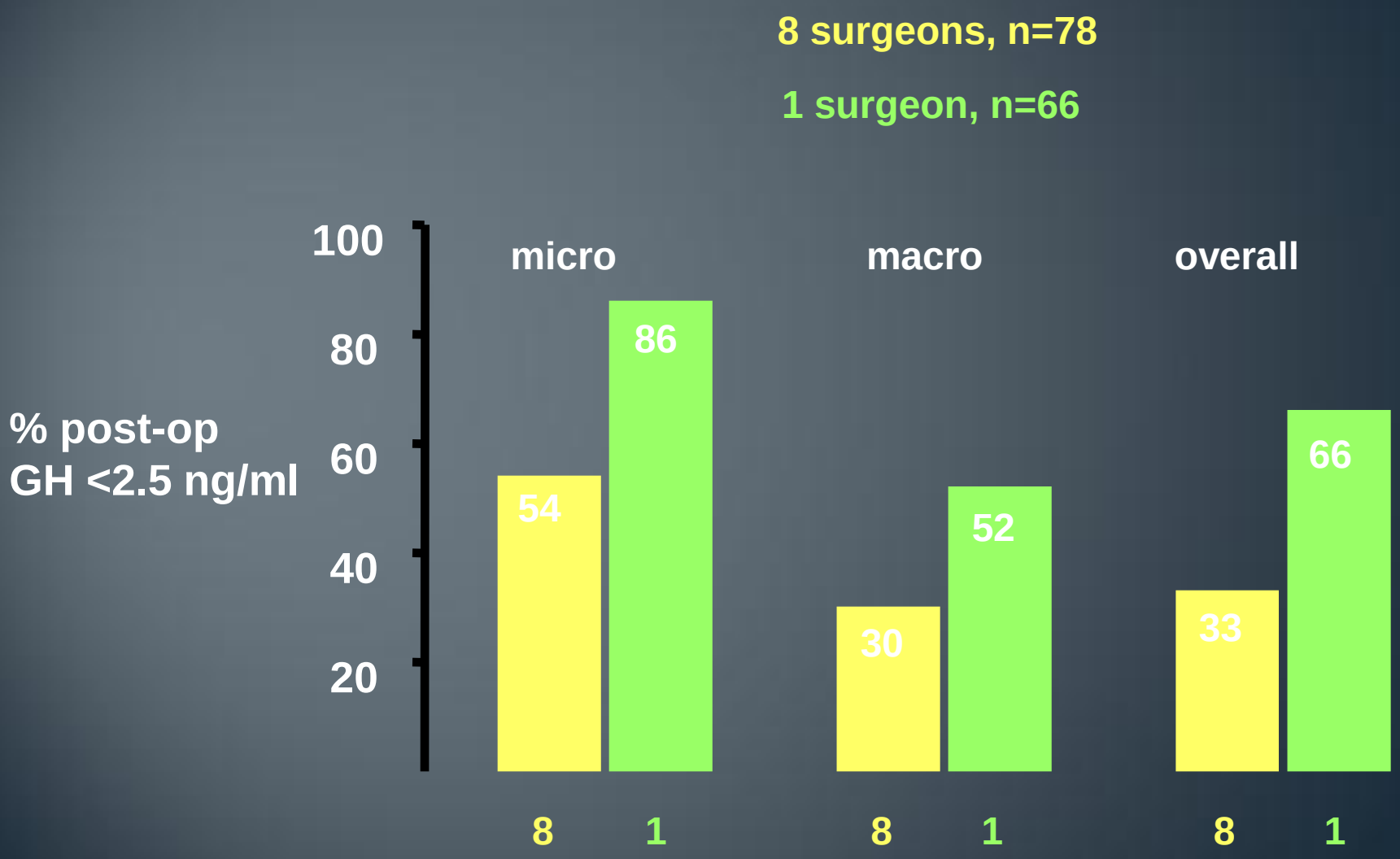
- 25 years ago:
  - Random GH < 5 ng/mL
  - GH < 2 ng/mL post oral glucose
- Today:
  - IGF-1 normal
  - Random GH < 1 ng/mL
  - GH < 0.4 ng/mL post oral glucose

Surgical Remission Rates

Pts Range N=98-181	% Cured Micros/Macros	Criteria
Swearingen	91/48	NL IGF-I and/or GH <2.5 OGTT
Freda	88/53	NL IGF-I and/or GH <2.0 OGTT
Beauregard	82/60	NL IGF-I and GH <1.0 OGTT
Shimon	84/64	NL IGF-I and GH <2.0 OGTT
Krieger	78/31	Random GH <2.0

Swearingen B, et al. *J Clin Endocrinol Metab*. 1998;83(10):3419-3426; Freda PU, et al. *J Neurosurg*. 1998;89(3):353-358; Beauregard C, et al. *Clin Endocrinol (Oxf)*. 2003;58(1):86-91; Shimon I, et al. *Neurosurgery*. 2001;48(6):1239-1243; Krieger MD, et al. *J Neurosurg*. 2003;98(4):719-724.

The Birmingham pituitary surgery experience

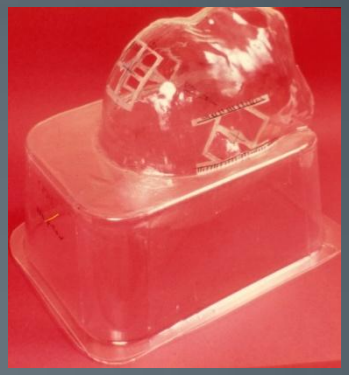


Gittoes et al QJM 1999:92;741-5

Post-op Follow-up and Whom To Treat– Current Clinical Practice?

	Nadir GH <1 µg/L	Nadir GH >1 µg/L
IGF-I Normal	No treatment	?
IGF-I Elevated	"Treat"	Treat

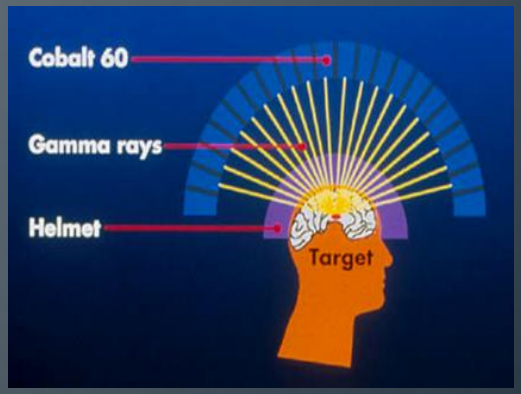
Radiotherapy



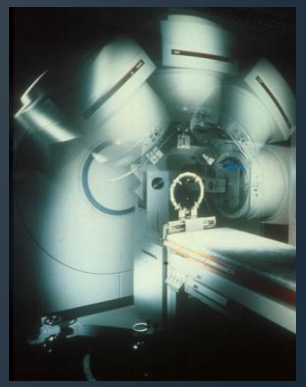
proton beam

- **Conventional**
  multi-fractional
- **Stereotactic**
  single fraction
  less radiation to surrounding tissues

