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Endokrinologisches Labor

2018全国儿科遗传代谢内分泌疾病诊疗新进展学习班暨高峰论坛

武汉, 2018年11月30日

GH治疗的生物标志物

Martin Bidlingmaier, MD

披露

I have received research support, travel and accommodation, lecture fees and/or consultancy honoraria from the following companies:

Antisense, Chiasma, Diasorin, Genexine, Genescience, IDS, Ionis, IPSEN, Midatech, Novartis, ONO, OPKO, Pfizer, Roche, Sandoz, StrongBridge

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大纲

背景: GH的生物标志物

我们对一个"好生物标志物"的期望?

IGF-I检测的临床应用

- 与GH分泌的关联, 对治疗的响应
- 对生物学变量的影响

IGF-I 浓度是什么? 分析问题

- 结果取决于实验室用什么样的方法
- 实验室方法会改变，会波动

好的参考区间 - 不容易

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背景: GH的生物标志物

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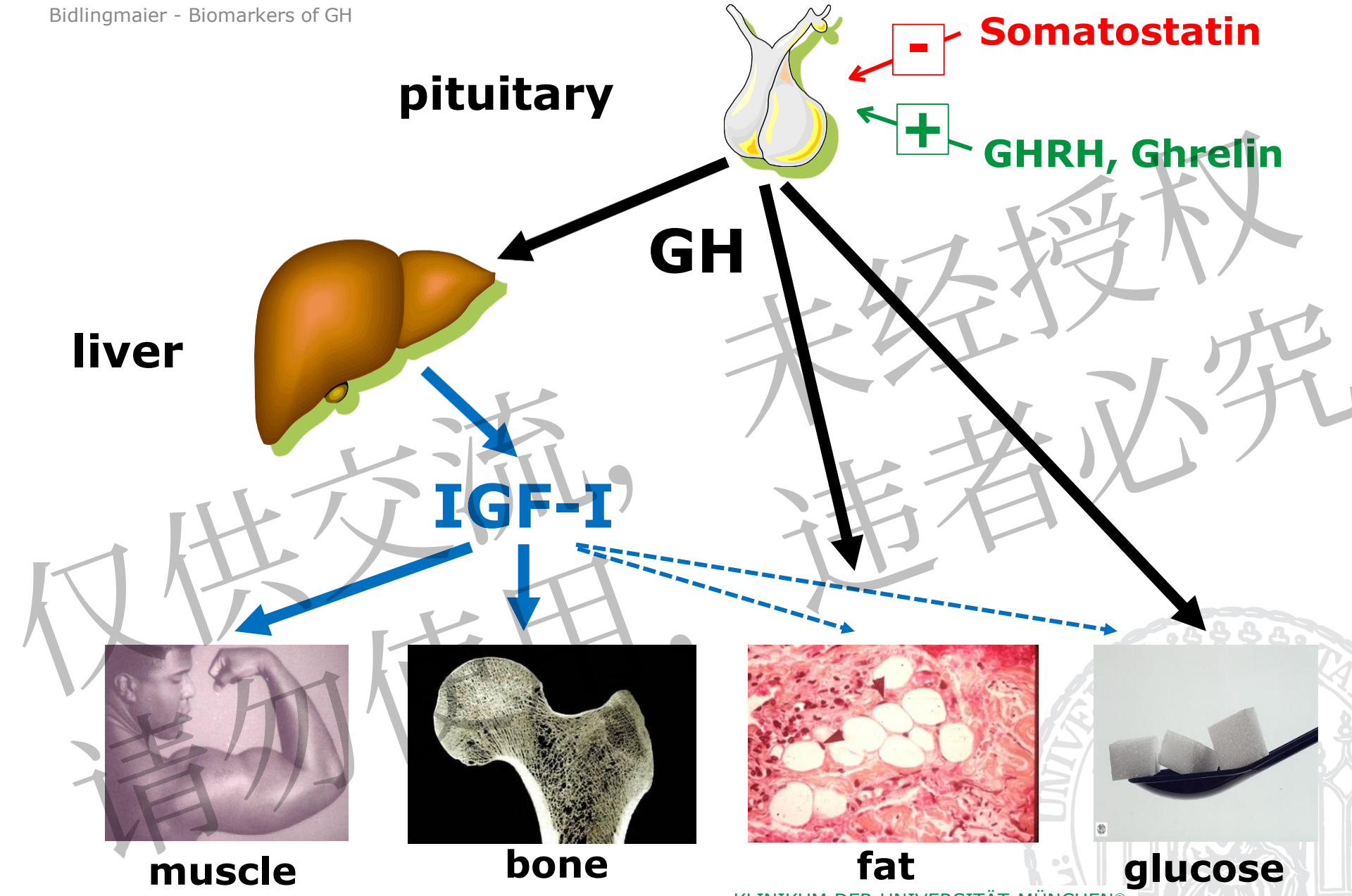

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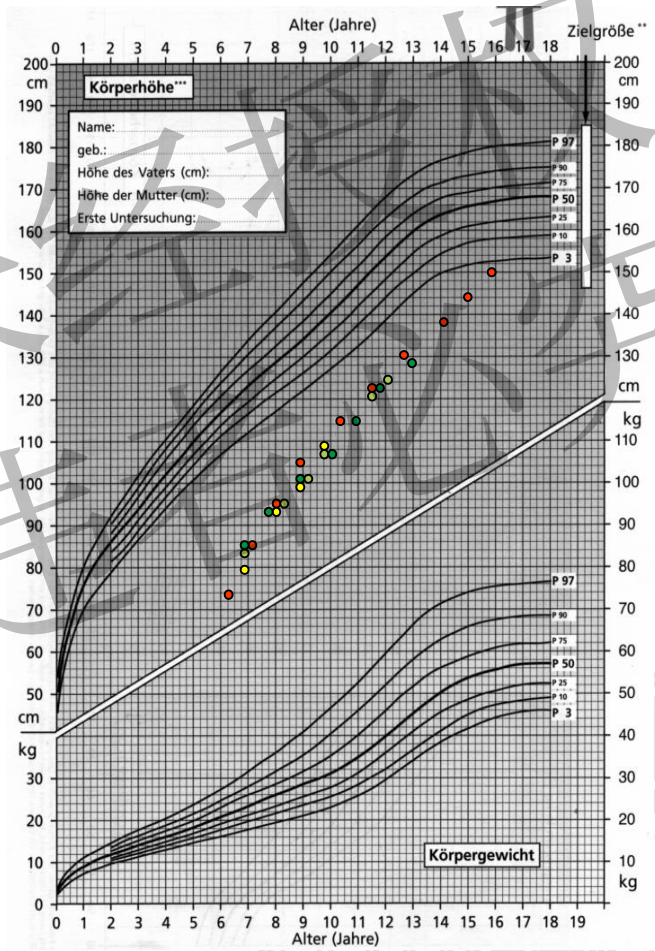
生长激素相关疾病

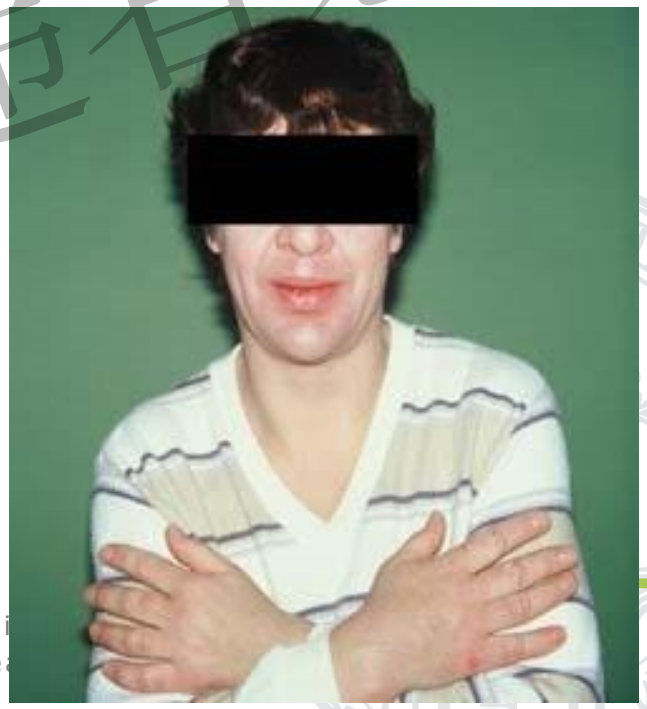
	GH 缺乏
儿童	<1/5.000-1/30.000
起病	遗传原因(eg. Pit-1-, GH-1-, GHRH-基因突变)
	创伤/肿瘤
	„特发性"
成人	<1/10.000
起病	儿童期起病 CO GHD
	创伤 (SAB)/肿瘤



- 矮身材
- 骨龄落后
- 肥胖

生长激素相关疾病

	GH 过剩
儿童	<1/200.000 (巨人症)
起病	垂体腺瘤
	遗传原因(eg. AIP-mutation, X-LAG)
成人	<1/20.0000 (肢端肥大症)
起病	垂体腺瘤
	GHRHoma



- **巨人症 (CO) / 肢端肥大 (AO)**
- **糖代谢受损**
- **器官肥大/心脏肥大**

生长激素相关疾病的生物标志物

原理很简单...

	GH 缺乏		GH 过剩 (肢端肥大)
hGH	↓		↑↑
IGF-I	↓		↑↑

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生长激素相关疾病的生物标志物

原理很简单...

	GH 缺乏	GH 抵抗 (受体缺陷)	GH 过剩 (肢端肥大)
hGH	↓	↑	↑↑
IGF-I	↓	↓↓	↑↑

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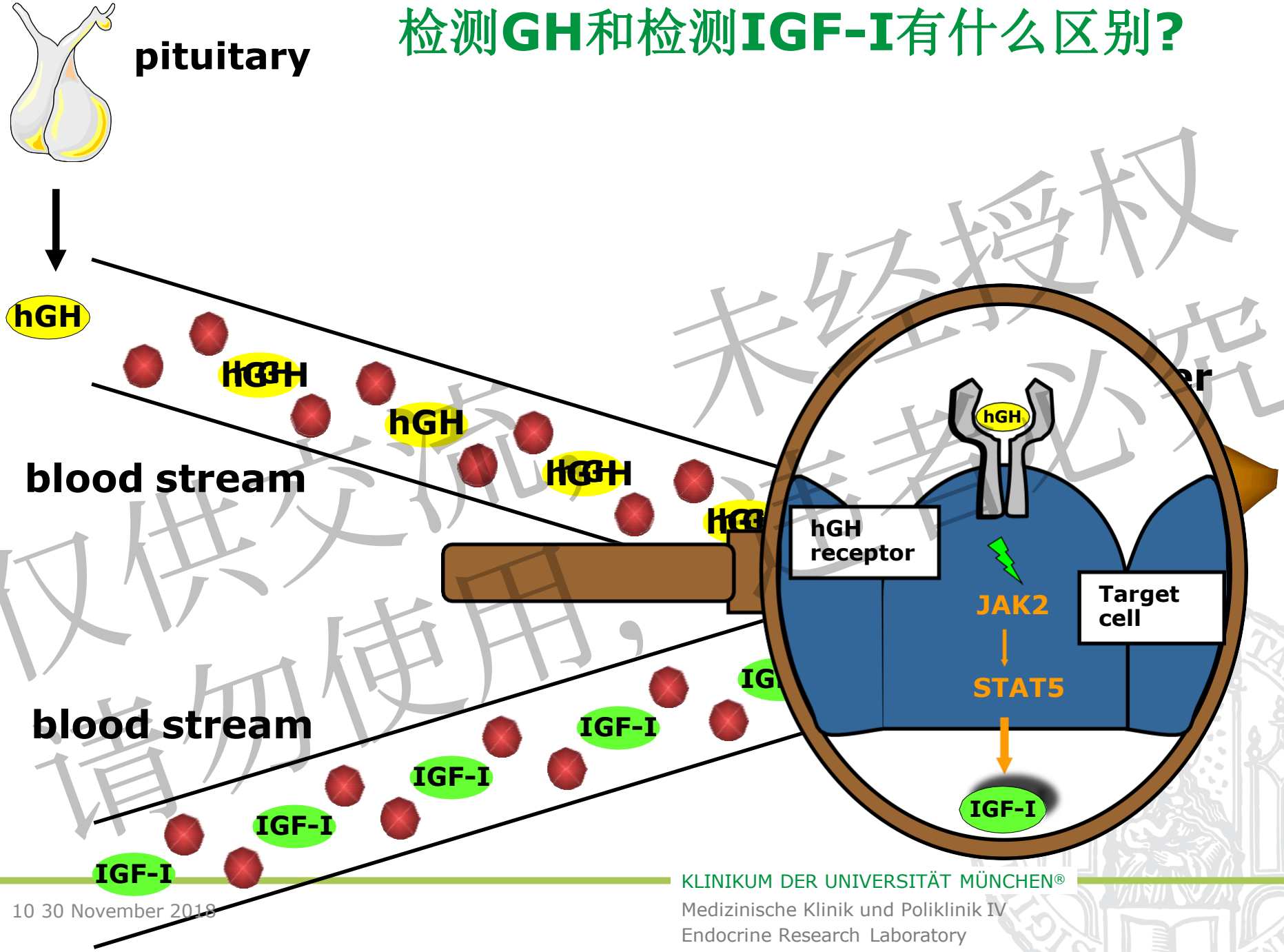
检测GH和检测IGF-I有什么区别?



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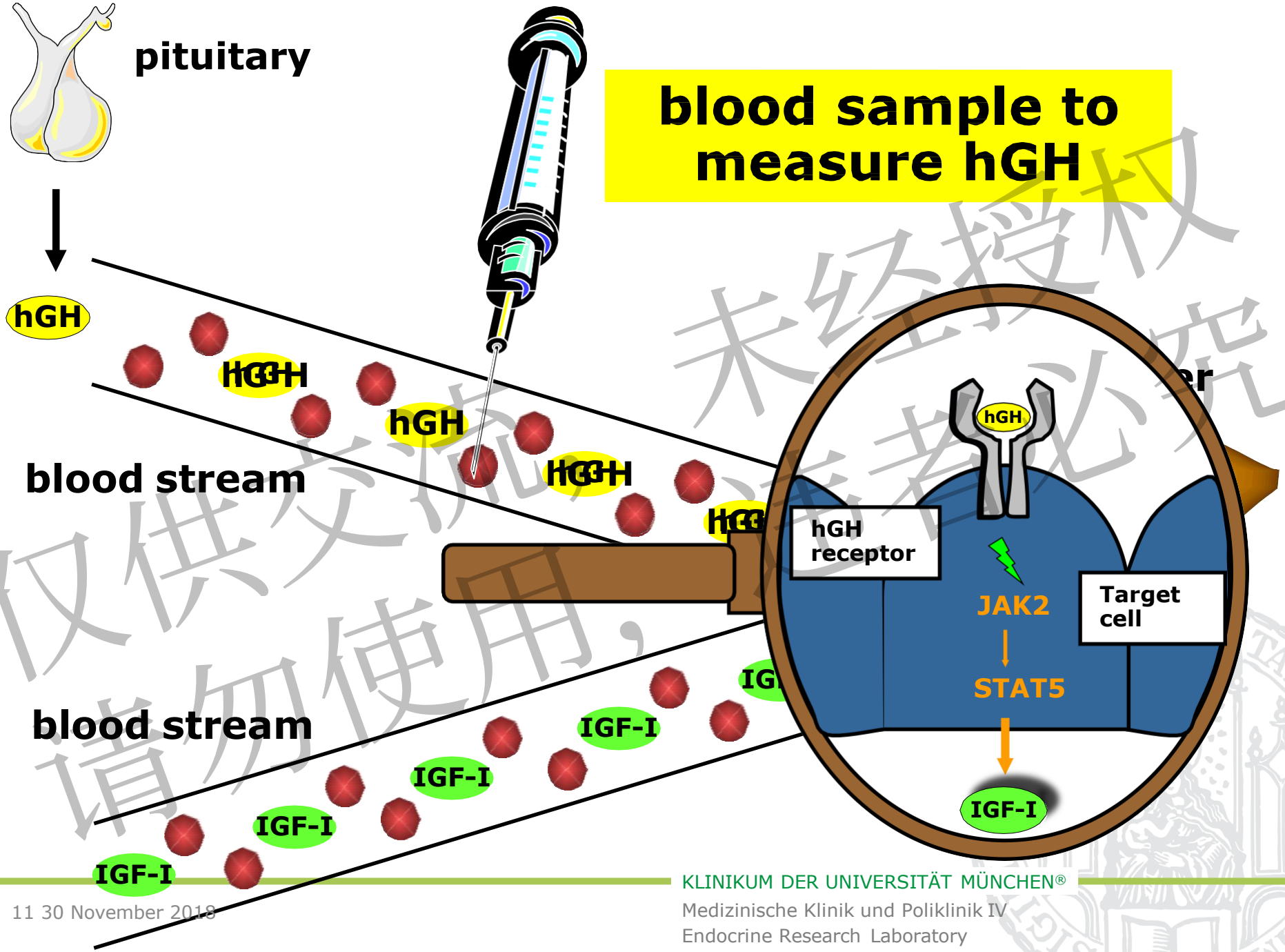

