Harry Jiménez MD, FACE

Medical Director HIMA San Pablo, Bayamón

Disclosure

ENDO2019

- Harry Jiménez MD, FACE
  - Has received honorarium as Speaker and/or Consultant for the following pharmaceutical companies:
    - Merck
    - Eli Lilly
    - Boehringer Ingelheim
    - Bristol-Myers Squibb
    - AstraZeneca
    - AbbVie
    - Janssen
    - Sanofi

Objectives

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- Review the clinical data of the conditions of diabetes, thyroid, osteoporosis, and Cushing disease as discussed in the Endocrine Society Meeting of 2019, March 23-26, New Orleans.
- Discuss important points of Diabetes, Osteoporosis and Cushing Disease in recent guidelines.

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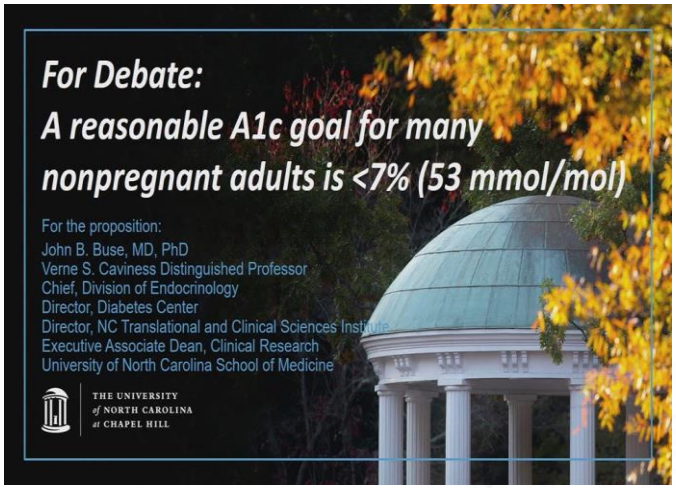
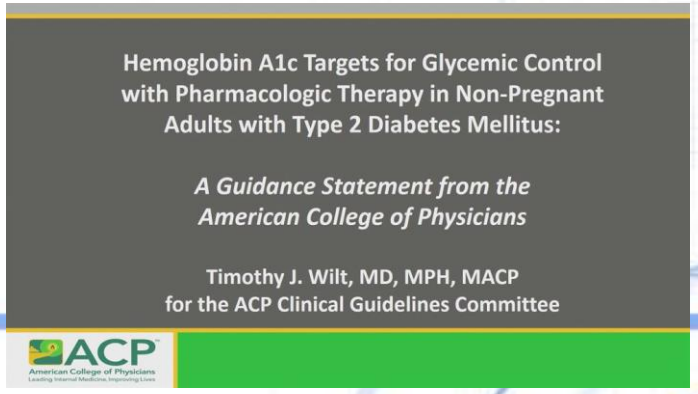
HbA1c Target in Diabetes: A Debate

<7%



>7%-8%



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HbA1c Target in Diabetes: **A Debate**

Debate Position

A reasonable A1C goal for many nonpregnant adults is **<7% (53 mmol/mol)**

Dr. Buse
- Will present the affirmative viewpoint on the statement

Dr. Wilt
- Will refute the statement

Rebuttals
- Rebuttals will follow from each speaker

Vote
- Audience vote through the Audience Response System

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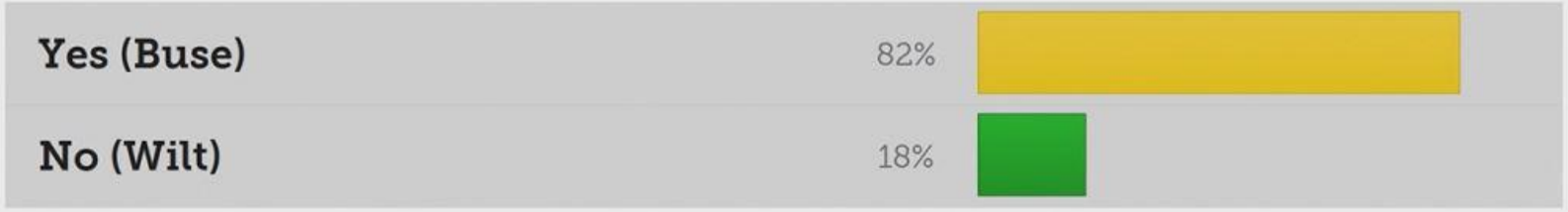
HbA1c Target in Diabetes: **A Debate**

Do you agree that a reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol)?