- ✓ **gamma knife**
- ✓ **LINAC**
- ✓ **proton beam**
- ✓ **CPK**

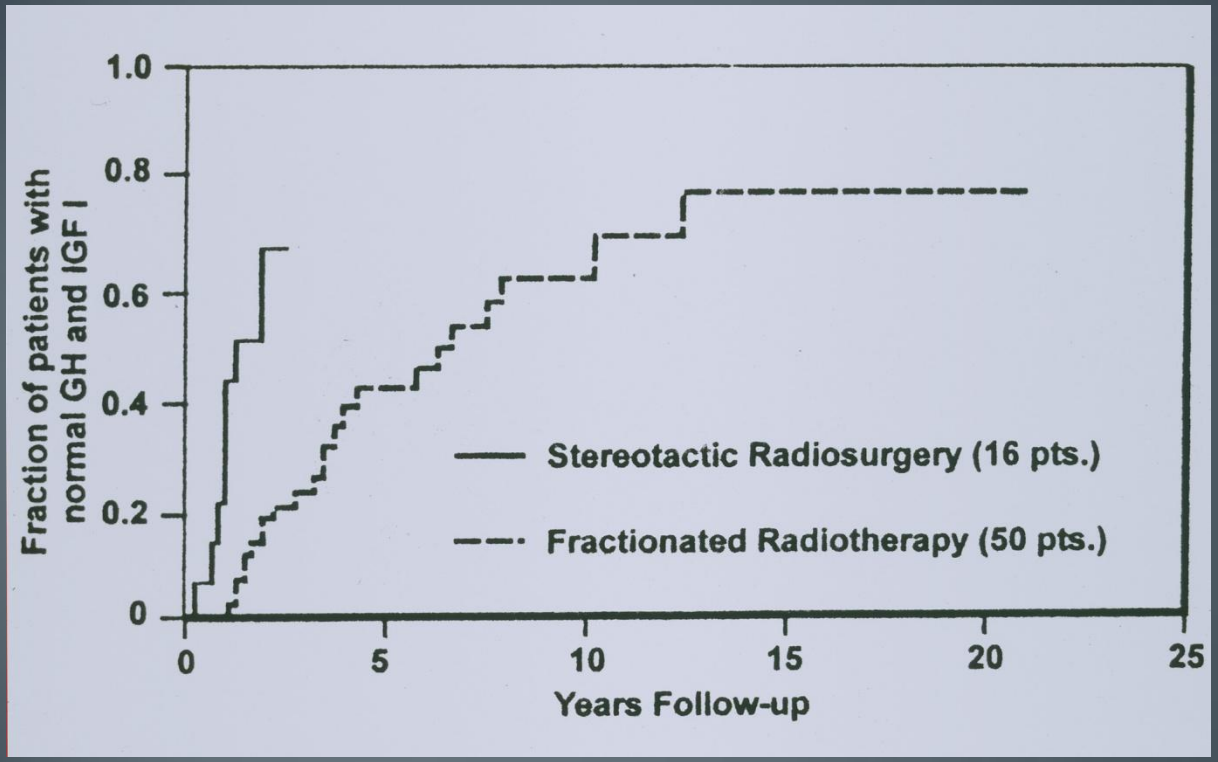


Gamma knife



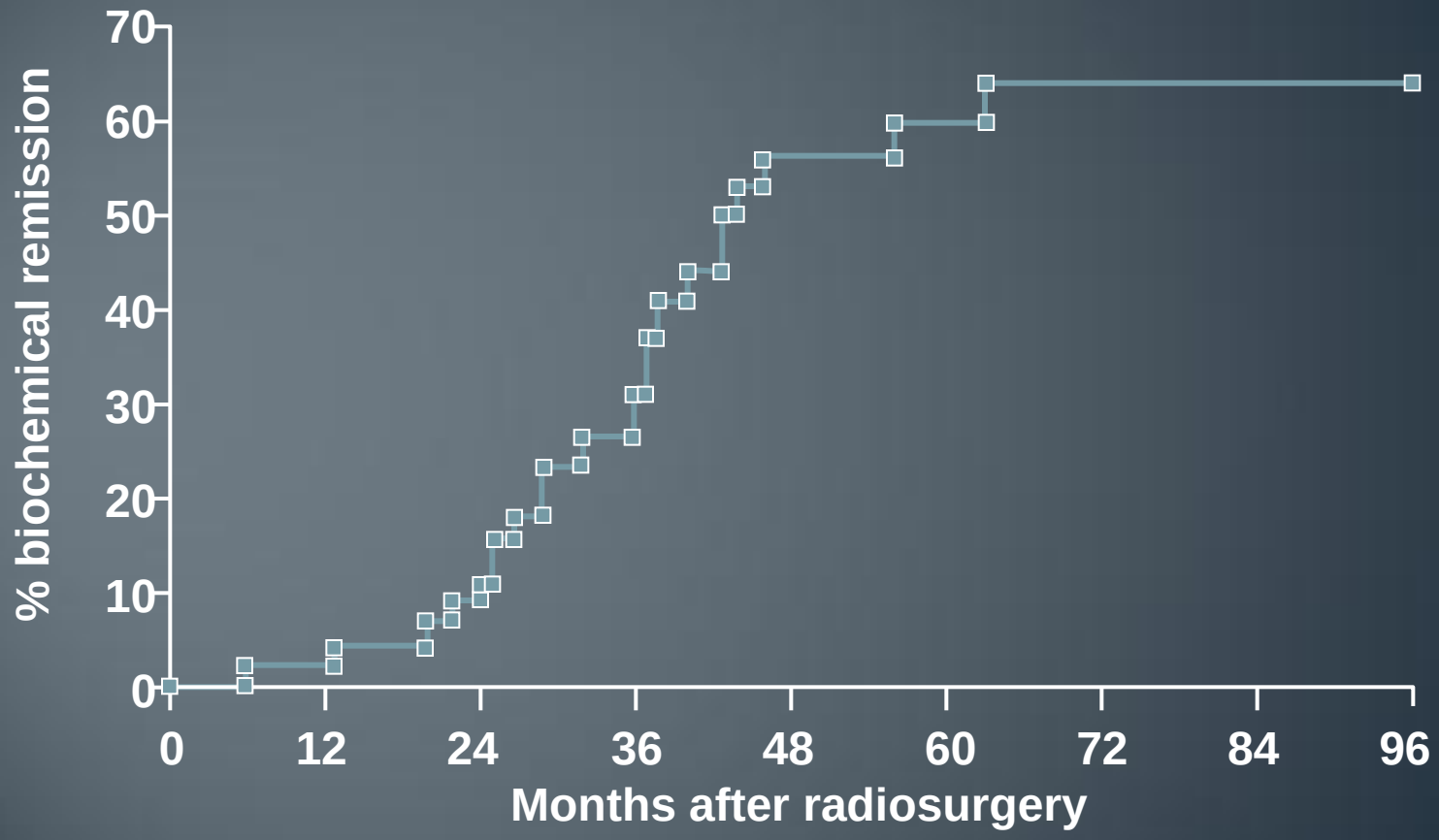
LINAC

Acromegaly: Radiotherapy



Hypopituitarism in 65%
Second neoplasms 60-fold increase
AVM's

Acromegaly Response to Radiosurgery



Pollock BE, et al. *J Neurosurg*. 2007;106(5):833-838.