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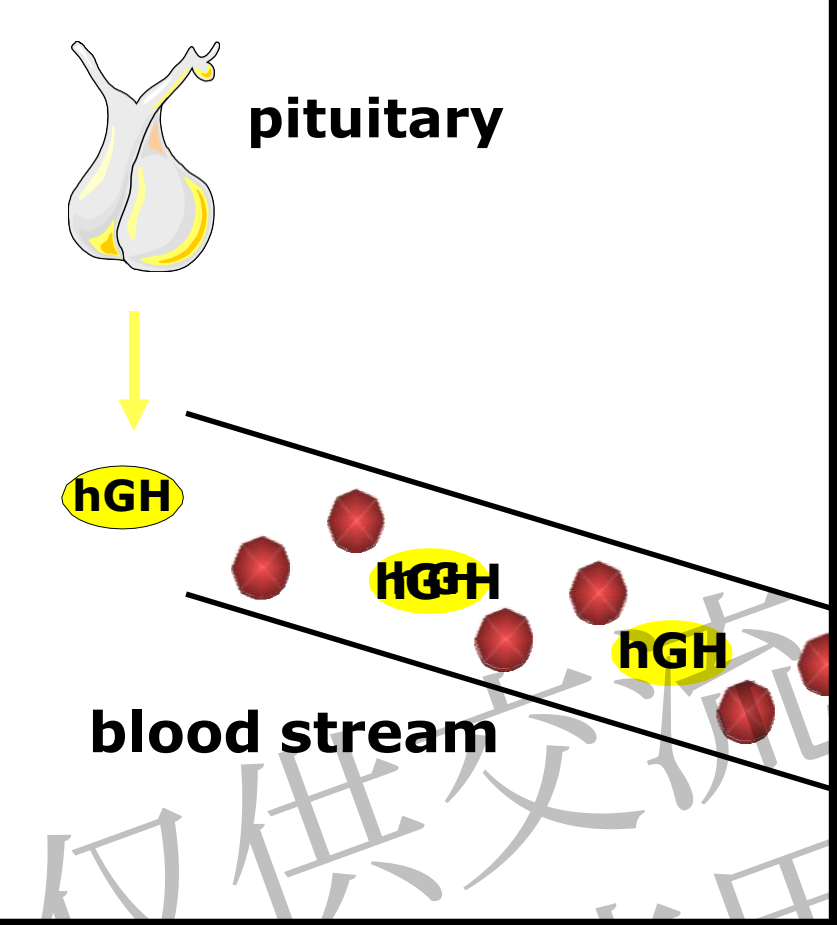
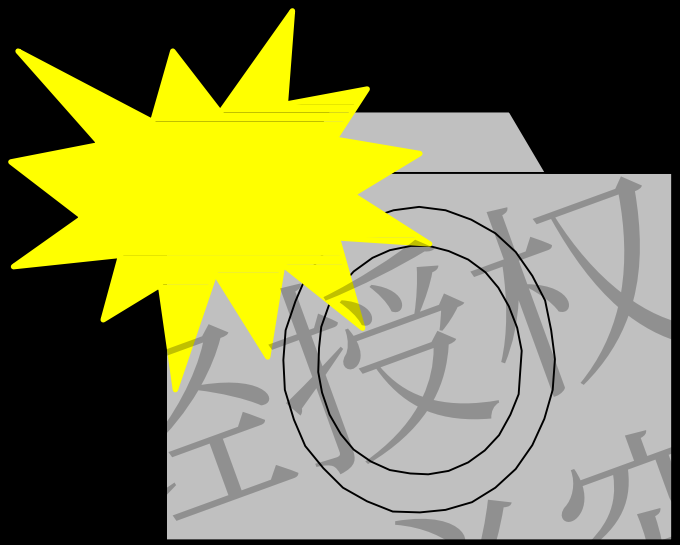
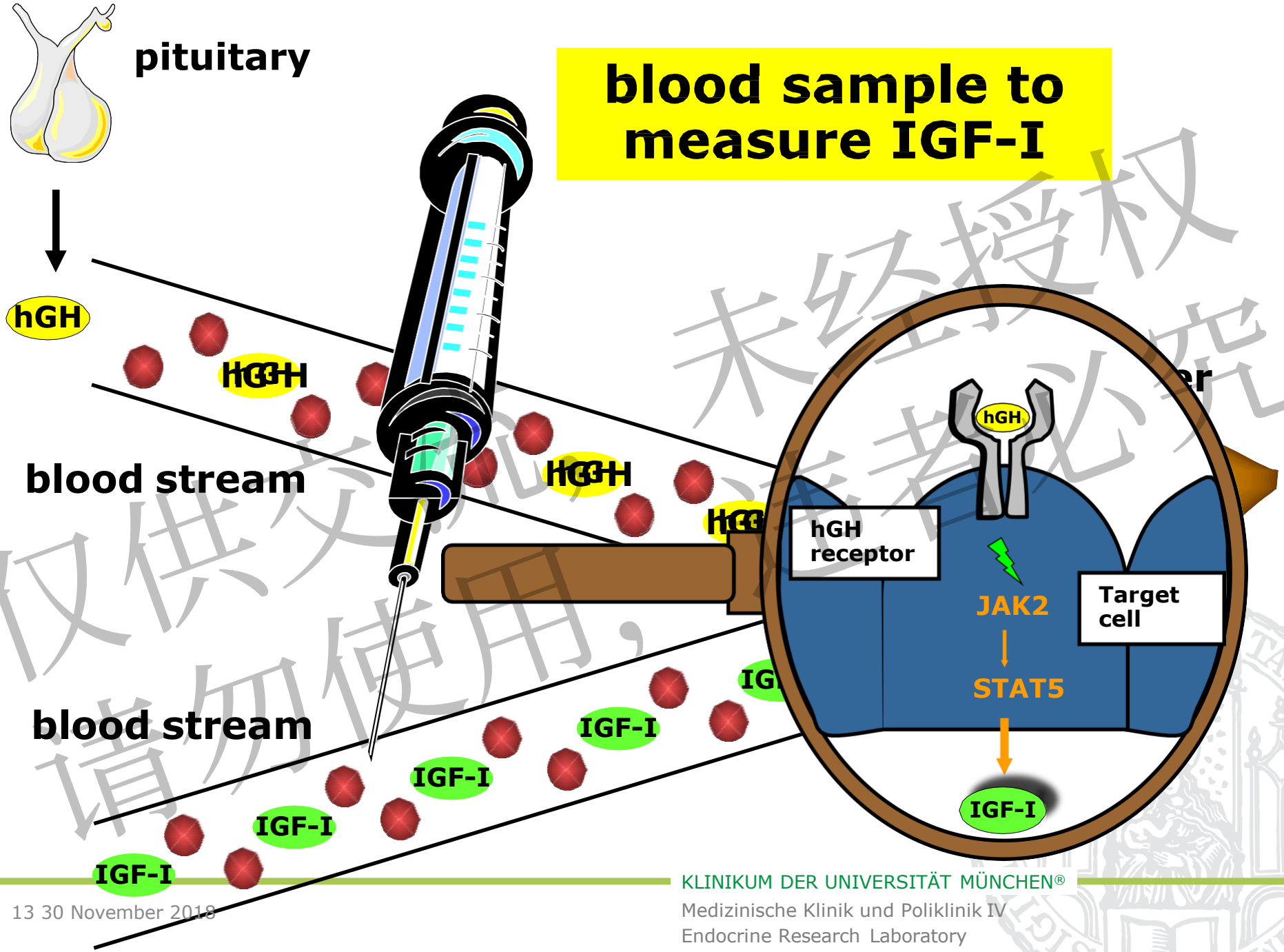




关注垂体的hGH分泌



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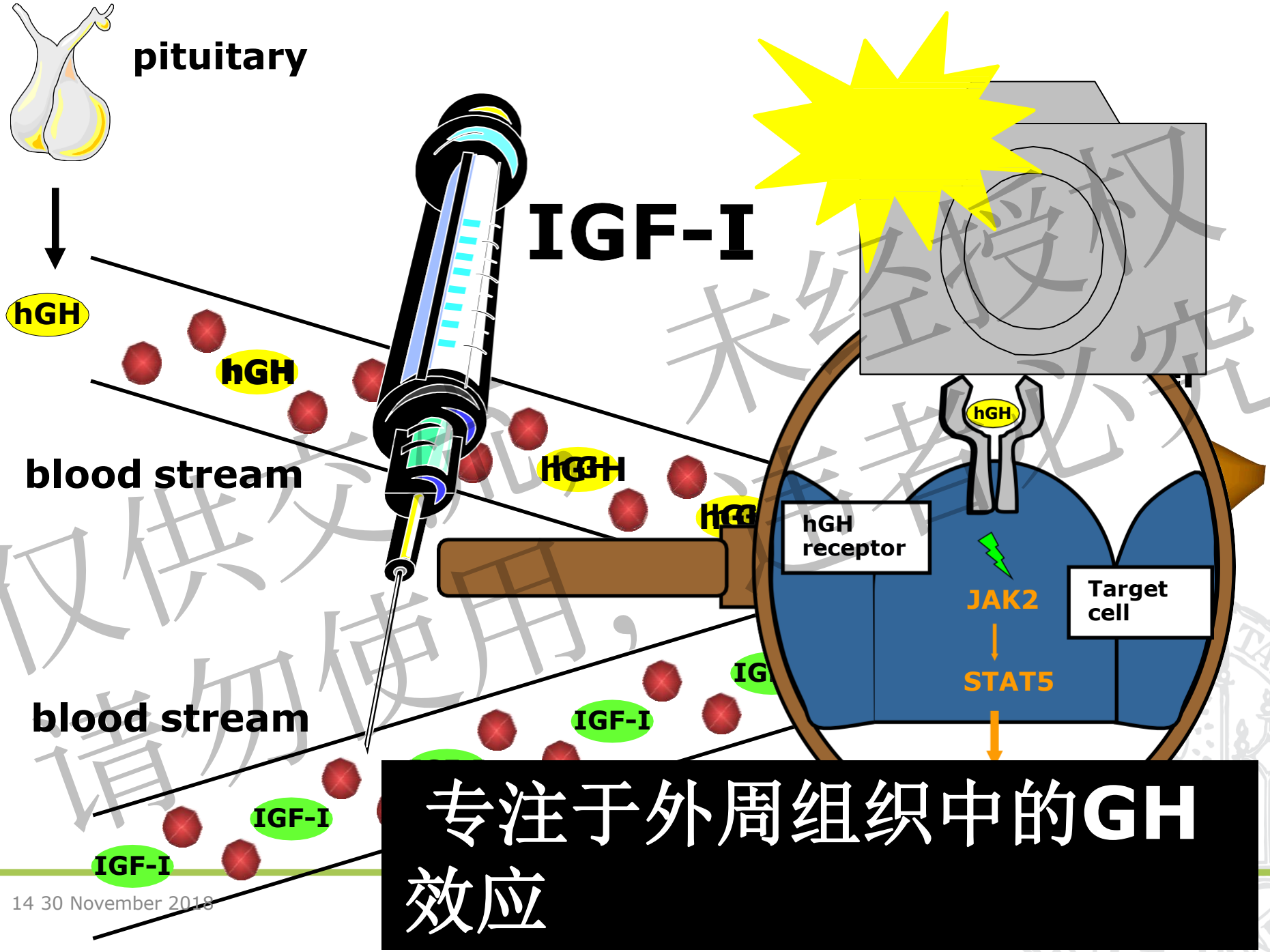

专注于外周组织中的GH效应

我们对生物标志物的期望是什么?

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几个定义....

生物标志物:

- "生物标志物是可以客观衡量的对一种特定治疗干预的正常或病理过程或药理反应指标"

临床终点

- "反应患者感受，功能或存活率的一个特征或变量"

替代终点

- "旨在替代临床终点的生物标志物"
- "期望通过科学实证来预测获益(或损害或无获益无损害)"

Biomarkers Definitions Working Group
Clin. Pharmacol. Ther. 69 (2001) 89–95.

Review article

Growth Hormone & IGF Research 40 (2018) 1–8

Biomarkers of GH action in children and adults

Katharina Schilbach[a,*,1], Daniel S. Olsson[b,1], Margaret C.S. Boguszewski[c], Martin Bidlingmaier[a], Gudmundur Johannsson[b], Jens-Otto Lunde Jørgensen[d]

用于诊断的生物标志物必须有

- 临床相关性
- 敏感性/特异性/可靠性
- 可行性/简便性

作为替代终点的生物标志物必须有

- 生物学合理性
- 流行病学数据支持使用
- 可预测的剂量反应关系
- 与不良反应的关系

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IGF-I作为生物标志物的标准化评估(FDA 指南)

	GHD/short stature in children
	Diagnostic biomarker
Clinical relevance	+ +
Sensitivity	+
Specificity	+ + +
Reliability	+ + / + + +
Practicality	+ + +
Simplicity	+ + +
	Surrogate endpoint
Biological plausibility	+ + +
Existence of supportive epidemiological data	+ + +
Predictable dose-response relationships between IGF-I and drug exposure	+ / + +
Predictable dose-response relationships between IGF-I and clinical endpoints	+
Capture of adverse effects	+ / + +
Consideration in the drug development process	+ + +
Consistency of effects on the surrogate marker across various drug classes	*

& adults

Schilbach K et al., Growth Hormone & IGF Research 40 (2018) 1–8

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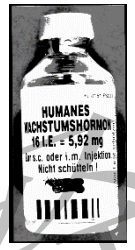
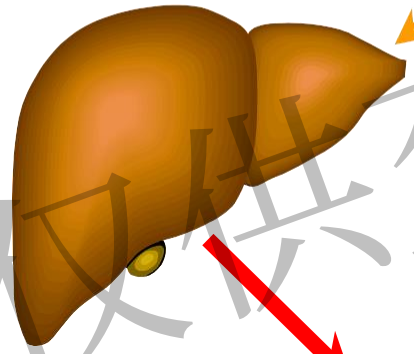
GH作用的生物标志物

pituitary derived

GH



recombinant



liver

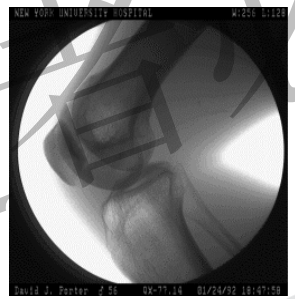
"Biomarkers"

IGF-I

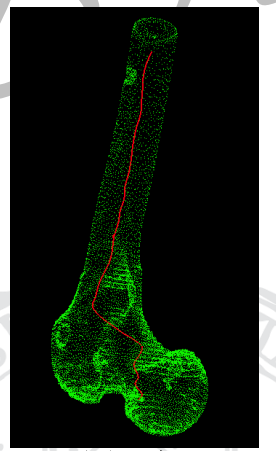
IGFBP 3

IGFBP 2

ALS…



软骨



骨骼

有许多生长激素作用的生物标志物....

Endocrine CONNECTIONS

G Johannsson *et al.* | Biomarkers of GH action | 7:3 | R126–R134

REVIEW

Growth Hormone Research Society perspective on biomarkers of GH action in children and adults

Gudmundur Johannsson[1], Martin Bidlingmaier[2], Beverly M K Biller[3], Margaret Boguszewski[4], Felipe F Casanueva[5], Philippe Chanson[6], Peter E Clayton[7], Catherine S Choong[8], David Clemmons[9], Mehul Dattani[10], Jan Frystyk[11], Ken Ho[12], Andrew R Hoffman[13], Reiko Horikawa[14], Anders Juul[15], John J Kopchick[16], Xiaoping Luo[17], Sebastian Neggers[18], Irene Netchine[19], Daniel S Olsson[20], Sally Radovick[21], Ron Rosenfeld[22], Richard J Ross[23], Katharina Schilbach[2], Paulo Solberg[24], Christian Strasburger[25], Peter Trainer[26], Kevin C J Yuen[27], Kerstin Wickstrom[28] and **Jens O L Jorgensen[29] on behalf of the Growth Hormone Research Society**

Free download from the journals website

...但今天只有一个在临床实践中非常重要:

IGF-I

Table 1 Current clinical endpoints, surrogate endpoints and biomarkers in GH therapy and acromegaly.

Patients and treatments	Clinical efficacy endpoints	Surrogate endpoints	Biochemical biomarker
Paediatric GH treatment			
GH deficiency	Adult height	Change in height SDS/growth velocity	IGF-I
GH deficiency in the transition period	Body composition	Peak bone mass, DXA *Z* score, LBM, and FM	IGF-I
CRI, Noonan syndrome, SHOX, Turner syndrome, SGA, SRS, ISS	Adult height	Change in height SDS/growth velocity	IGF-I
Prader–Willi syndrome	Body composition Adult height	Neuro-cognition Muscle tone	IGF-I
Adult GH treatment	Body composition Quality of life	Anthropometry, DXA *Z* score, LBM and FM Questionnaires	IGF-I
Acromegaly treatment	Serum IGF-I and GH reduction Symptom relief	IGF-I, GH Symptom scores	IGF-I

Johannsson G et al., Endocr Connect. 2018 Mar;7(3):R126-R134.