Radiotherapy
A Recommended Approach

- 25 years ago:
  - Conventional XRT in all patients following pituitary surgery

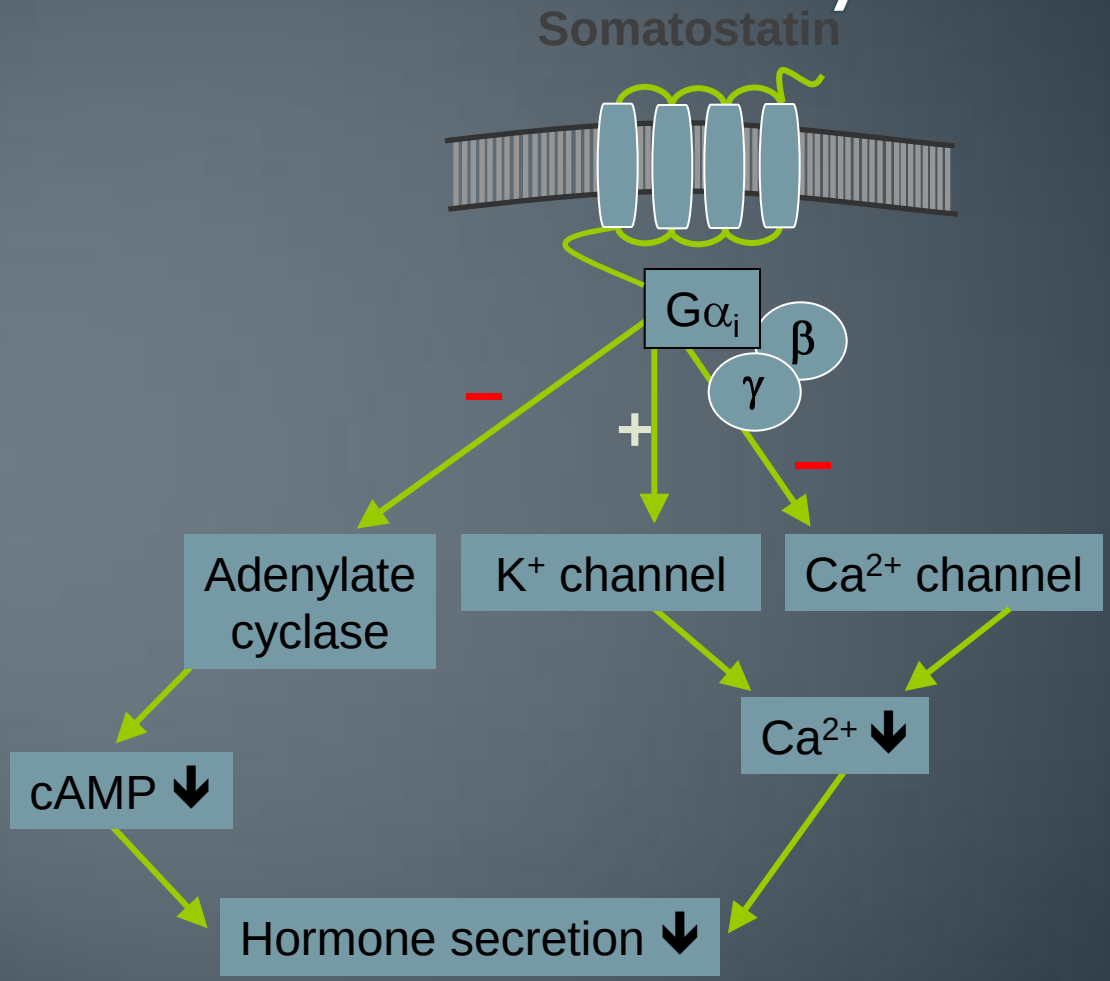
- Today:
  - GKRS when able
  - Age < 45 years
    - Progressive tumor
    - > 1cm residual tumor
    - Biochemically refractory patients

  - Age > 45 years
    - Identifiable residual, recurrent, progressive disease
    - Patient preference

Medical Management of Acromegaly

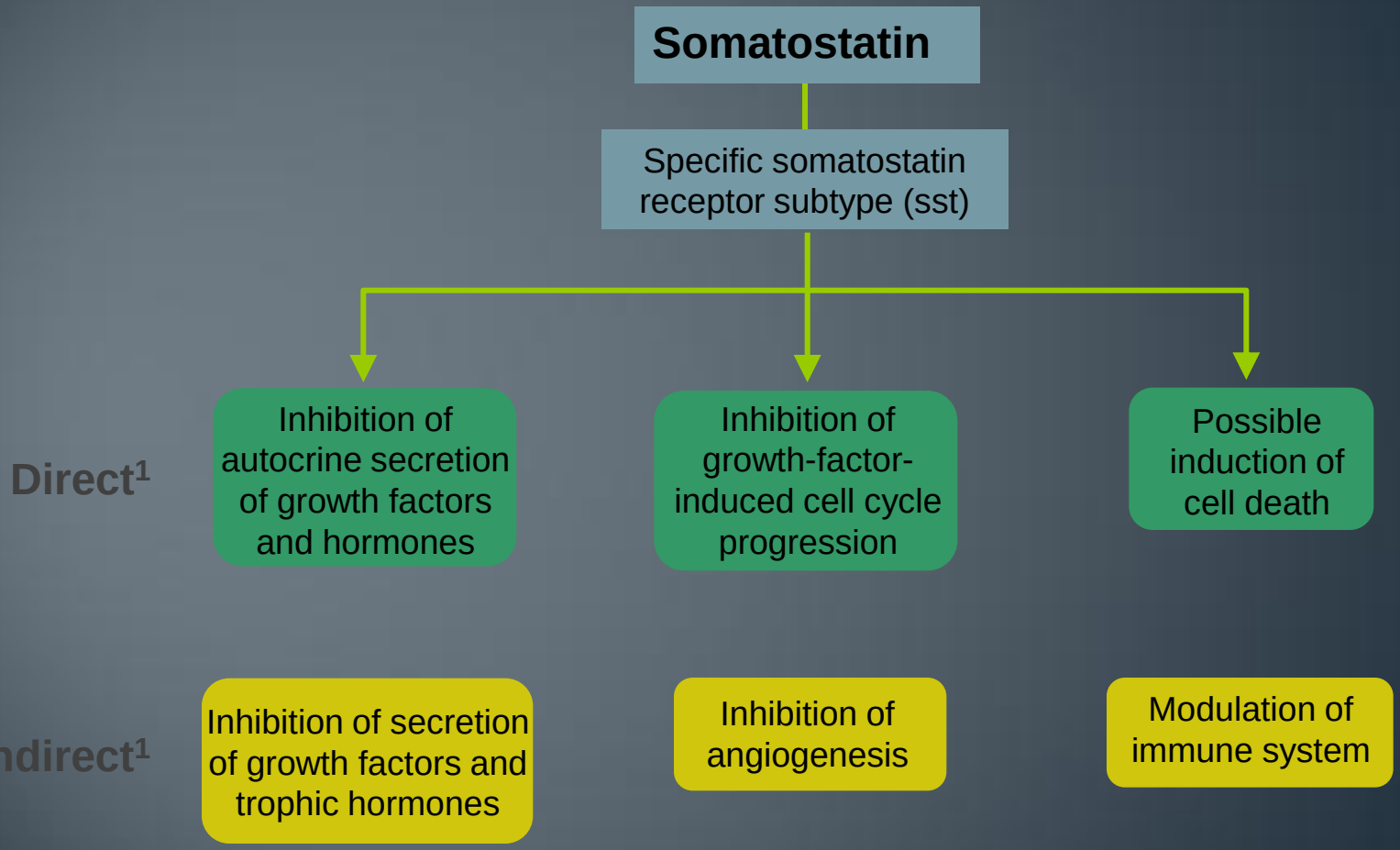
- Somatostatin Analogs
  - Bind to Somatostatin receptor
  - Octreotide , Lanreotide, and Pasireotide
- GH receptor antagonist
  - Antagonizes GH receptor
  - Pegvisomant
- Dopamine agonist drugs
  - Bind to D2 DA receptor
  - Cabergoline and Bromocriptine

Somatostatin Antisecretory Effects[1]



1. Guillermet-Guibert J et al. Somatostatin receptors as tools for diagnosis and therapy: Molecular aspects. Best Pract Res Clin Gastroenterol 2005;19:535–51.

Somatostatin Antiproliferative Effects



1. Guillermet-Guibert J et al. Somatostatin receptors as tools for diagnosis and therapy: molecular aspects. Best Pract Res Clin Gastroenterol 2005;19:535–51

Somatostatin Receptor Affinity

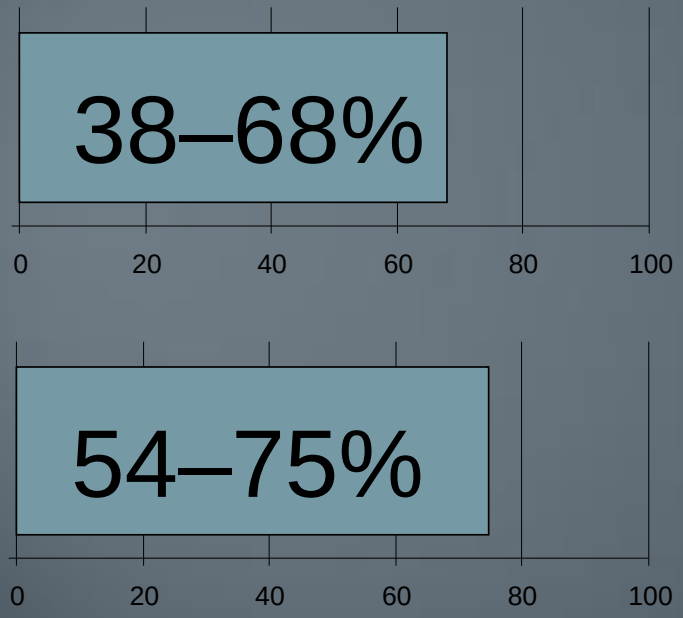
	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
			IC^{50} (nM)		
Somatostatin-14	1.1	1.3	1.6	0.5	0.9
Octreotide	>1000	2.1	35	>1000	5.6
Lanreotide	>1000	1.8	43	66	0.6

Receptor Distribution

Pituitary	+	+	+	+
GH Adenoma	+	+	+	+

Greenman, 1994, Miller 1995, Panetta 1995, Lamberts 1996, Reisine, 1995.

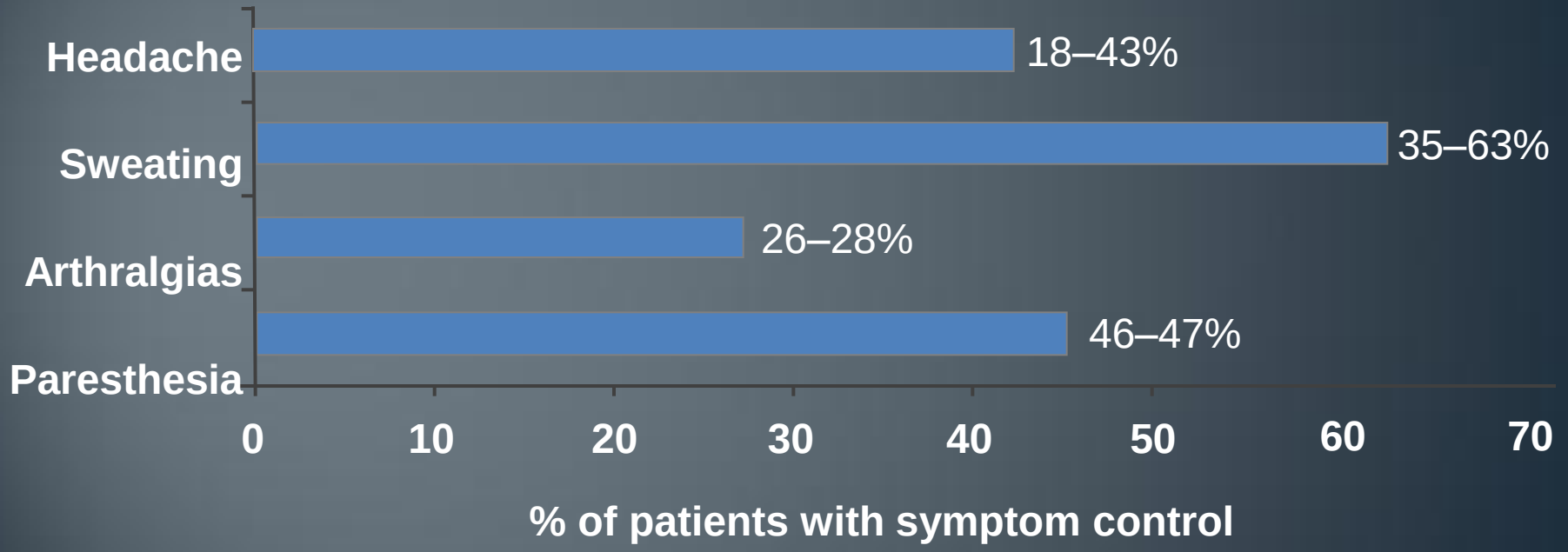
Long-Acting Somatostatin Analogues – GH and IGF-1 Control



- 38–68% of patients experienced both GH <2.5 ng/mL + IGF-1 normalization[1,2]
- 54–75% of patients experienced IGF-1 normalization[1,2]

1. Somatuline Depot (lanreotide) [prescribing information]. Brisbane, CA: Tercica; 2008.
2. Cozzi R et al. Four-year treatment with octreotide-long-acting repeatable in 110 acromegalic patients: predictive value of short-term results? J Clin Endocrinol Metab 2003;88:3090–8.

Long-Acting Somatostatin Analogues – Proven Efficacy in Symptom Control



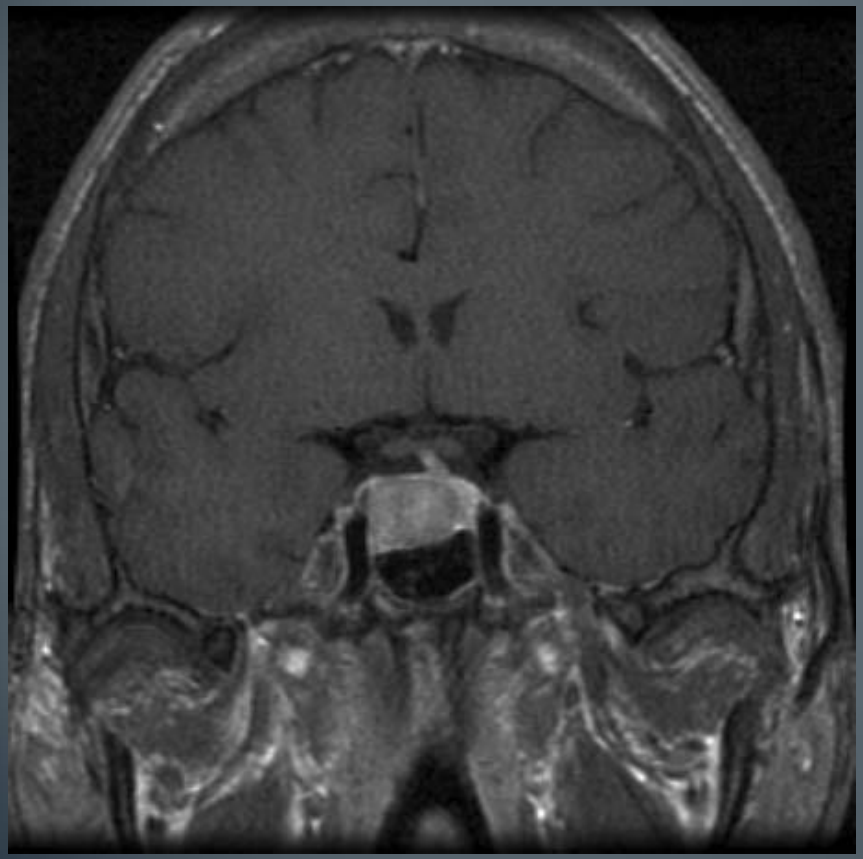
1. Lancranjan I et al. Results of a European multicentre study with Sandostatin LAR in acromegalic patients. Pituitary 1999;1:105–14.
2. Giusti M et al. Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly: six-month report on the Italian multicenter study. J Clin Endocrinol Metab 1998;83:2089–97.