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Clinical use of IGF-I assays

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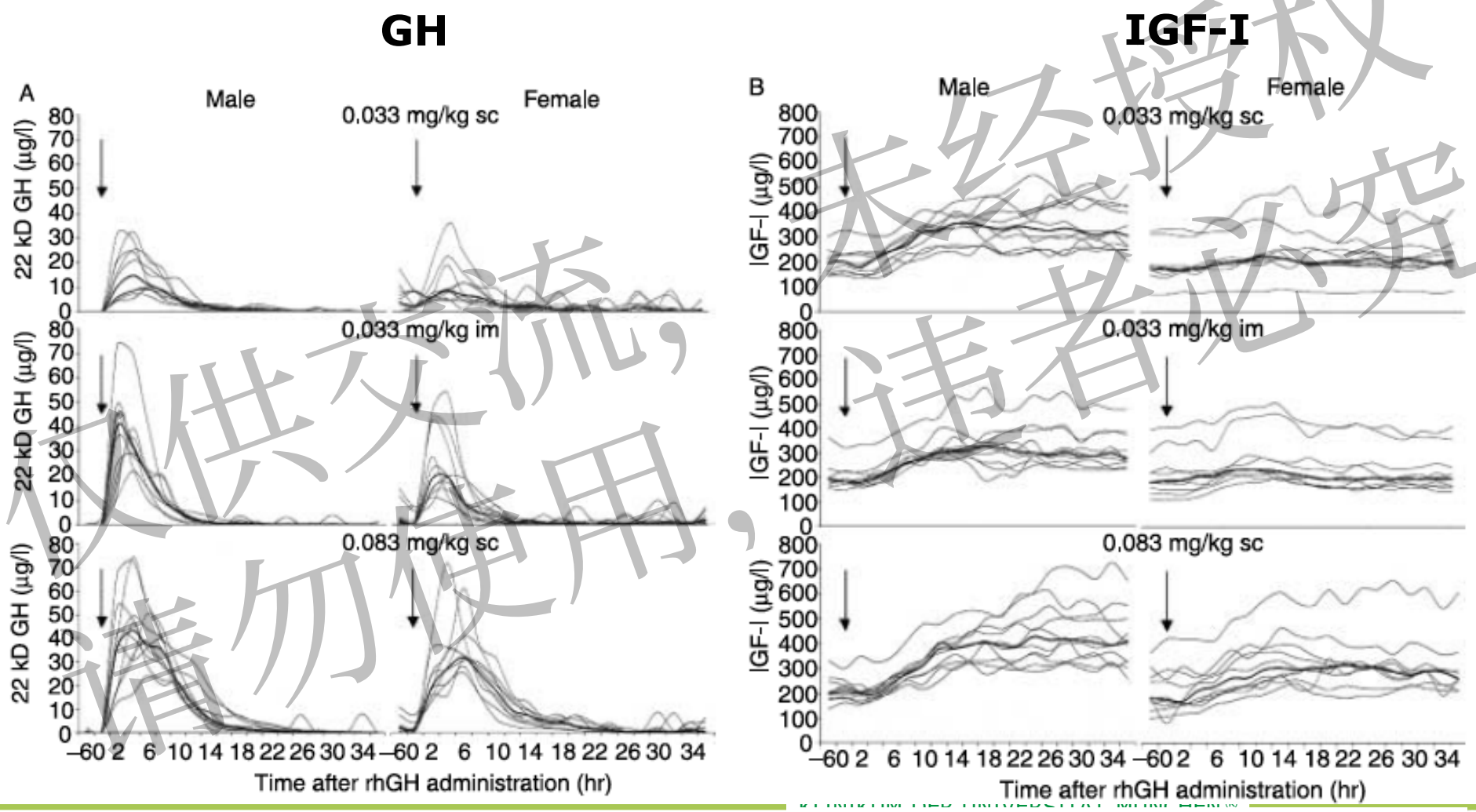
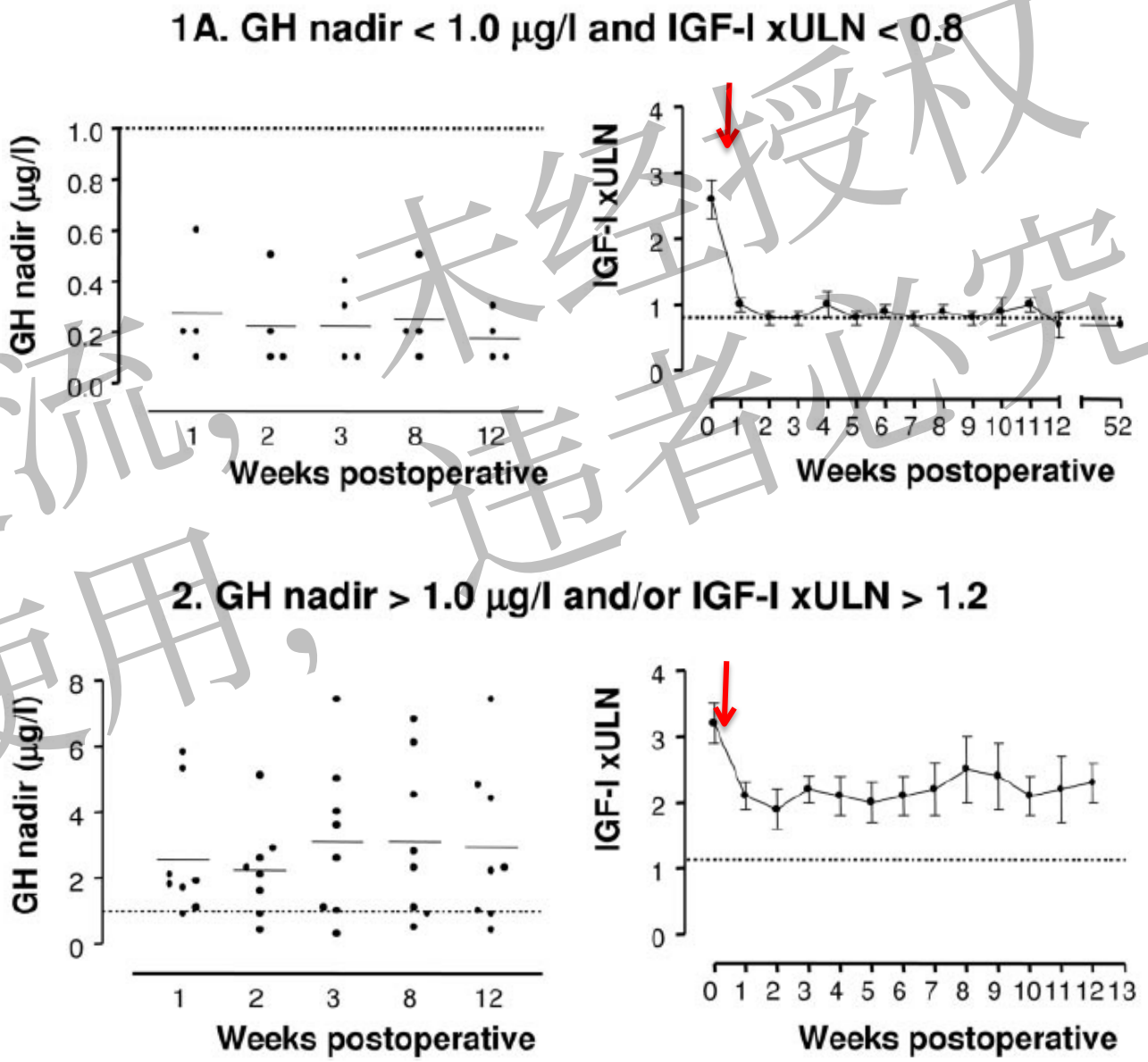
GH用药后的IGF-I响应 (健康青壮年)



Keller et al. EJE (2007) 156. 647-653

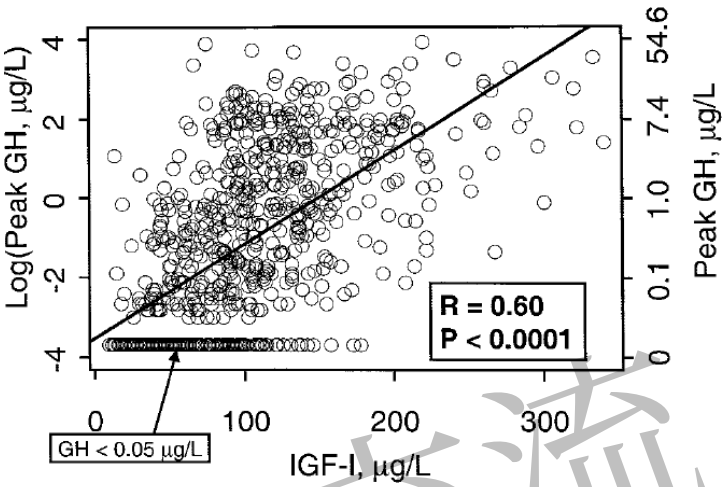
肢端肥大症手术治疗后的IGF-I响应

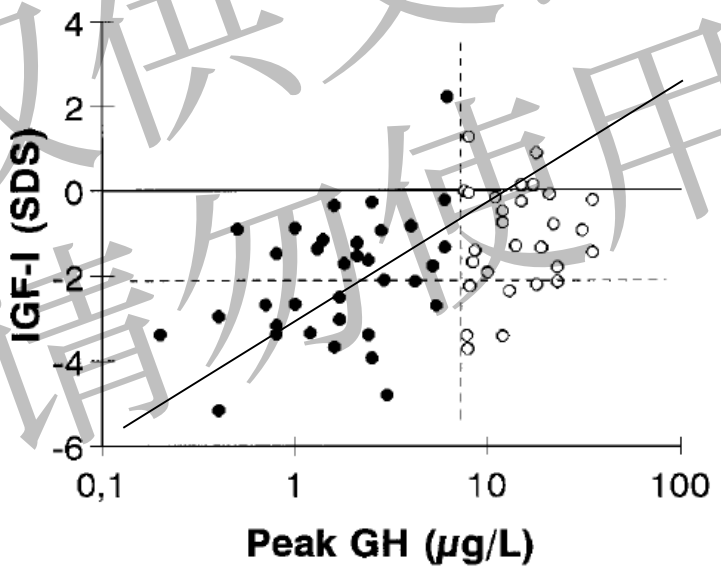
- IGF-I平均在术后1周后下降
- 个体差异 – IGF-I在手术3个月后稳定



Feelders RA et al.
JCEM 90: 2005

GHD患者GH峰值和IGF-I的关联





Hartman ML et al., JCE&M 2002

关联存在，但很微弱!

Juul A et al., JCE&M 1997

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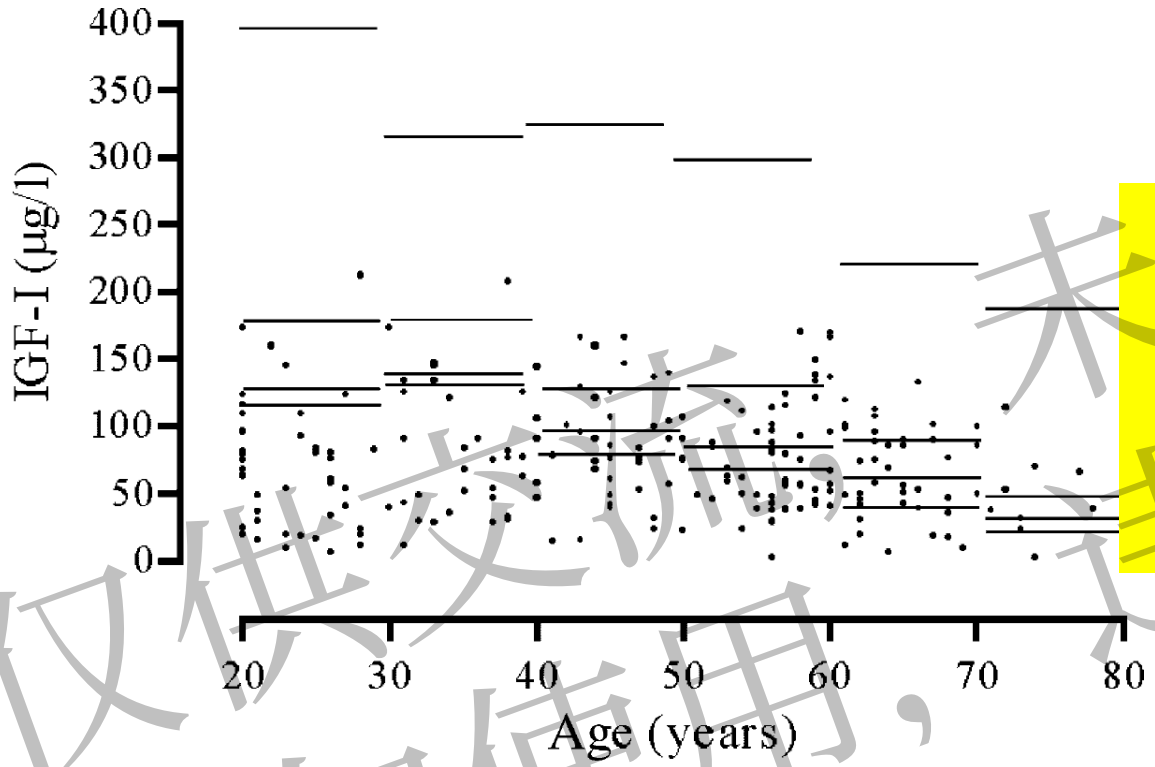
年龄的影响：GHD患者的IGF-I



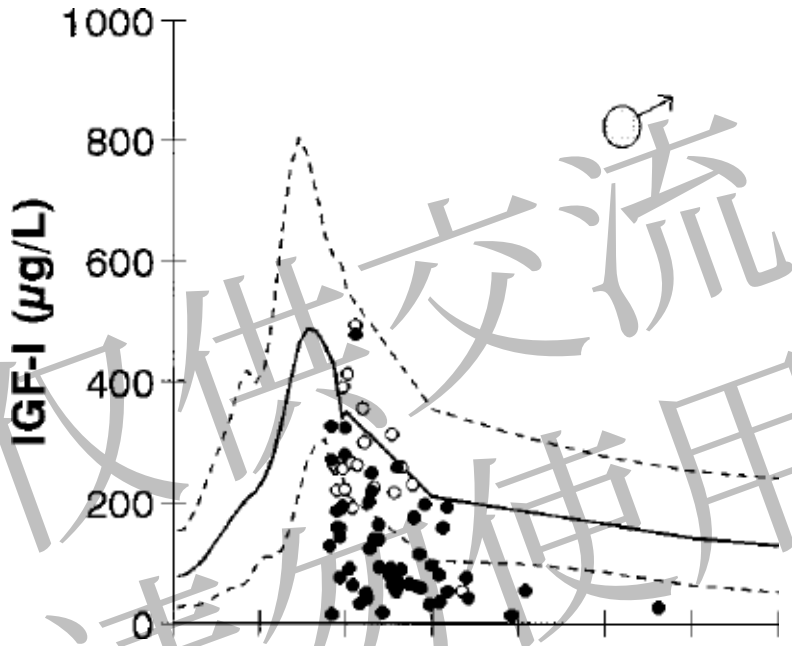
GHD患者年纪越大，IGF-I越正常！

Fig. 2 Individual IGF-I levels (●) in 237 adult panhypopituitary patients (lines represent the 3rd, 10th, 25th and 97th centile, age-related limit in normal subjects).

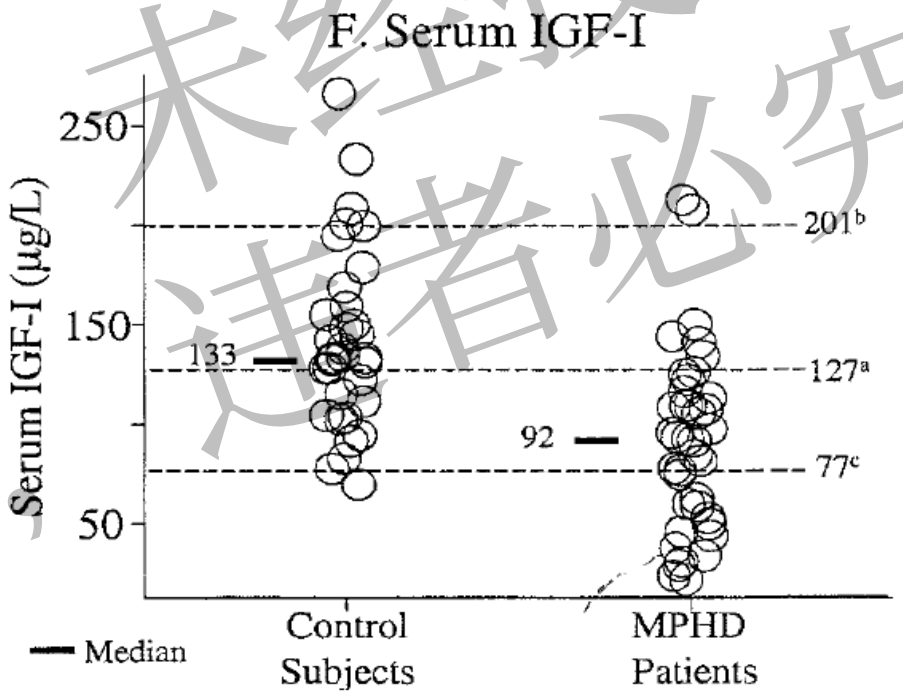
Aimaretti G et al., Clinical Endocrinology (2003) 59, 56–61

健康人和GHD患者的IGF-I存在交叉

Juul A et al., JCE&M 1997



Biller BMK et al., JCE&M 2002



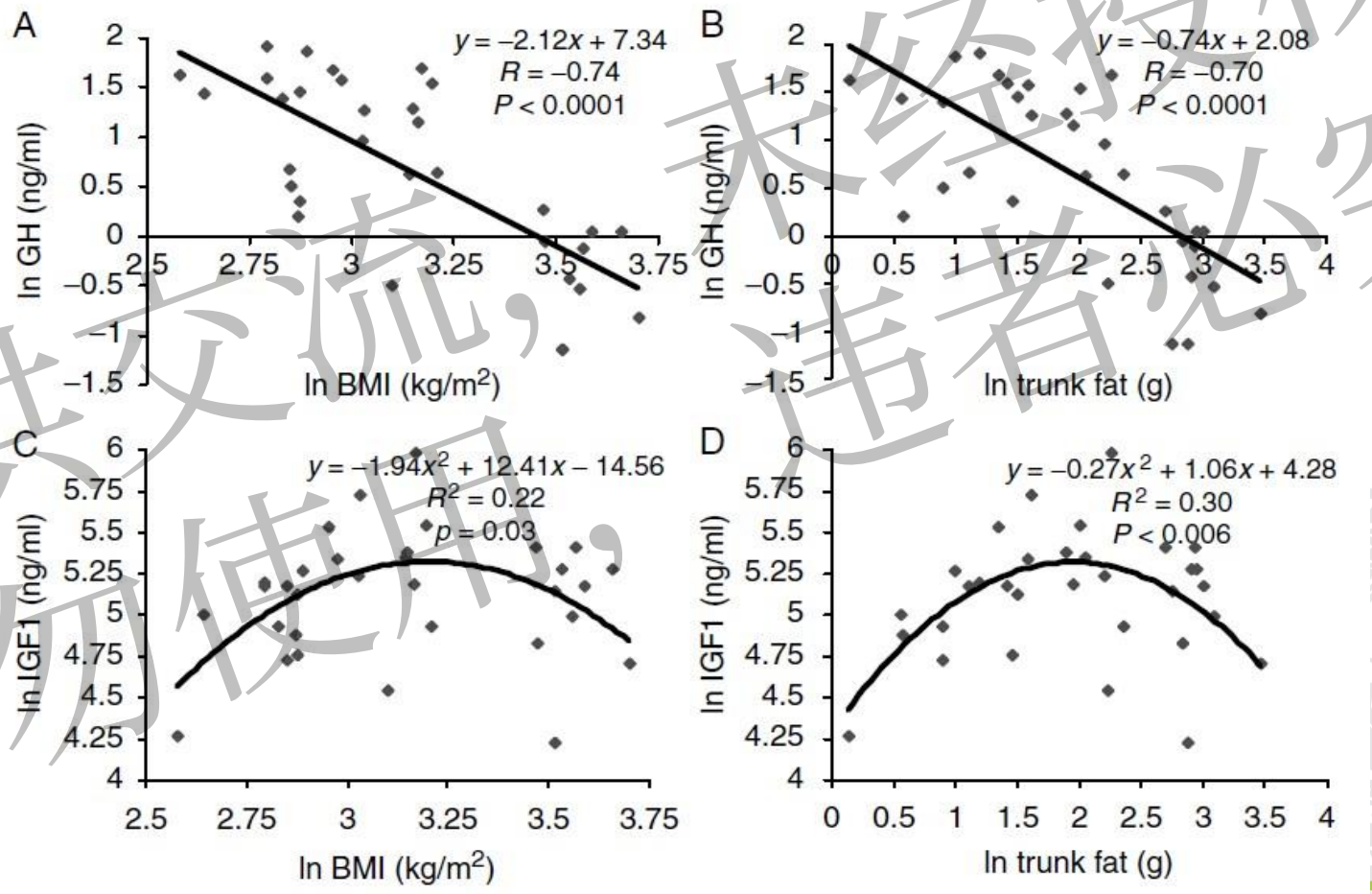
IGF-I 对于检测GHD即不特异性又不敏感

IGF-I 和 BMI

32 位女性:神经性厌食症(n=11), 体重正常 (n=11), 肥胖 (n=10)
每小时汇集一次血样

GH

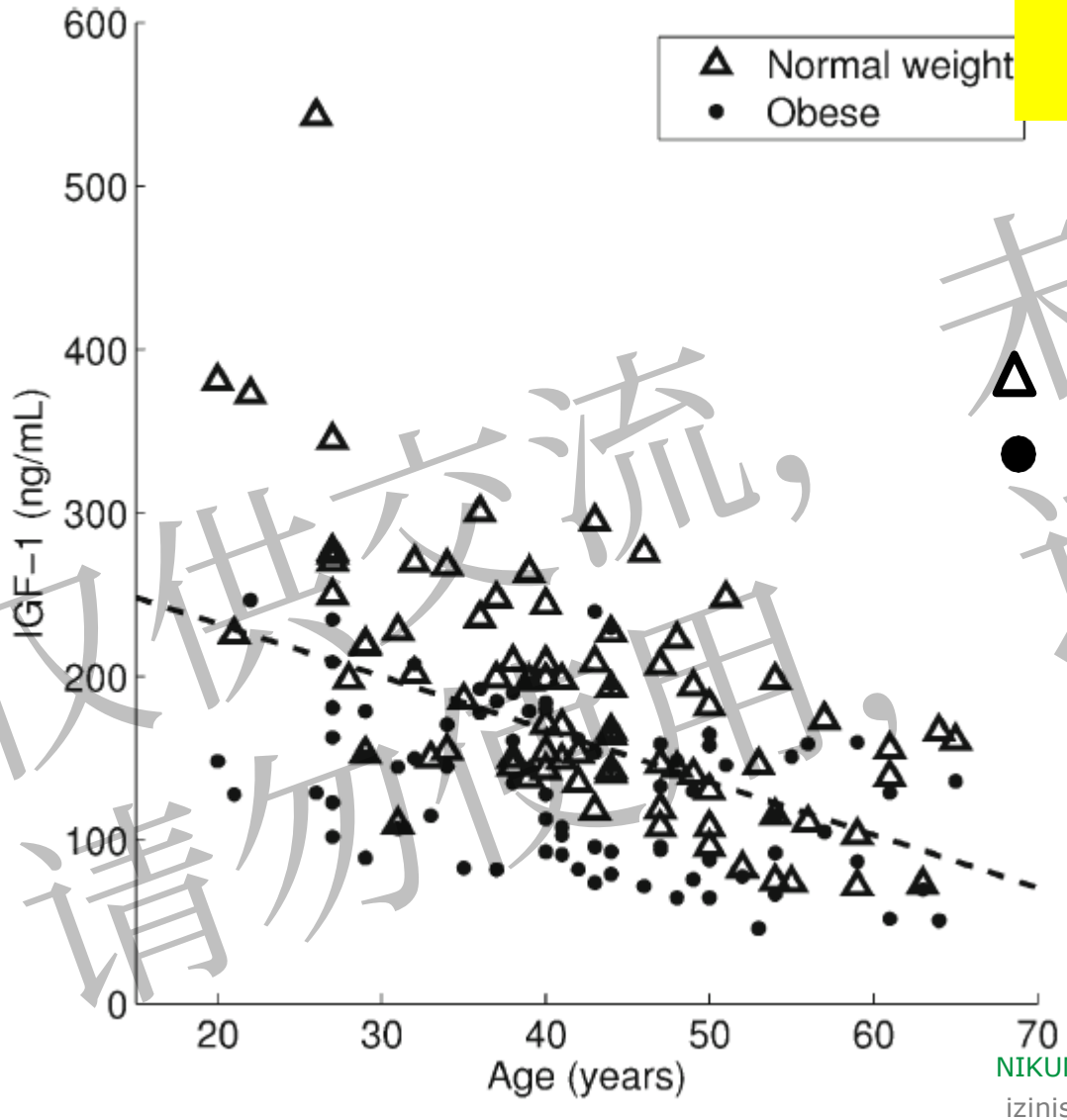
IGF-I



Brick DJ et al. Eur J Endocrinol. 2010 Aug;163(2):185-91

IGF-I 和 BMI: 肥胖

平均IGF-I在肥胖人群中更低

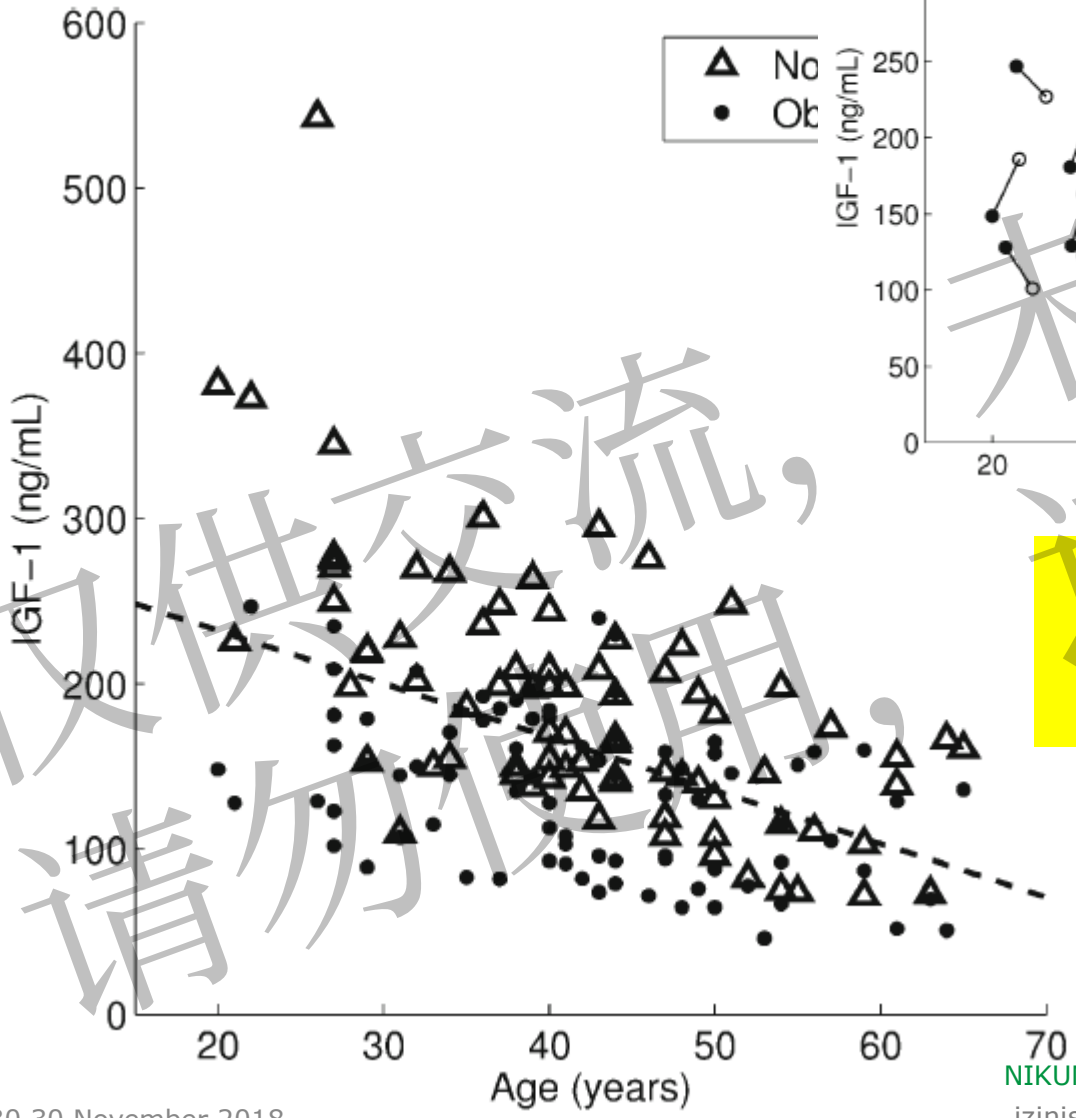


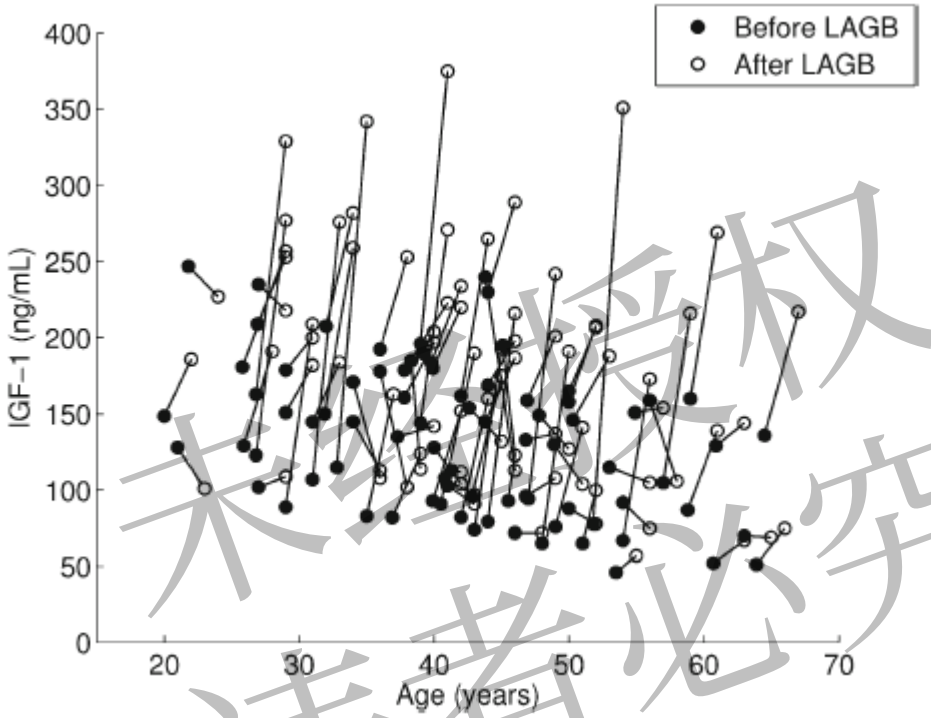
△ normal weight

● obese

Galli G et al. Obes Surg. 2012 Aug;22(8):1276-80

IGF-I 和 BMI: 肥胖





胃束带术后

IGF-1在体重降低后下降

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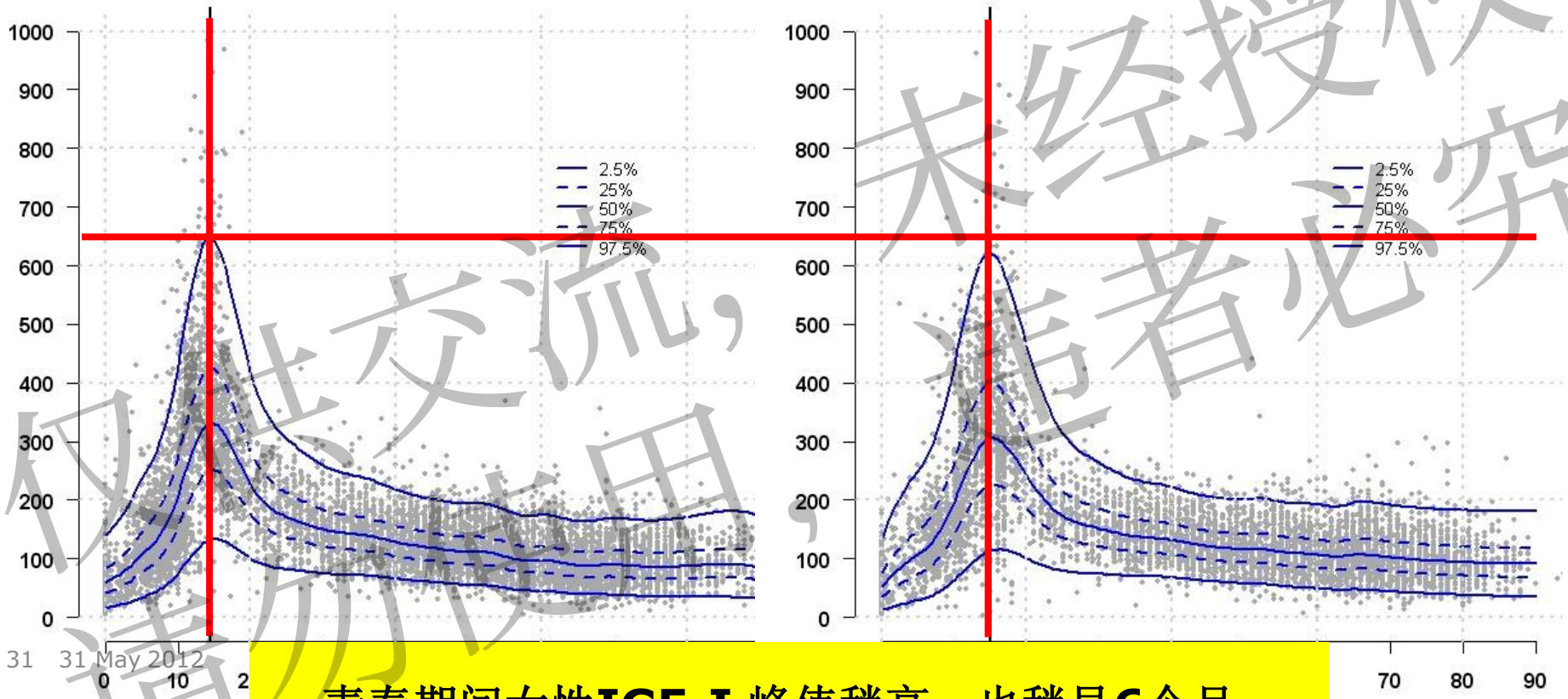
Galli G et al. Obes Surg. 2012 Aug;22(8):1276-80

性别的影响?