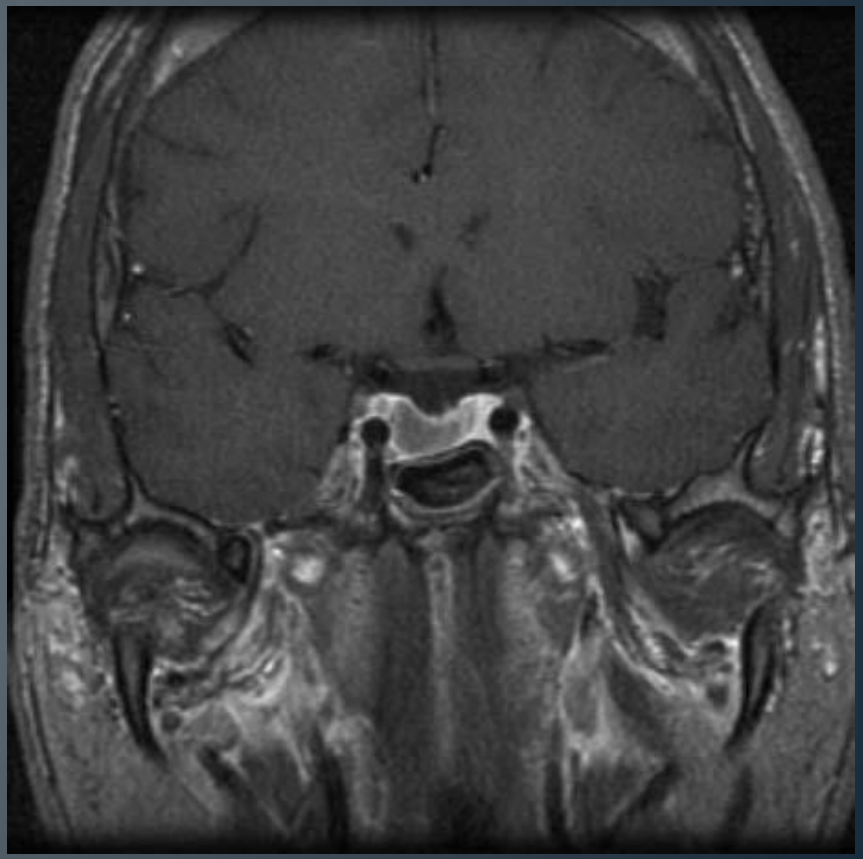
Somatostatin Analogs Tumor Shrinkage

	> 50%	20-50%	% with any shrinkage
Octreotide LAR	0	35	43 (22/51)
Lanreotide SR	1	11	17 (33/194)
Primary therapy	7	32	48 (122/256)

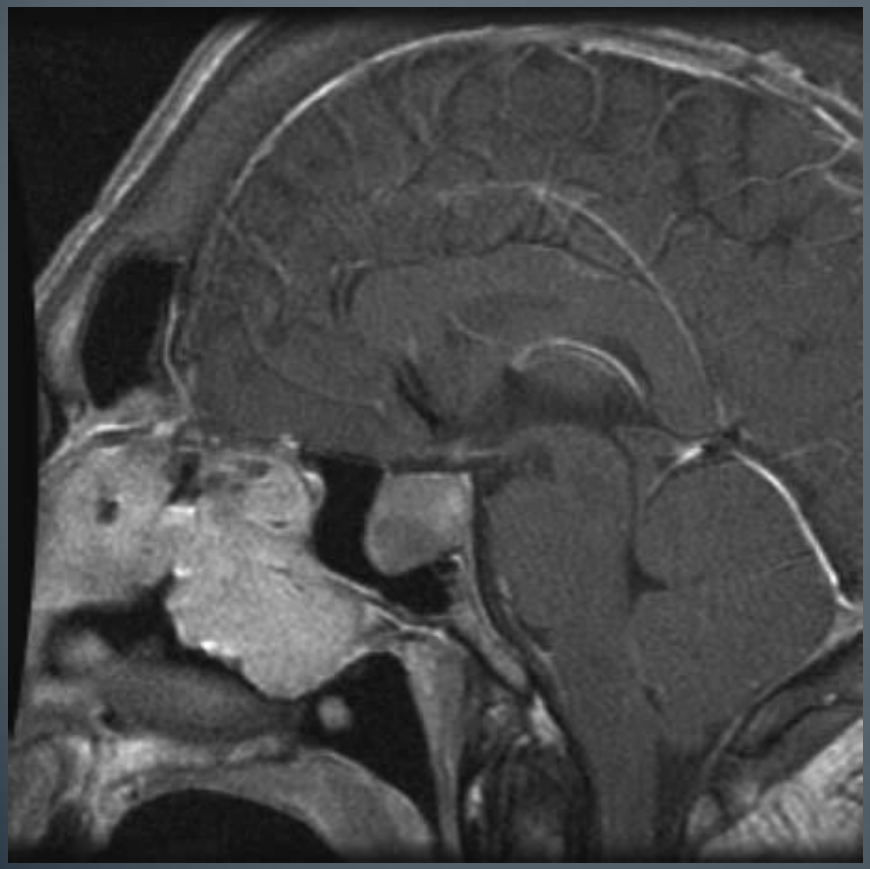
Freda PU. *J Clin Endocrinol Metab.* 2002;87:3013-3018.