女 (n=8353)

男 (n=6697)



青春期间女性**IGF-I** 峰值稍高，也稍早**6**个月

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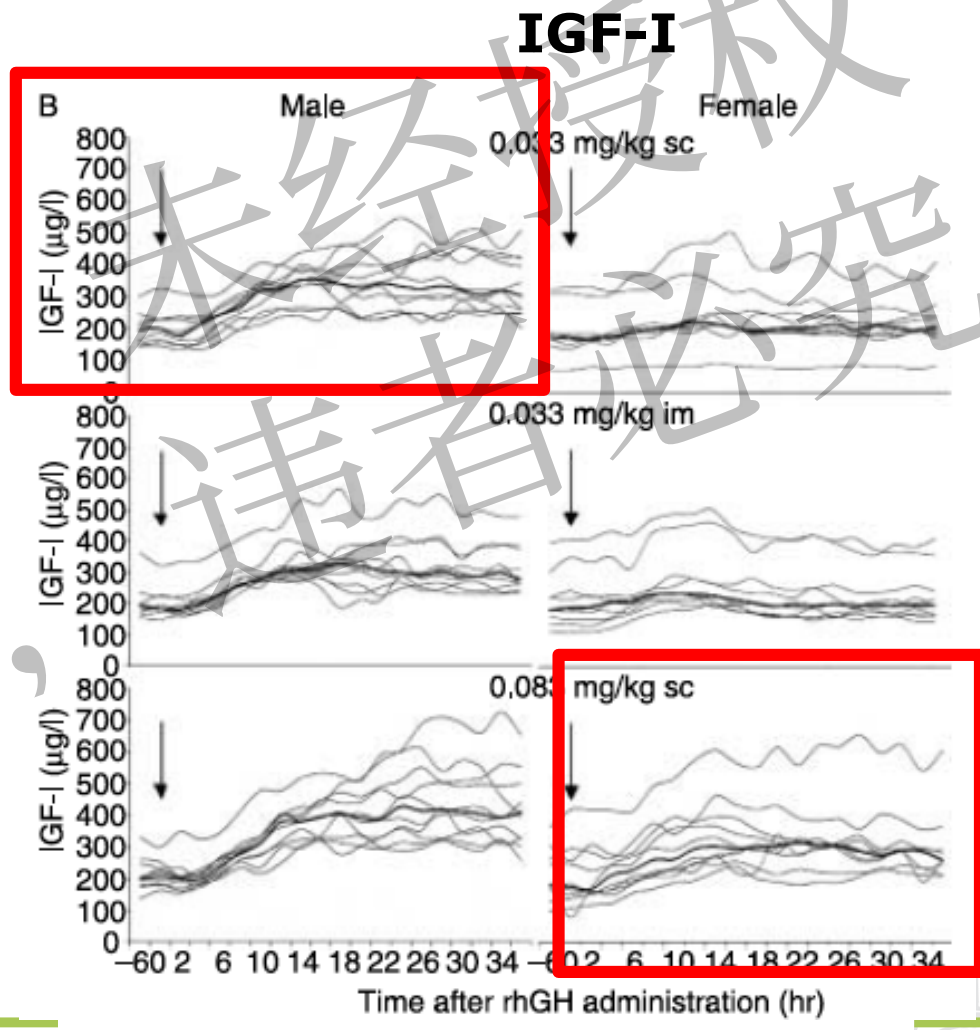
Bidlingmaier et al. JCEM 2014

Endocrine Research Laboratory

GH用药后的IGF-I响应（健康青壮年）

雌激素充足的女性
需要更高的**GH**剂量来达到
同样的**IGF-I**增量

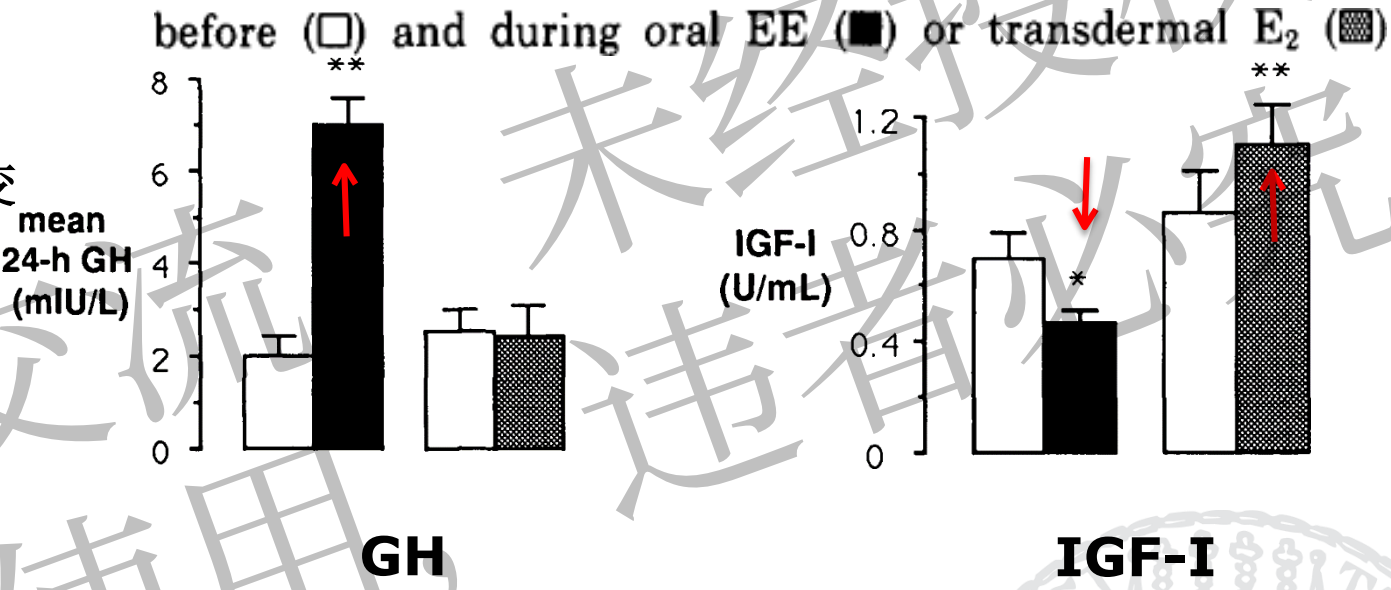


Keller et al. EJE (2007) 156. 647-653

口服与透皮雌激素：对GH和IGF-I的影响

绝经后妇女

IGF在口服组下降，
透皮雌激素组未见改变



口服雌激素的"GH 抵抗状态"

Weissberger AJ et al. JCEM. 1991;72(2):374-81

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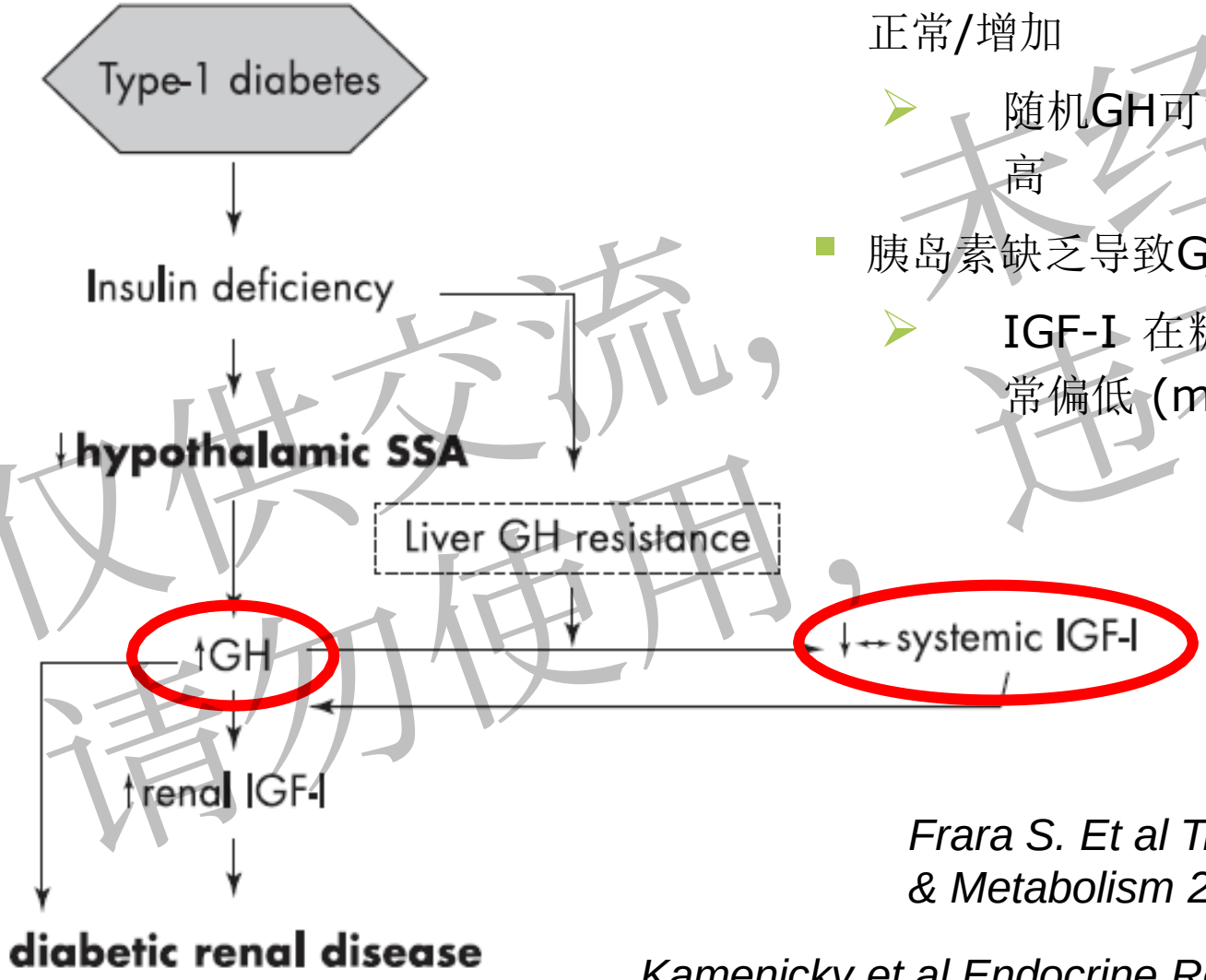
1型糖尿病患者GH分泌异常



- 在胰岛素治疗的糖尿病换这种GH分泌正常/增加
  - 随机GH可能非正常增高
- 胰岛素缺乏导致GH 抵抗
  - IGF-I 在糖尿病换这种可能非正常偏低 (most studies in T1D)

Frara S. Et al Trends in Endocrinology & Metabolism 2016

Kamenicky et al Endocrine Rev 2014

IGF-I 浓度是什么？分析问题

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临床观点1

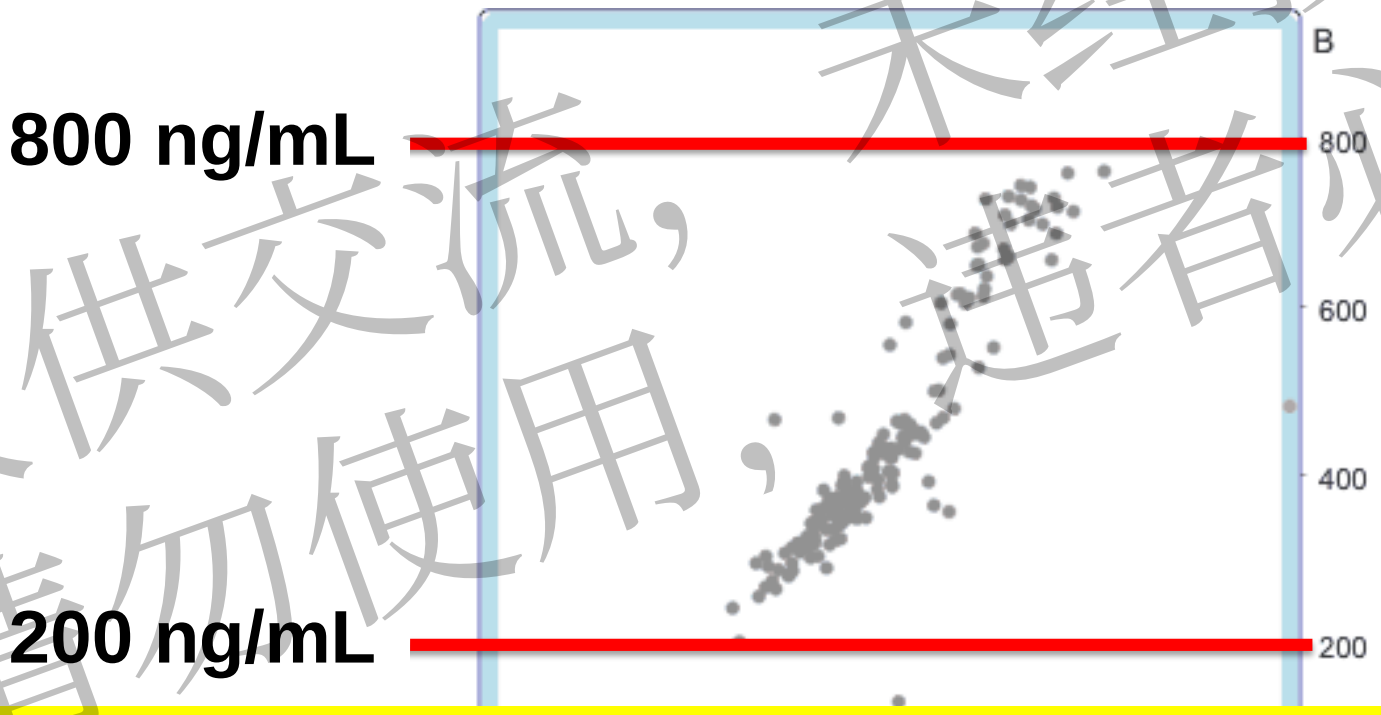
患者（ GH相关疾病）

- 带着不同实验室做出来的IGF-I值过来
- 在不同医院/医生中转来转去

理想的 IGF-I 浓度值应与实验室或检测方法无关

IGF-I 使用不同检测方法:外部质量评估方案

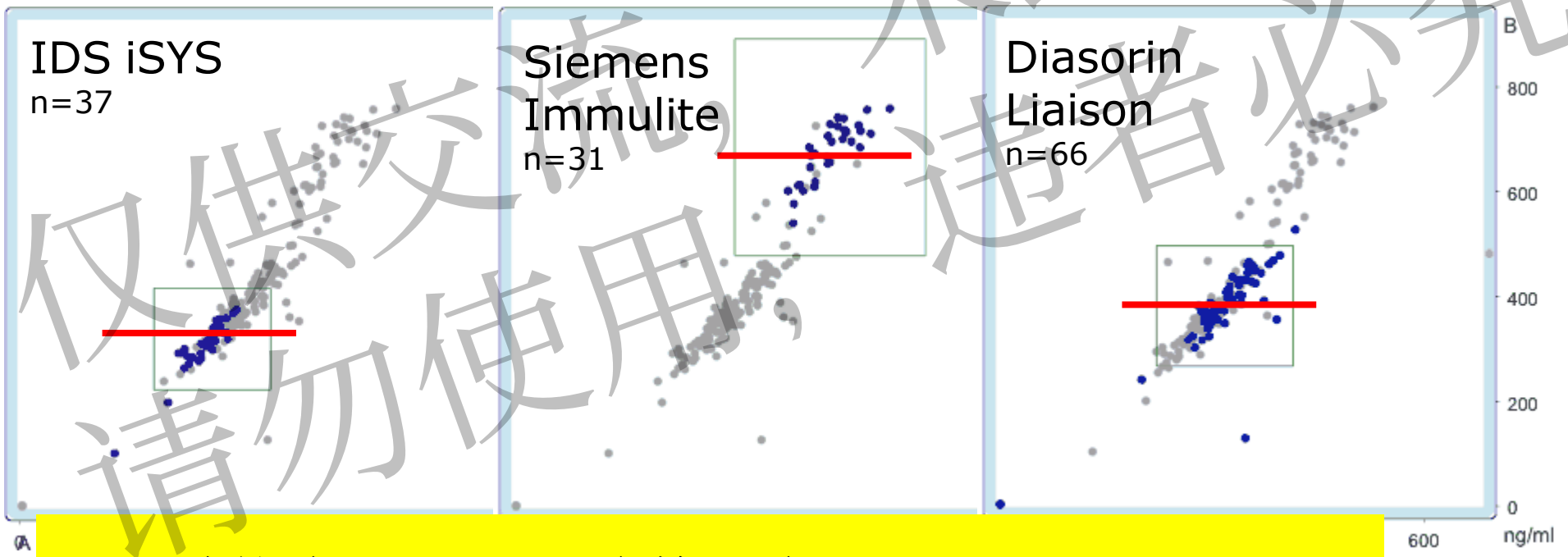
2 个血样给各家实验室分析 (n>150) (每个点代表1家实验室的2个检测结果)



反馈的结果：每个实验室都有不同结果!

IGF-I 结果使用不同检测平台：German EQAS 3/2013

2 个血样给各家实验室分析 (n>150)
(每个点代表1家实验室的2个检测结果)



反馈的结果：不同平台检测结果不同!

IGF-I 结果使用不同检测平台：German EQAS 3/2013

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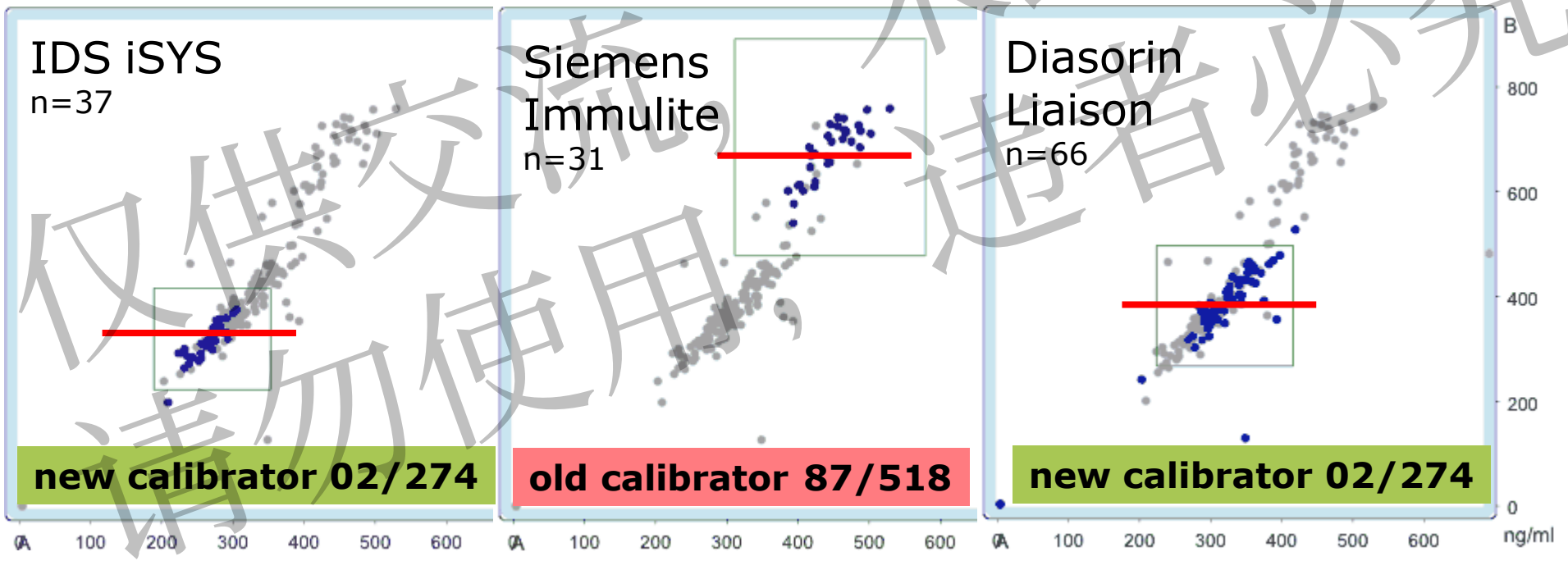

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IGF-I 结果使用不同检测平台：German EQAS 4/2018

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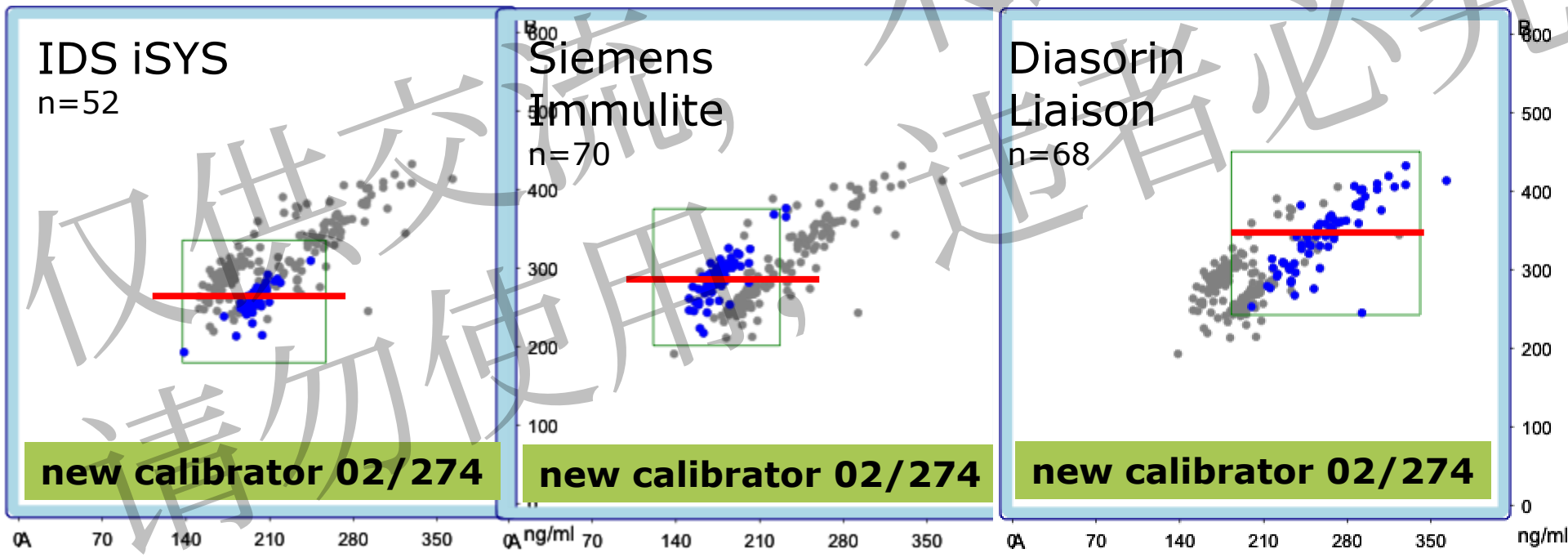

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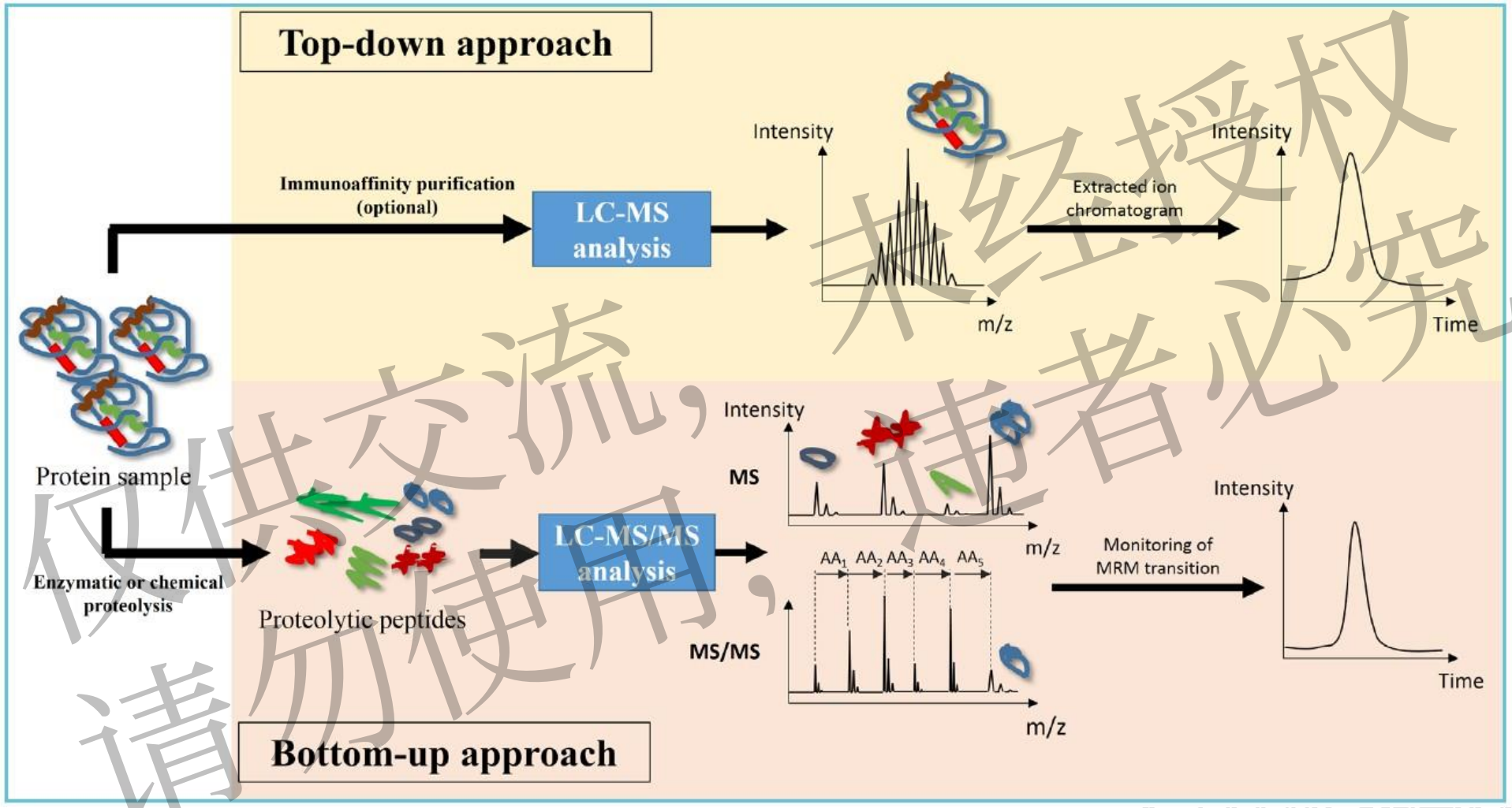
质谱法测IGF-I



MS ≠ MS

Kam et al., eJIFCC 2016

质谱法测IGF-I

质谱法测IGF-I的跨实验室协议

使用质谱法的跨实验室协议并没有让数据更好!

Sample	Mean concentration, ng/mL	Central calibrator, CV, %[a]	Local calibrator, CV, %[b]
1	85	4.0	16.4
2	90	5.6	19.3
3	210	6.1	10.6
4	356	6.9	5.5
5	179	3.5	11.8
Mean CV, %[c]		5.2	12.8

Cox et al., Clin Chem 2014

质谱法是测量IGF-I的另一个选择吗?

Clinical Chemistry 60:3
541–548 (2014)

问题与免疫法相似:

- 实验室间没有统一的方案
- 不同质谱的产品质量不同
- 标准品的来源不同
- 实验室间的可比性比免疫法更差，除非统一制备标准品
- 缺少试剂的长期稳定性数据
- 参考区间的质量?

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临床观点2

患者（ GH相关疾病）

- 有慢性疾病
- 需要长期监测

实验室报告的IGF-I 浓度值需要有长期的可重复性

Siemens Immulite IGF-I 试剂的‘长期’ 问题

Clinical Chemistry 59:8
1187–1194 (2013)

Laboratory Management

Failure of Current Laboratory Protocols to Detect Lot-to-Lot Reagent Differences: Findings and Possible Solutions

Alicia Algeciras-Schimnich,[1] David E. Bruns,[2] James C. Boyd,[2] Sandra C. Bryant,[3] Kristin A. La Fortune,[2] and Stefan K.G. Grebe[1*]

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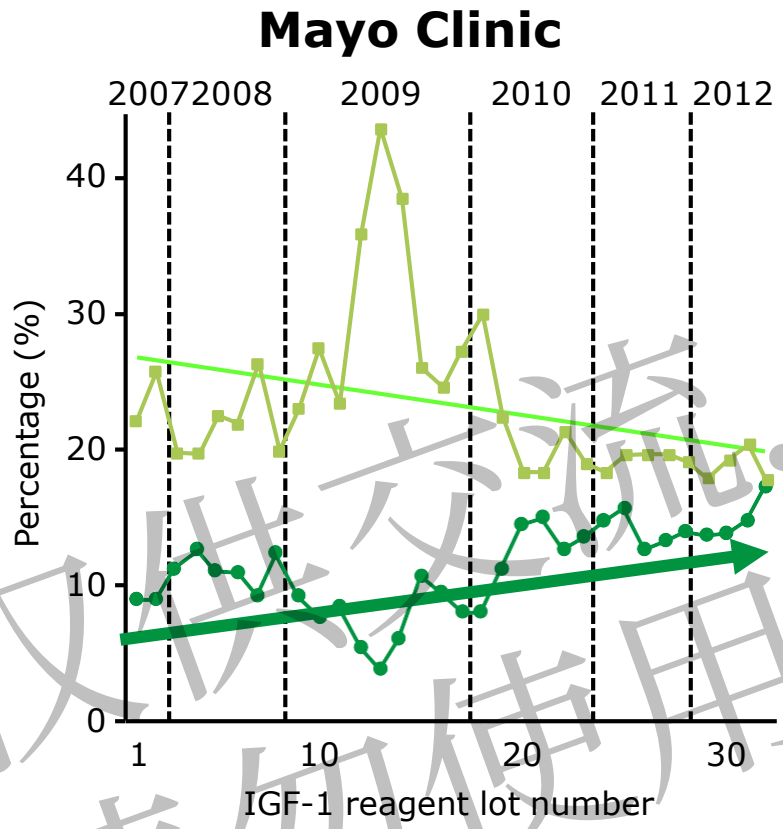
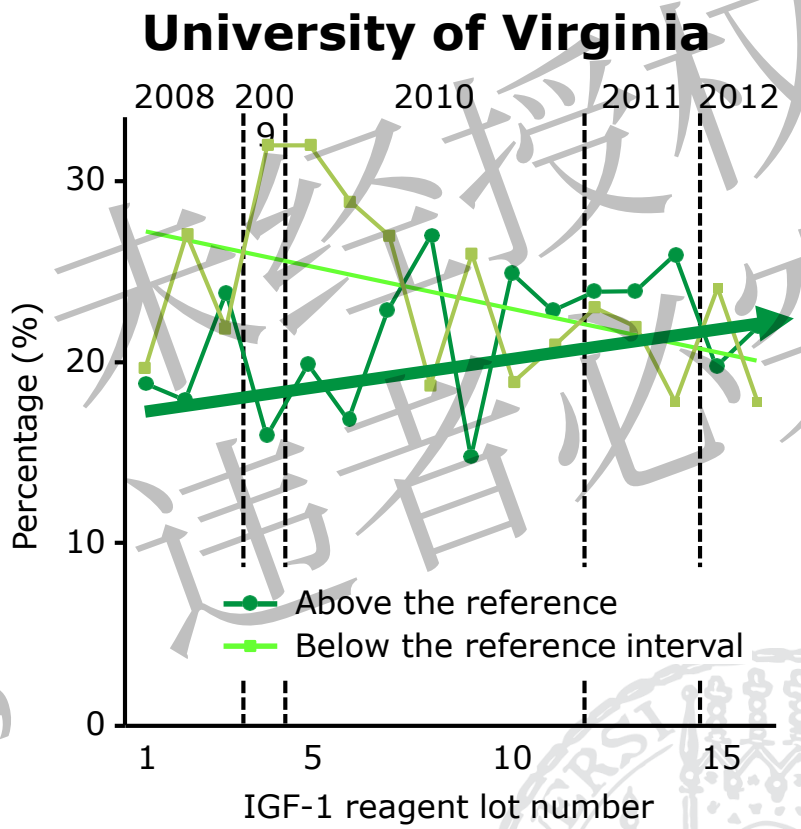
IGF-I 试剂的‘长期’ 问题



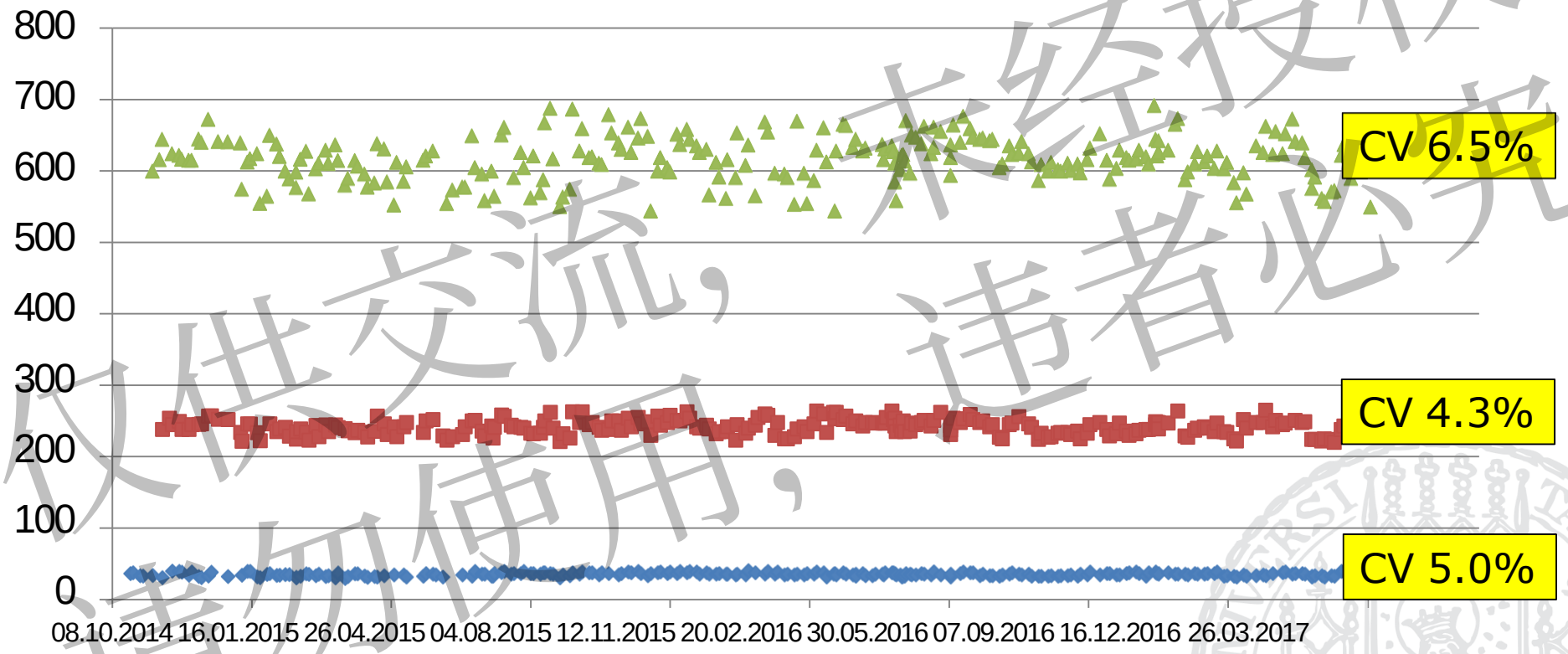


高于正常范围的百分比显著上升

实验室必须严格监控试剂批次之间IGF-I检测的性能

29个月的IGF-I对照池

汇集患者血清, Munich Endocrine Laboratory（IDS iSYS IGF-I assay, October 2014 – March 2017)