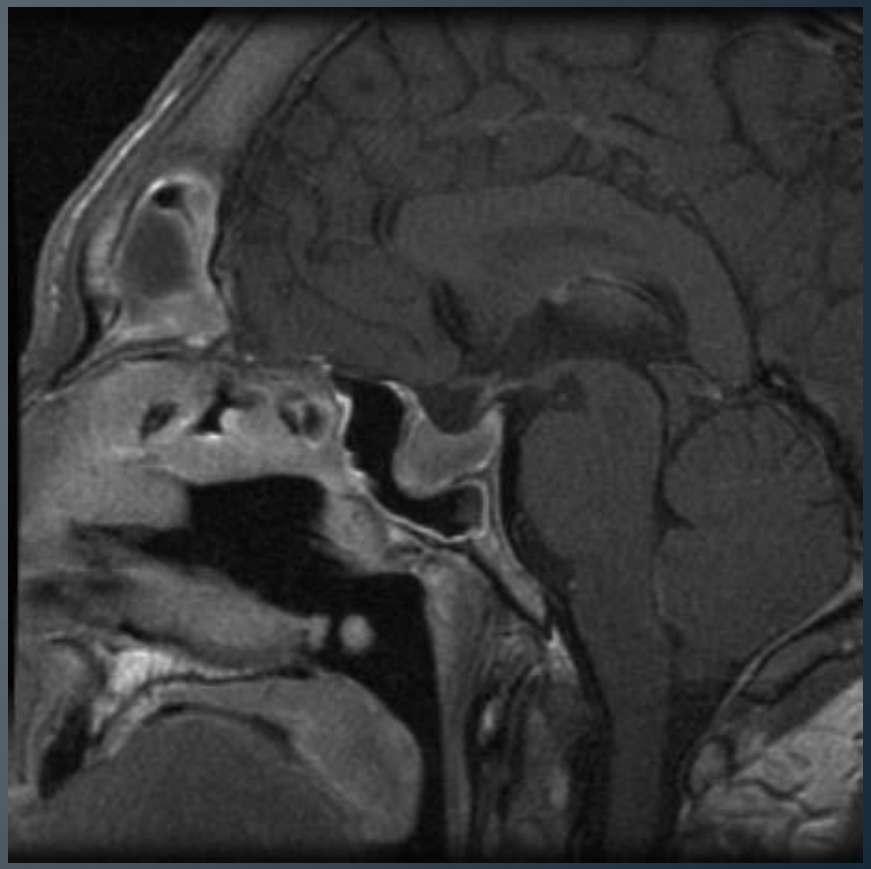
Pre and post treatment MRI studies





Pre and post treatment MRI studies



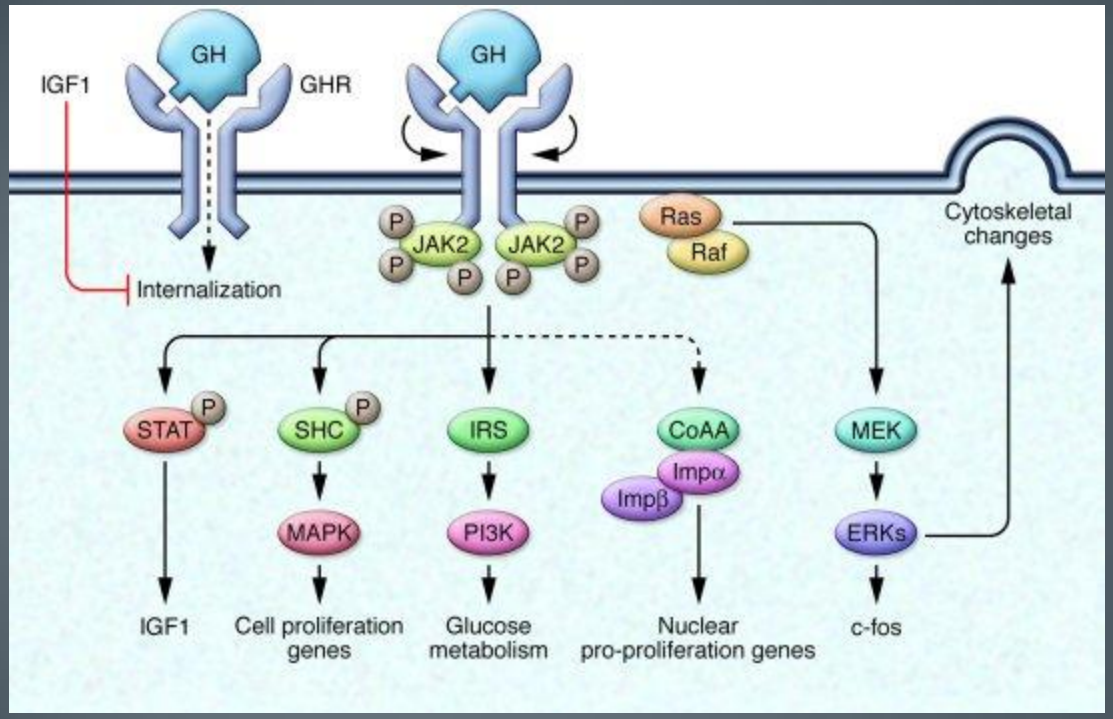


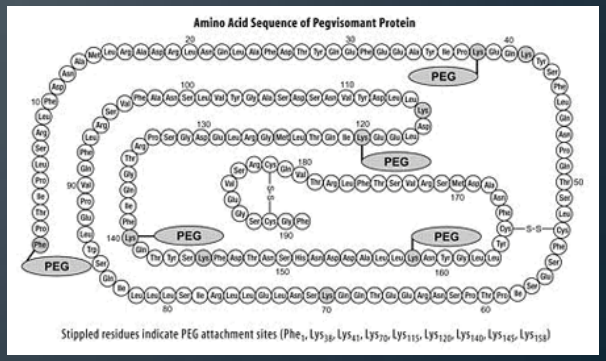
Most Common Adverse Reactions

	Number and percentage of patients			
	Studies 1 & 2 (N=170)		Overall pooled data (N=416)	
	N	%	N	%
Patients with any adverse reactions	157	92	356	86
Gastrointestinal disorders				
Diarrhea	81	48	155	37
Abdominal pain	34	20	79	19
Nausea	15	9	46	11
Constipation	9	5	33	8
Flatulence	12	7	30	7
Vomiting	8	5	28	7
Loose stools	16	9	23	6
Hepatobiliary disorders				
Cholelithiasis	45	27	85	20

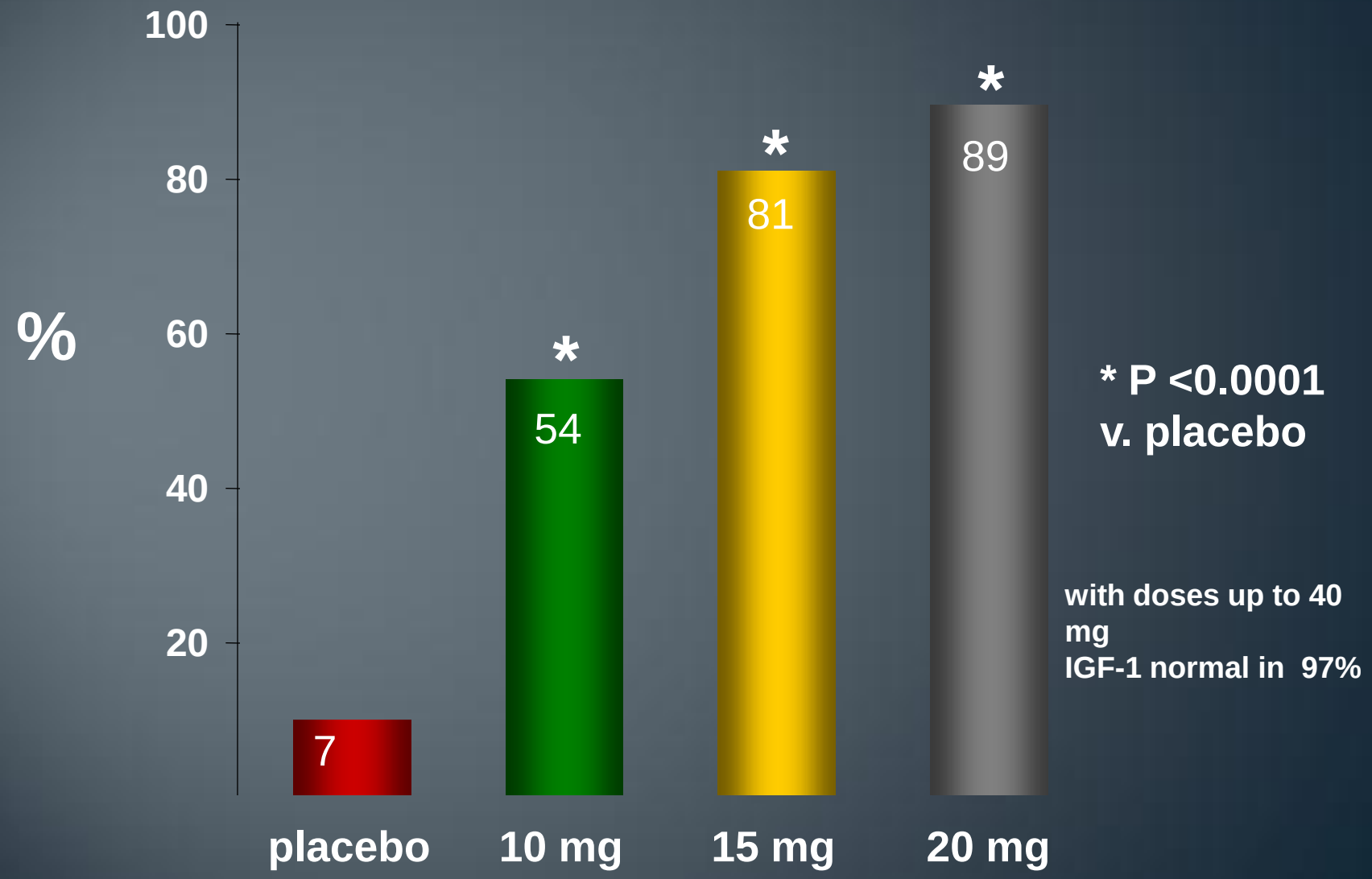
Somatuline® Depot [Prescribing Information]. Brisbane, CA: Tercica, Inc; August 2007.

GH Action action and Pegvisomant



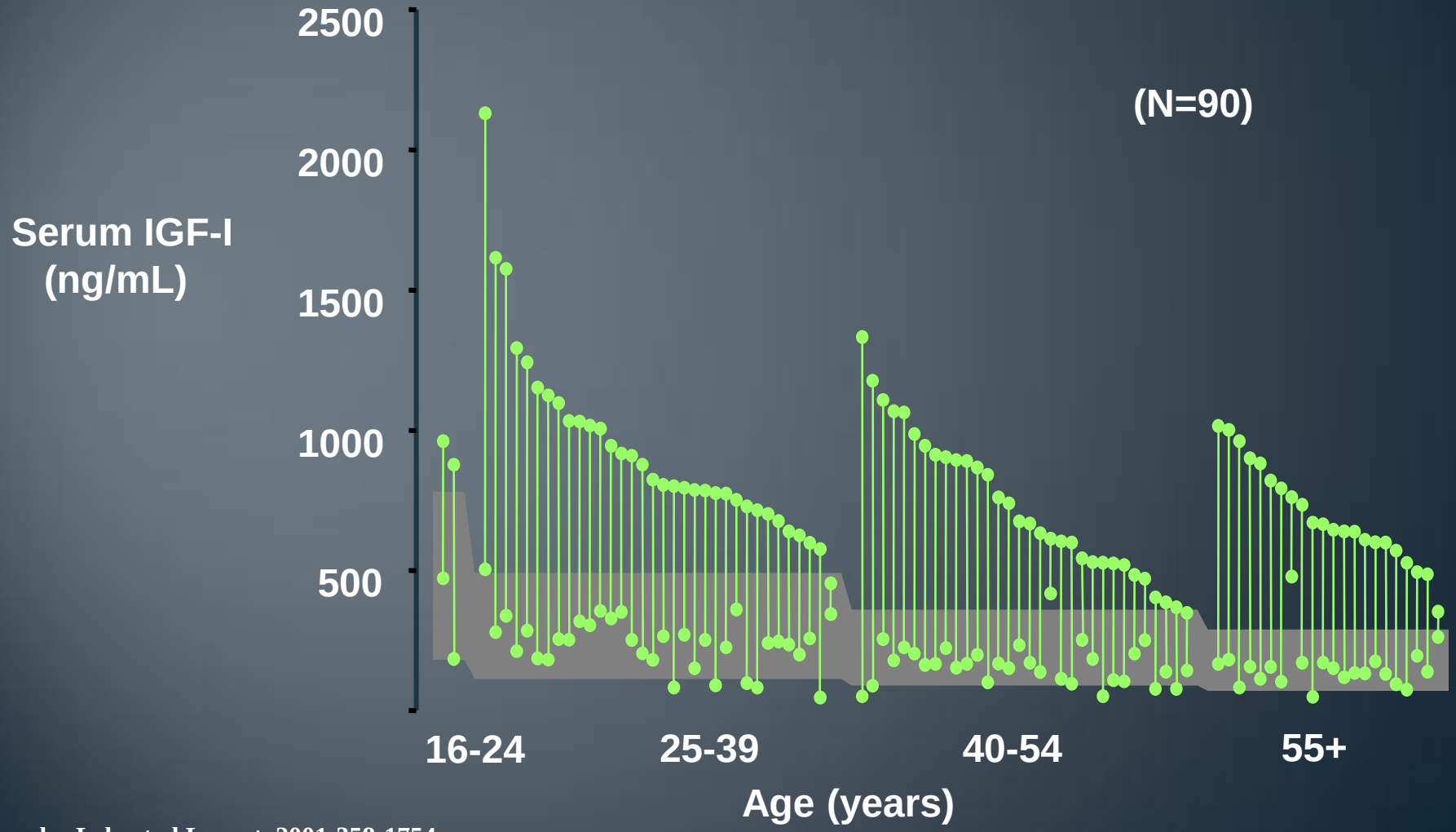


Percentage of Patients Achieving a Normal Age-Related Serum IGF-I with Pegvisomant



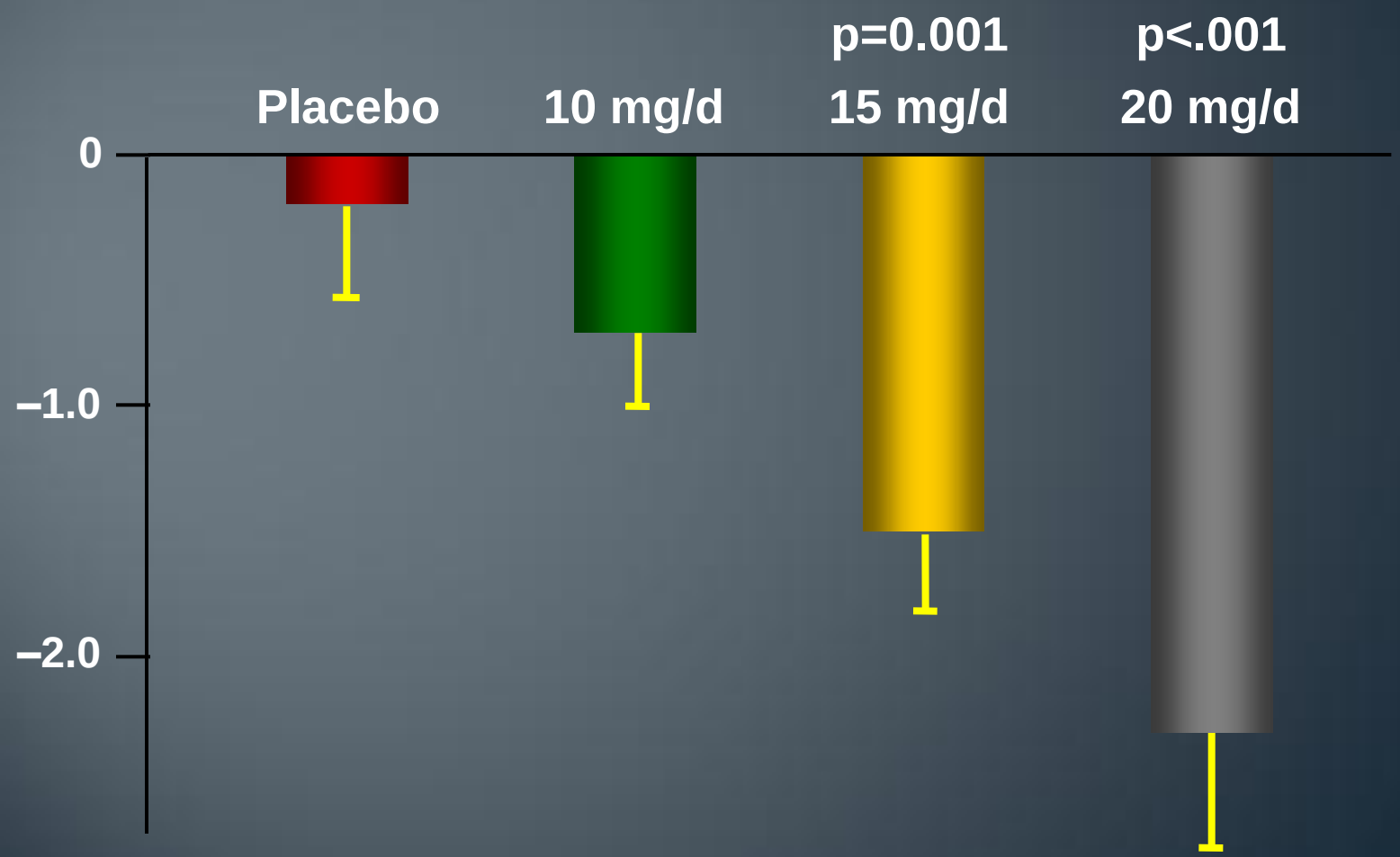
Trainer et al NEJM 2000:342;1171-1177

IGF-I at baseline and after 12 months pegvisomant



van der Lely et al Lancet 2001:358;1754

Change in Ring Size following Pegvisomant Treatment



Trainer et al NEJM 2000:342;1171-1177

AcroStudy
Pegvisomant in routine clinical use

- 1288 treated patients
- Mean of 3.7 years
- Pituitary tumor increases in size in 3.2% of patients
- Abnormal LFT's in 2.5%
- Injection site reactions in 2.2% of patients
- 63% of patients after 5 years with a normal IGF-1 on mean dose of 18 mg.