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好参考区间
– 并不容易

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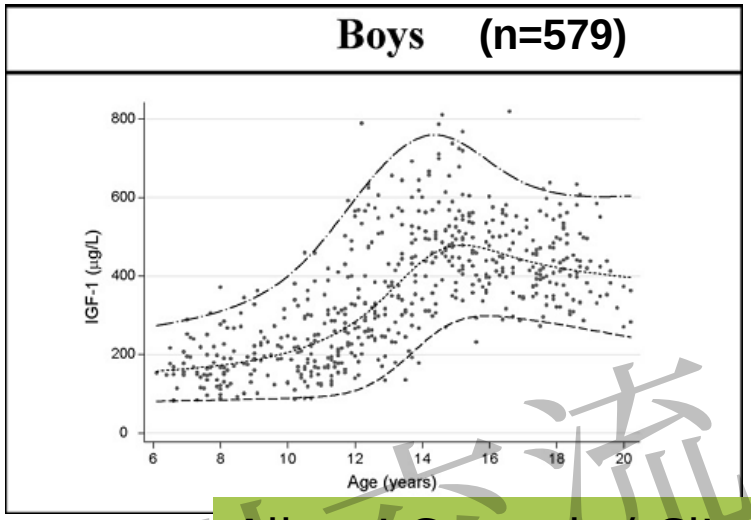
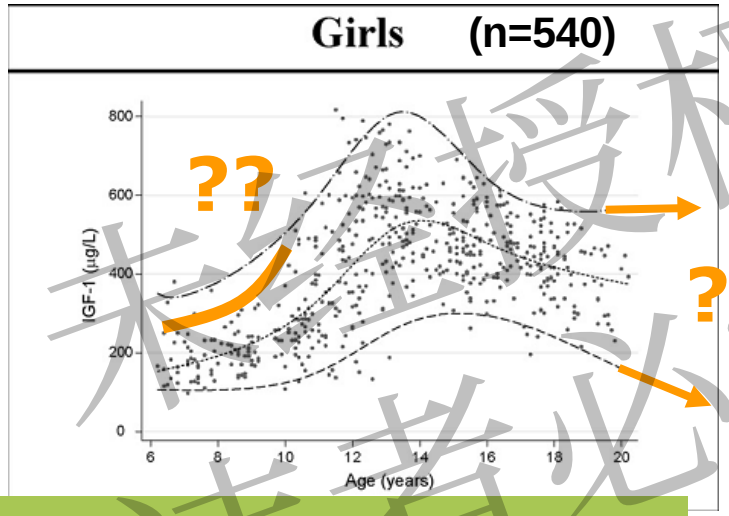
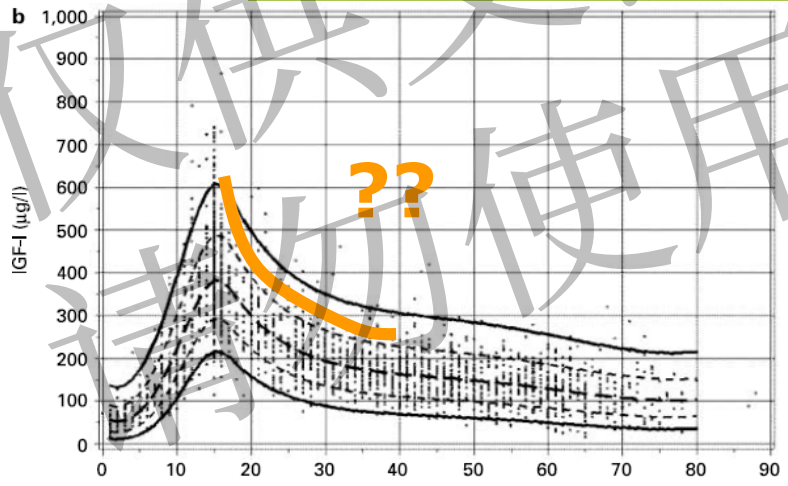
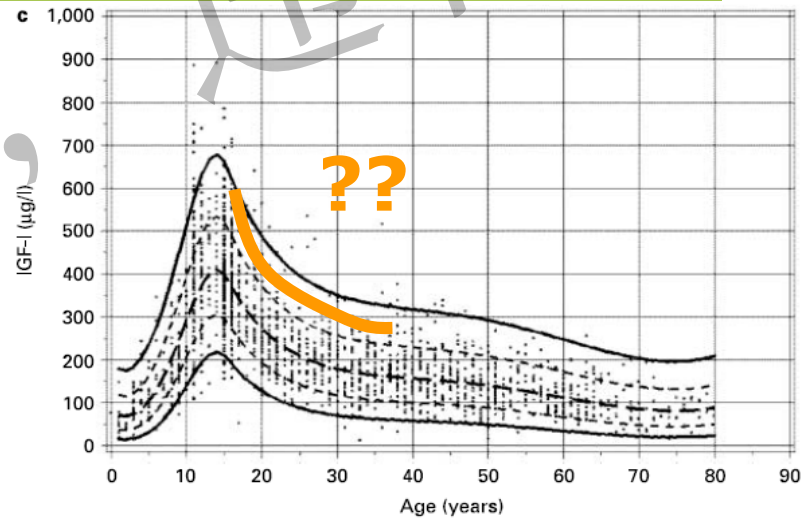
如何计算参考区间?





Alberti C. et al. / Clin Chem 57:10; 1424–1435 (2011)

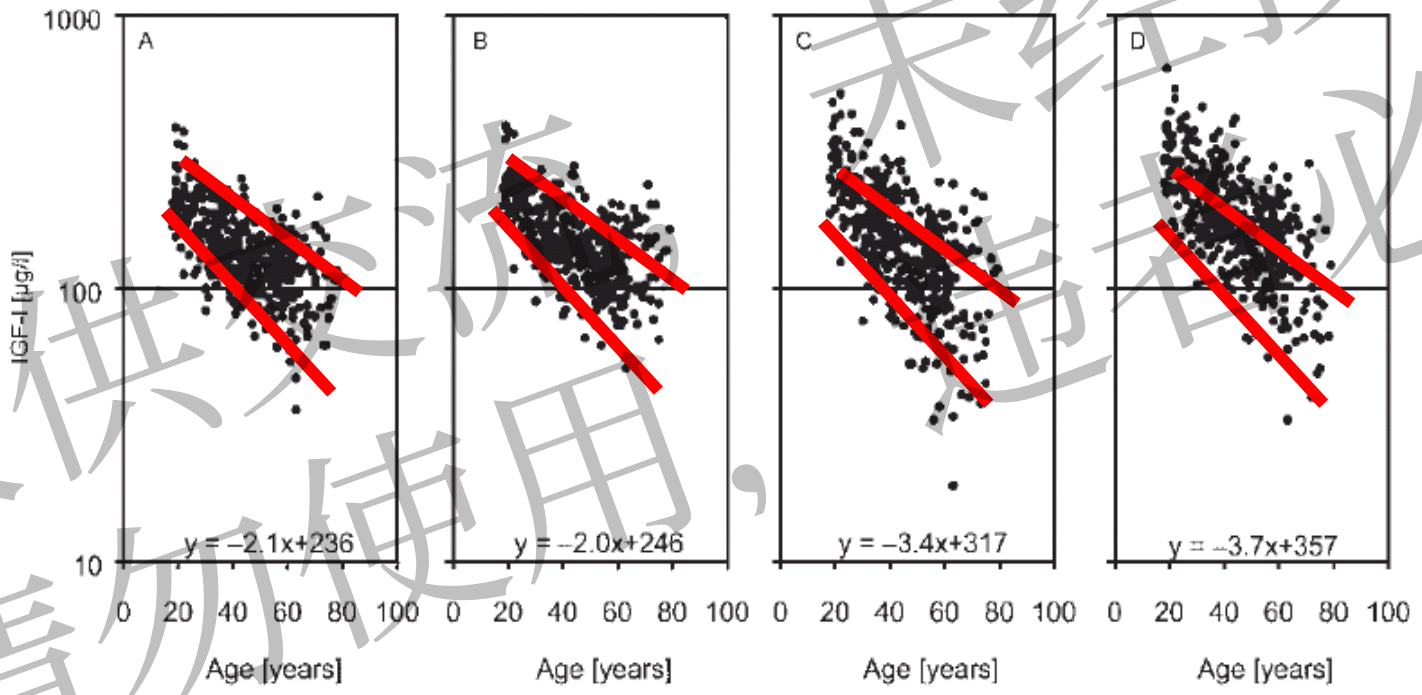




Brabant G. et al. / Horm Res 2003

参考区间必须与方法相关

700 samples from healthy adults
measured by 4 IGF-I assays



Ranke et al., Clin Chem Lab Med 2003

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已发表的 IGF-I参考值，受试人群不同，统计方法也不同 (examples)

study	受试 (male/female)	统计方法
Löfqvist et al. 2001	468 (468, 0)	log transformation, multiple linear regression (best linear model: age, gender and puberty)
Brabant et al. 2003	3961 (1469, 2492)	polynomial modelling
Ranke et al. 2003	427 (0, 427)	log transformation, linear regression
Elmlinger et al. 2004	1584 (881, 703)	local regression analysis
Ivan et al. 2005	88(?, ?)	not detailed
Bereket et al. 2006	807 (807, 0)	square root transformation, least linear regression
Massart 2007	693 (?, ?)	not detailed
Kong et al. 2007	1692 (1692, 0)	LMS
Aimaretti et al. 2008	547 (0, 547)	grouped linear regression
Friedrich et al. 2008	2499 (0, 2499)	linear and quantiles regression
Granada et al. 2008	405 (0, 405)	log transformation, means for different age-groups
Brugts et al. 2008	426 (0, 426)	linear regression (with bioactivity)

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Bidlingmaier et al. JCEM 2014

已发表的 IGF-I参考值，受试人群不同，统计方法也不同 (examples)

study	participants (male/female)	statistical method
Löfqvist et al. 2001	468 (468, 0)	log transformation, multiple linear regression (best linear model: age, gender and puberty)
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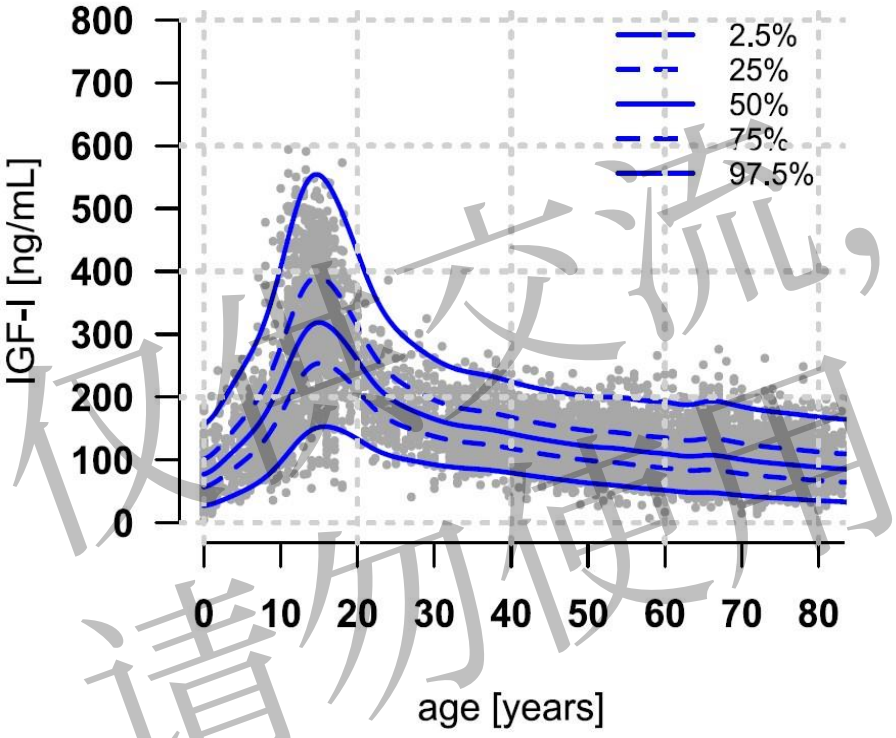
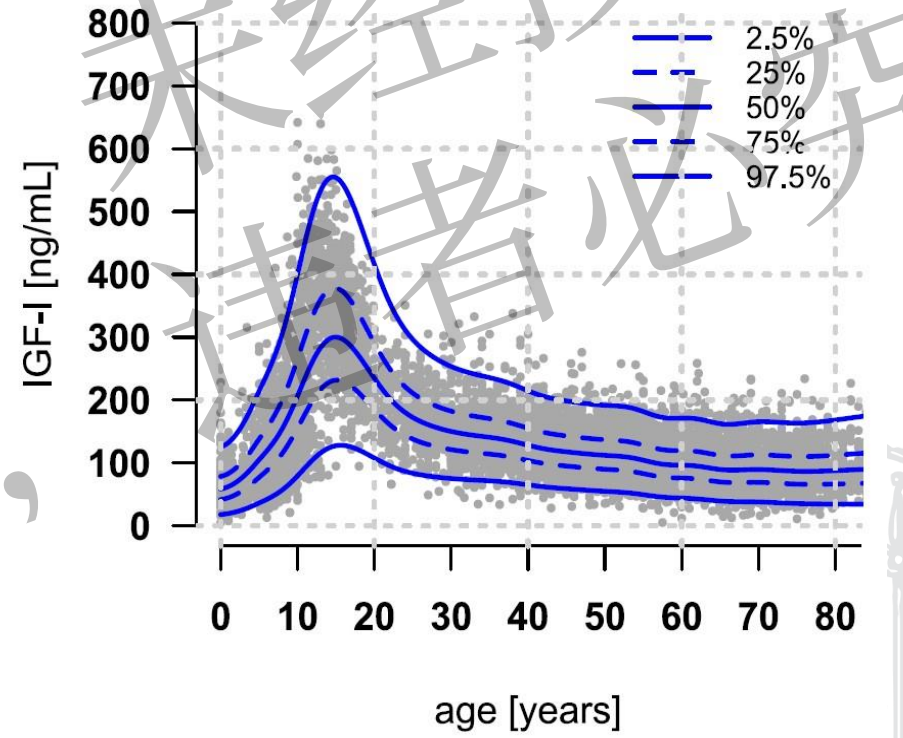
Bidlingmaier et al. JCEM 2014

IDS iSYS IGF-I 检测的参考区间 (国际多中心研究)

Males (n=6697)



Females (n=8353)