Van der Lely et al. J Clin Endocrinol Metab Feb 22, 2012

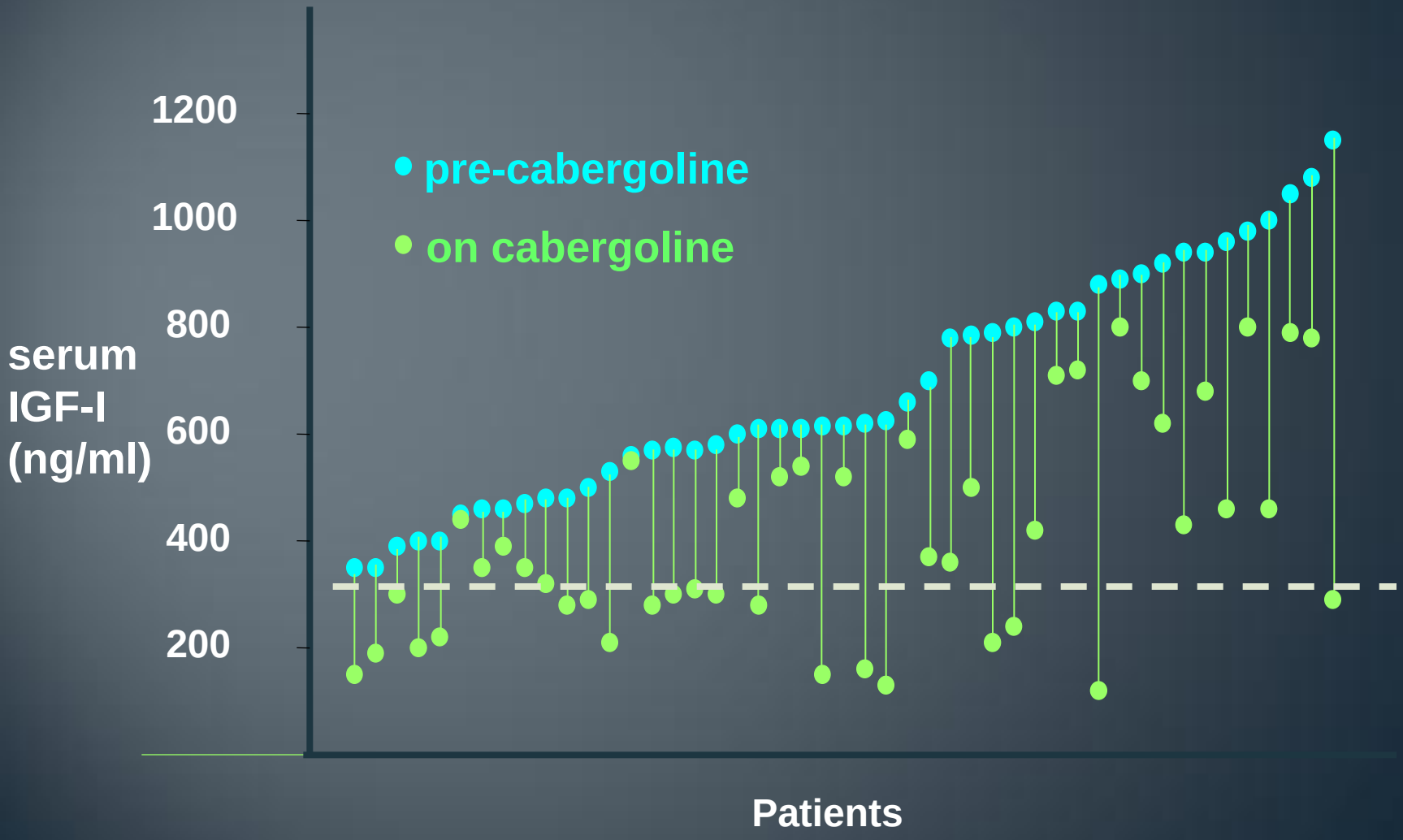
Acromegaly
Efficacy of DA Agonist drugs

- Bromocriptine
  - High doses (30 mg/d) oft required
  - 15% of aptietns normalize IGF-1

- Cabergoline
  - 3-5 mg/week in divided doses
  - 20-40% normalize IGF-1
  - Greater likelibood of response in patients with mixed tumors that co-secrete PRL

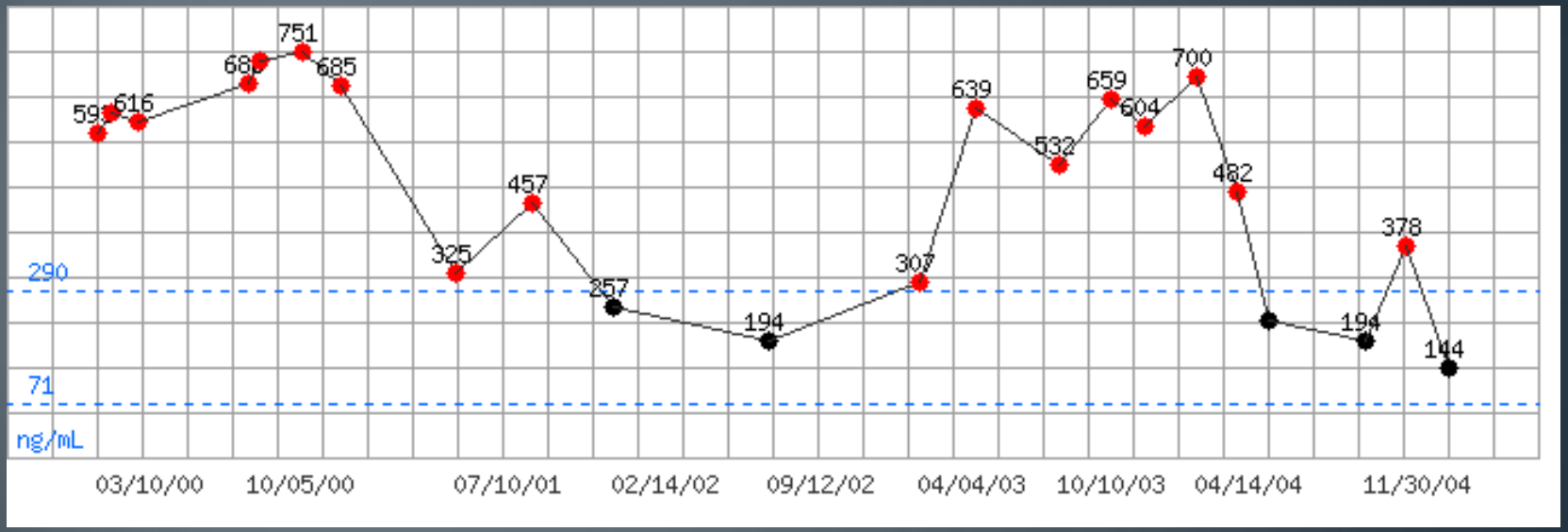
I often utilize these agents in elderly patients and find a surprisingly high response rate in elderly women.

Serum IGF-I in patients with acromegaly on cabergoline (max. dose 3.5 mg/week)



Abs JCEM 1998:83;374-8

Case 3
IGF-I data



TSA

TSA & CPK

Start-Sandostatin LAR-Stop

Start-Somavert-Stop

Cabergoline

Management of Acromegaly

- Individualize therapy
  - Algorithms don't work very well
  - Patient preference
  - Specific needs
- Dovetail strategic use of surgery and radiotherapy as well as specific medical therapy
- Growth and change is inevitable!