Centiles: LMS method

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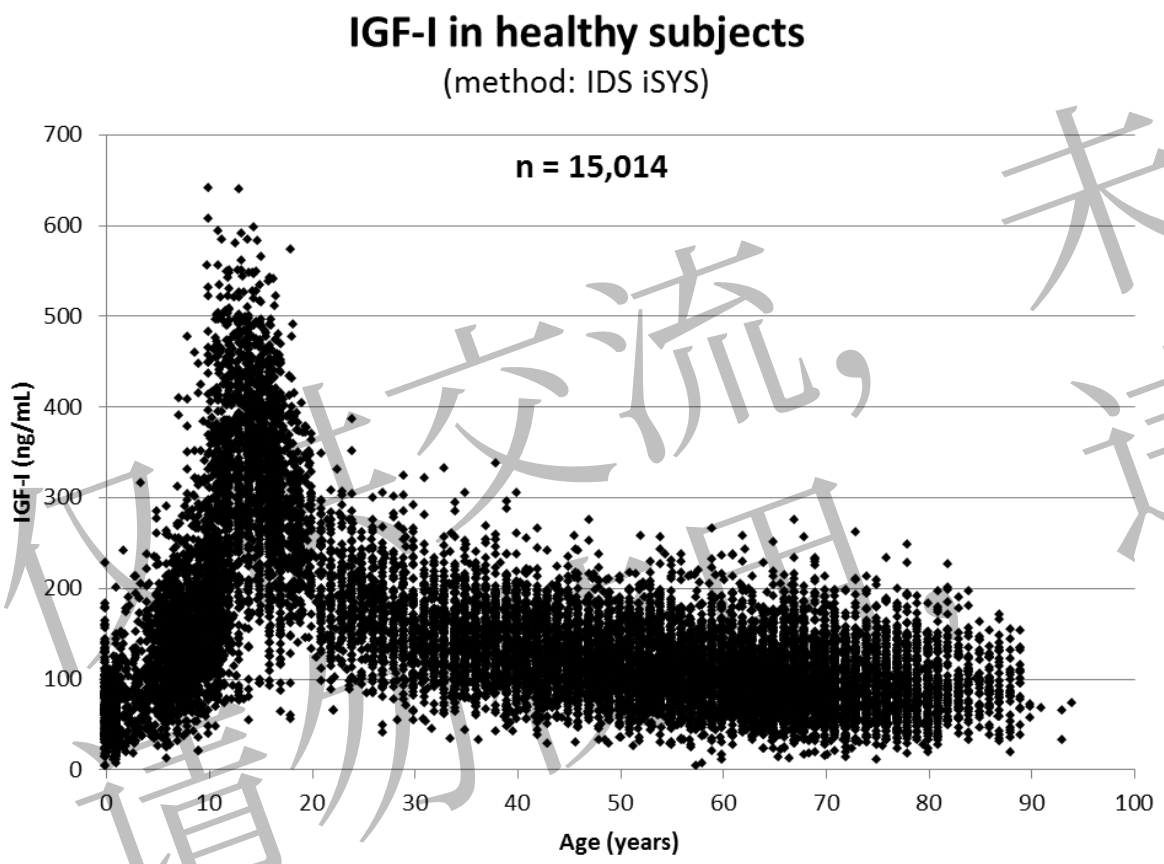
Bidlingmaier et al. JCEM 2014

为IDS iSYS IGF-I 试剂定制参考区间的多中心研究:



Cohort	n
Munich, Germany	146
CALIPER, Canada	1360
CALIPER new, Canada	588
Aarhus, Denmark	854
Gothenburg, Sweden	319
Leipzig, Germany	193
Athens, Georgia, USA	737
Graz, Austria	55
Berlin, Germany	2623
Greifswald, Germany	4109
KORA F4, Germany	2989
KORA Age, Germany	1041
Total	**15014**

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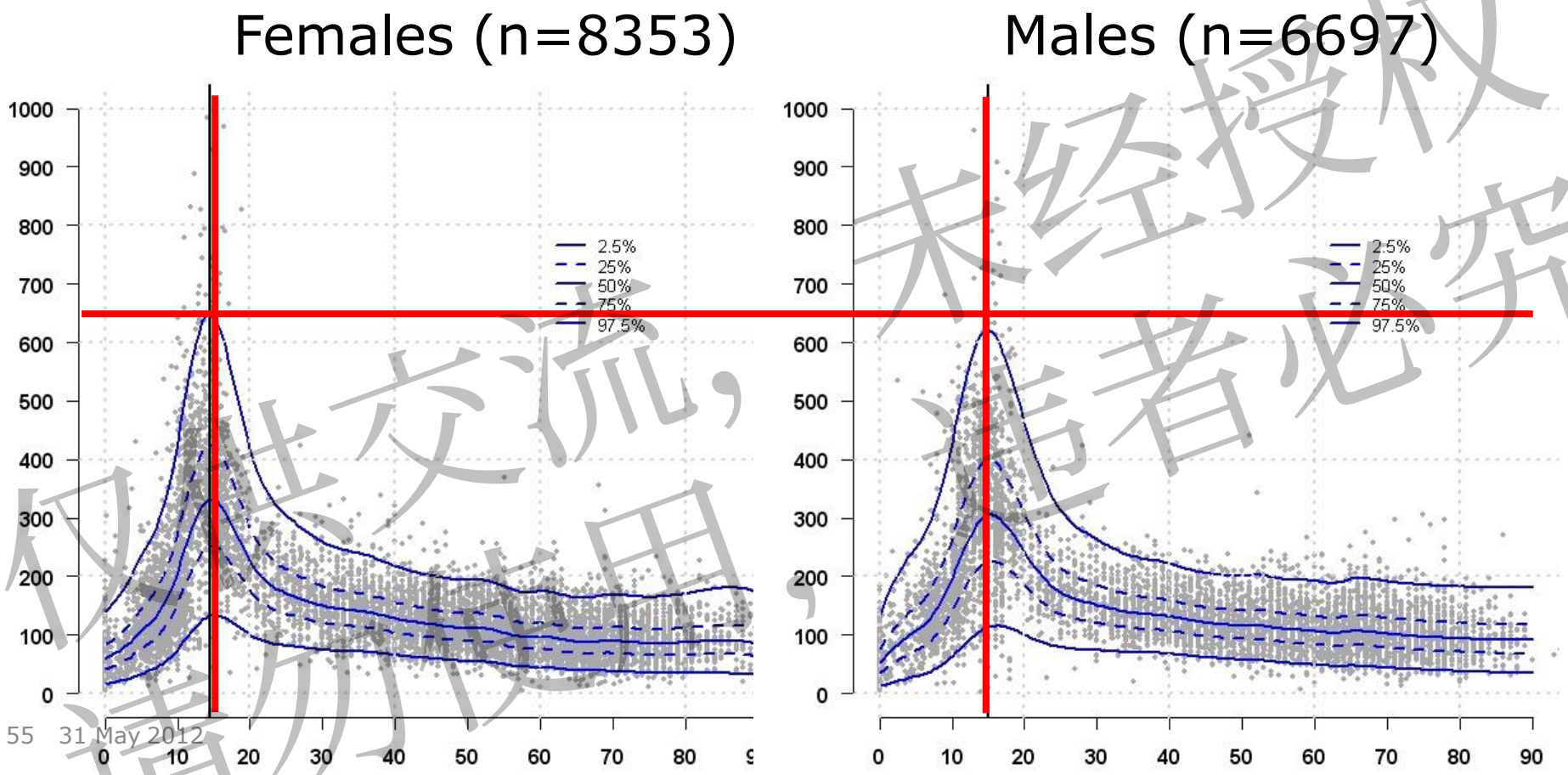
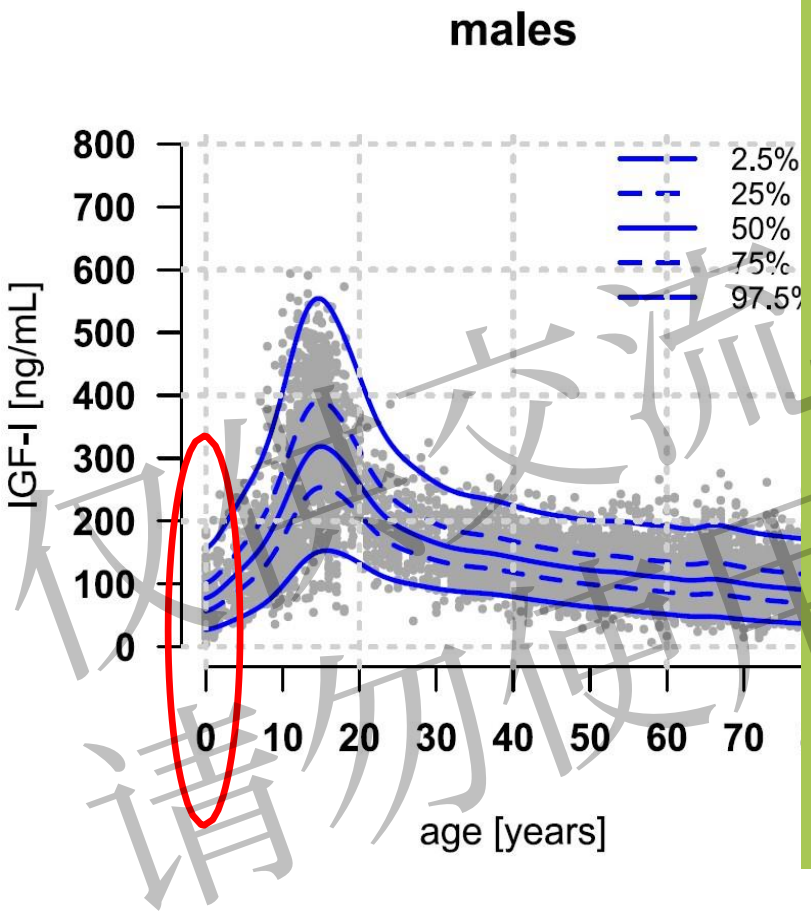
性别的影响?

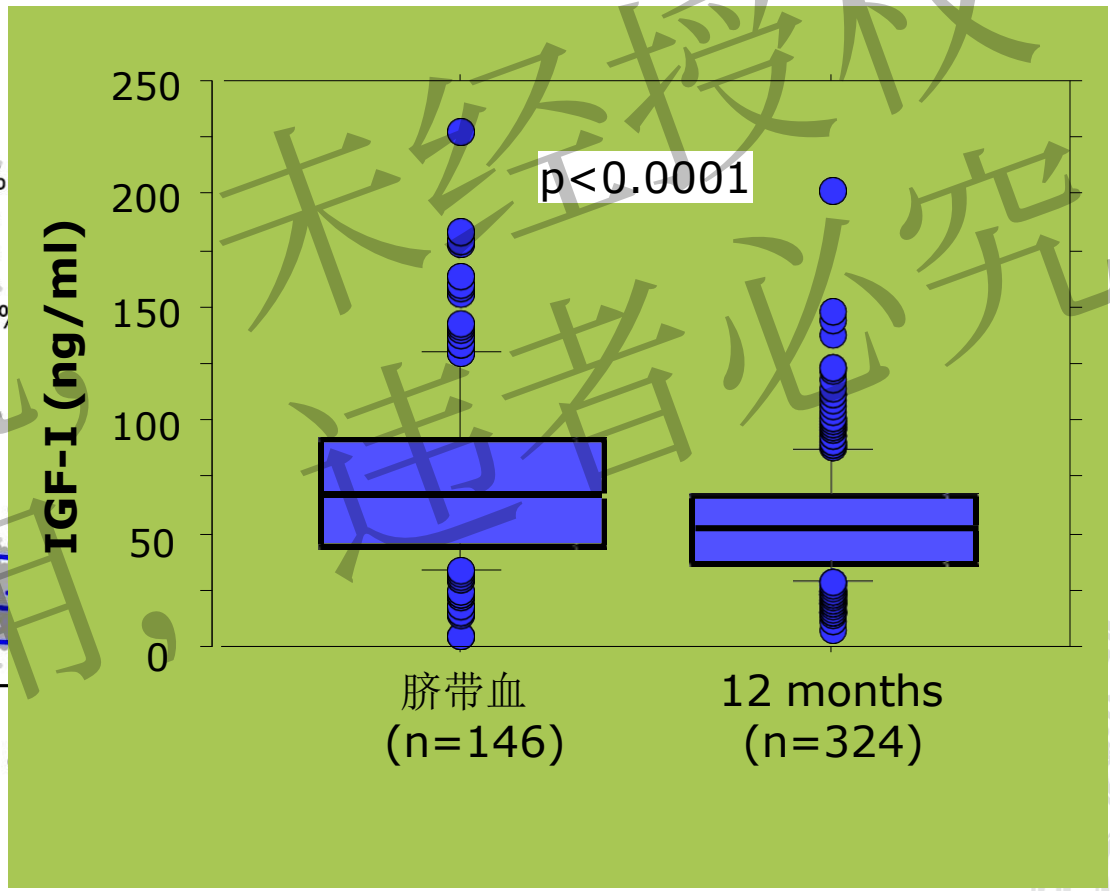


青春期间女性IGF-I 峰值稍高，也稍早6个月

Bidlingmaier et al. JCEM 2014

IGF-I 参考区间: 没有统计模型能覆盖所有年龄!





Bidlingmaier et al. JCEM 2014

IGF-I 参考区间: 看实际年龄还是Tanner分期?

Table 3. Percentiles for IGF-I According to Tanner Stages Based on the Danish Cohort (n = 854)

Tanner	Age Range, y	IGF-I, ng/mL 2.5%	25%	50%	75%	97.5%
Males						
I	6.1–12.9	81.3	132.5	160.0	187.9	255.3
II	8.1–14.8	106.2	212.4	276.9	331.8	432.3
III	10.9–16.0	244.9	341.2	407.2	449.0	511.4
IV	12.4–17.1	222.6	364.5	439.0	492.4	577.7
V	13.5–20.0	227.4	308.6	355.7	412.3	517.8
Females						
I	5.8–12.1	85.9	152.6	187.7	235.3	323.0
II	9.3–14.1	117.5	190.0	247.3	323.2	451.3
III	9.3–15.1	258.3	335.5	382.8	430.8	528.5
IV	11.8–16.6	224.2	339.8	378.3	437.5	585.8
V	12.5–19.9	188.2	277.4	339.1	394.9	511.6

Estimated percentiles (2.5%, 25%, 50%, 75%, and 97.5%) derived by Harrell-Davis estimate of quantiles are provided.

Bidlingmaier et al., JCEM 2014

- 如果只看Tanner分期IGF-I-“峰值”在女孩中更早
- 如果根据实际年龄来看，10-16岁女孩的参考区间会更宽
- 无论男女，正常值的下限(P2.5)在根据Tanner分期计算时更低

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为IDS iSYS IGF-I 试剂定制参考区间的多中心研究:

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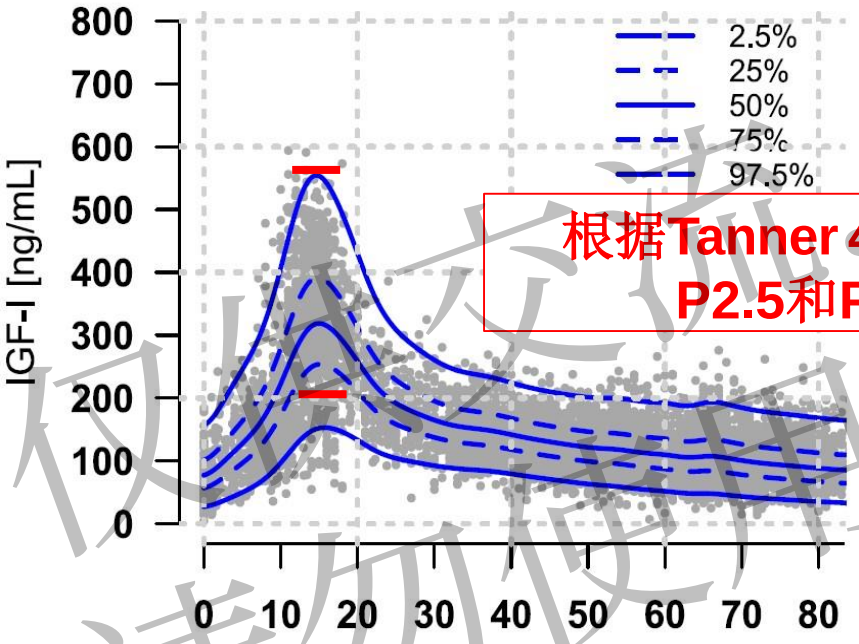
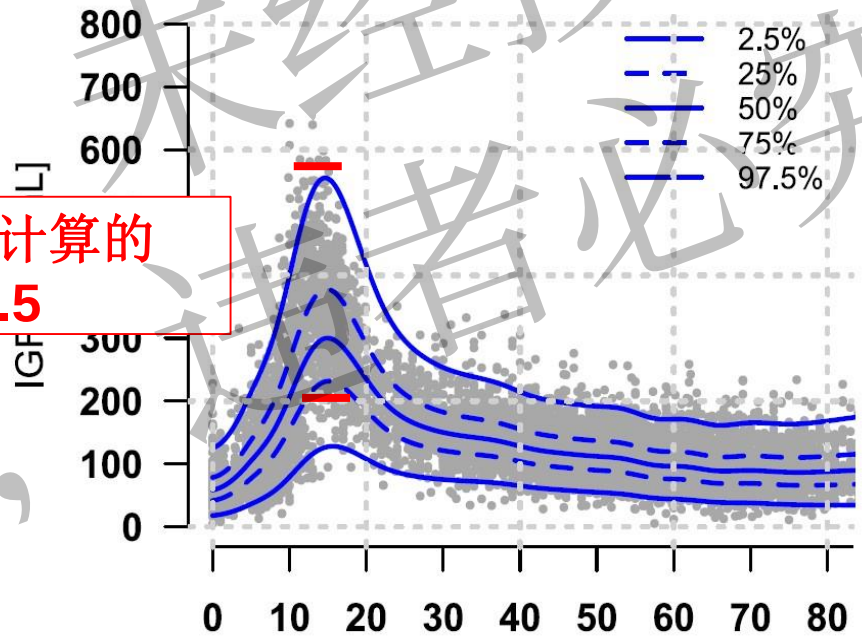


Females (n=8317)



根据Tanner 4期计算的
P2.5和P97.5

百分位根据. LMS-Methode (VGAM)方法计算

Bidlingmaier et al., JCEM 2014

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总结: GH治疗的生物标志物

- 血液中有许多标志物会根据GH的作用而变化
- 唯一被广泛接受的生物标志物是IGF-I
- 年龄，青春期和口服雌激素是IGF-I的主要生物混杂因素
- IGF-I 检测试剂的质量不同，产生的结果也不同
- 参考区间必须根据检测试剂定制
- 样本大小，参考人群的选择，统计模型对参考区间的质量有较大影响

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Thank you!

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