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HbA1c Target in Diabetes: A Debate

CLINICAL STUDIES DISCUSSED

- DCCT
- EDIC
- UKPDS
  - Legacy Effect
- Accord
- VA-DT
- Advance
- GLP1, Leader
- SGLT2, EMPA-REG

John B. Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Chief, Division of Endocrinology
Director, NC Translational and Clinical Sciences Institute
Executive Associate Dean, Clinical Research
University of North Carolina School of Medicine
Chapel Hill, NC

- He claims that the clinical studies shows benefit of an A1C less than 7% in patient with new onset, young, low cardiovascular risk diabetes type 2 patients without micro and macrovascular complications.
- He emphasized the benefits of micro and macrovascular complications in diabetes with A1c less than 7%
- The importance of cardiovascular benefit in the new studies and the low risk of hypoglycemia with these alternatives

Timothy J. Wilt, MD, MPH
Core Investigator and Staff Physician: Minneapolis VA Center for Care Delivery and Outcomes Research
Professor of Medicine, University of Minnesota School of Medicine
Minneapolis, MN

- He claims that he was unable to find a clinical study that shows a clear benefit with A1C less than 7% when compares with A1c 7% – 8%
- He emphasized the risks of mortality in the ACCORD study in addition to the risks of hypoglycemia and its complications.
- He discussed the high cost of GLP1 and SGLT2 alternatives for cardiovascular benefit, in GLP1 with liraglutide treat more than 100 patients to reduce a death and in SGLT2 with empagliflozin treat 39 patients to reduce a death.

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HbA1c Target in Diabetes: **A Debate**

Do you agree that a reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol)?

Yes (Buse)	58%
No (Wilt)	42%

Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

- 65 years and older with diabetes
- In patients aged 65 years and older without known diabetes, we recommend fasting plasma glucose and/or HbA1c screening to diagnose diabetes or prediabetes.
- In patients aged 65 years and older without known diabetes who meet the criteria for prediabetes by fasting plasma glucose or HbA1c, we suggest obtaining a 2-hour glucose post–oral glucose tolerance test measurement.
- In patients aged 65 years and older with diabetes, we suggest that periodic cognitive screening should be performed to identify undiagnosed cognitive impairment.

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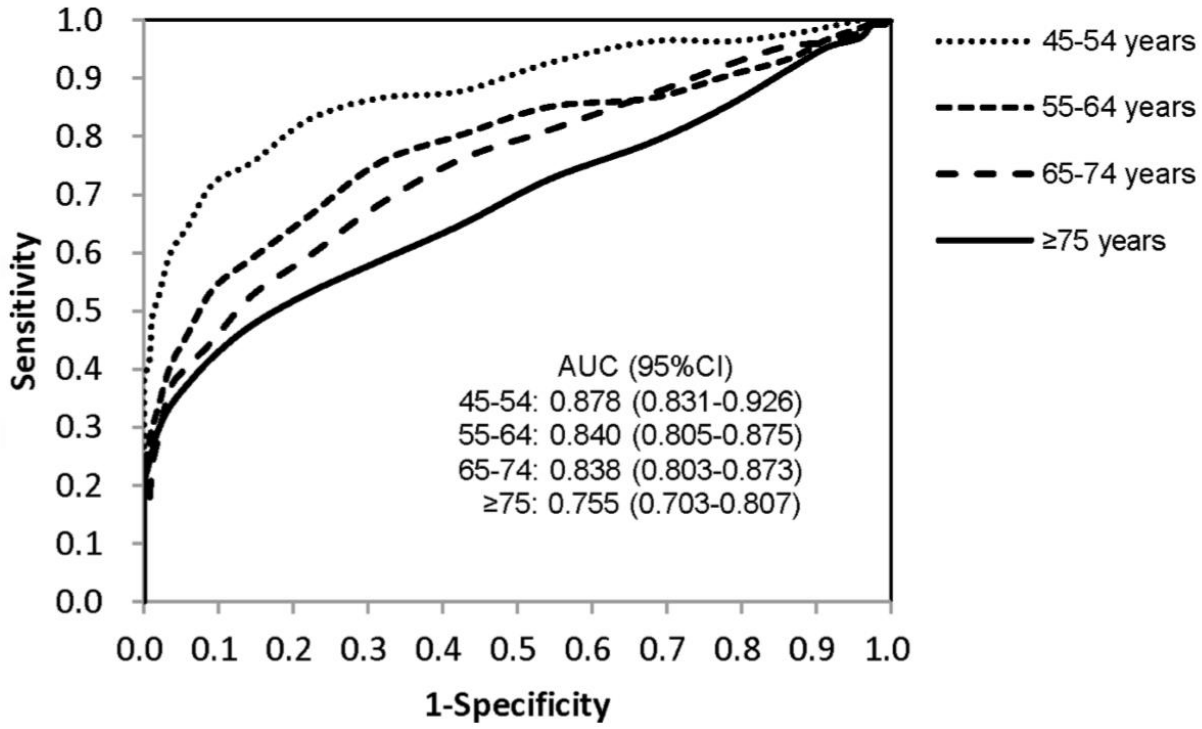
Age and Diagnostic Accuracy of HbA1c

The diagnostic accuracy of HbA1c decreases with age.



Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

- In patients aged 65 years and older with diabetes, we recommend that outpatient diabetes regimens be designed specifically to minimize hypoglycemia.
  - Therapeutic agents that are not associated with hypoglycemia
    - Metformin
    - GLP1
    - SGLT2
    - DPP4
  - Avoid sulfonylureas, glinides, and minimize and simplify insulin use.

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Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

- In patients aged 65 years and over with diabetes in hospitals or nursing homes, we recommend establishing clear targets for glycemia at 100 to 140 mg/dL (5.55 to 7.77 mmol/L) fasting and 140 to 180 mg/dL (7.77 to 10 mmol/L) postprandial while avoiding hypoglycemia.

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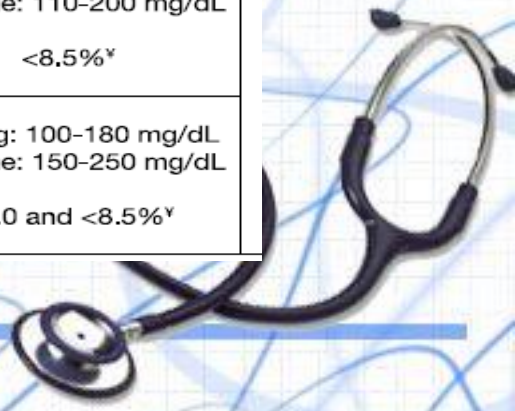
Conceptual Framework for Considering Overall Health and Patient Values in Determining Clinical Targets in Adults Aged 65 yrs and Older

Overall Health Category		Group 1: Good Health	Group 2: Intermediate Health	Group 3: Poor Health
Patient characteristics		No comorbidities **or** 1–2 non-diabetes chronic illnesses* **and** No ADL[ε] impairments and ≤1 IADL impairment	3 or more non-diabetes chronic illnesses* **and/or** Any one of the following: mild cognitive impairment or early dementia; ≥2 IADL impairments	Any **one** of the following: End-stage medical condition(s)**; Moderate to severe dementia; ≥2 ADL impairments; Residence in a long-term nursing facility
		Reasonable glucose target ranges and HbA1c by group		
		Shared decision-making: individualized goal may be lower or higher		
Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)	No	Fasting: 90–130 mg/dL Bedtime: 90–150 mg/dL <7.5%	Fasting: 90–150 mg/dL Bedtime: 100–180 mg/dL <8%	Fasting: 100–180 mg/dL Bedtime: 110–200 mg/dL <8.5%[¥]
	Yes[£]	Fasting: 90–150 mg/dL Bedtime: 100–180 mg/dL ≥7.0 and <7.5%	Fasting: 100–150 mg/dL Bedtime: 150–180 mg/dL ≥7.5 and <8.0%	Fasting: 100–180 mg/dL Bedtime: 150–250 mg/dL ≥8.0 and <8.5%[¥]

IADL, Instrumental activity of daily living
ADL, Activity of daily living



Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

Management of hypertension in older adults with diabetes

- In patients aged 65 to 85 years with diabetes, we recommend a target blood pressure of 140/90mm Hg to decrease the risk of cardiovascular disease outcomes, stroke, and progressive chronic kidney disease.
- 130/80 mm Hg, for patient with previous stroke or progressing chronic kidney disease; estimated glomerular filtration rate, <60 mL/min/1.73 m2 and/or albuminuria.

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Treatment of Diabetes in Older Adults: An Endocrine Society Clinical Practice Guideline

Management of hyperlipidemia in older adults with diabetes

- Annual lipid profile
- No specific low-density lipoprotein cholesterol targets
  - Statin as first choice of treatment
  - Alternative or additional ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors if needed
  - For fasting triglycerides >500 mg/dL, we recommend the use of fish oil and/or fenofibrate to reduce the risk of pancreatitis.

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Pharmacological Management of Osteoporosis in Postmenopausal Women:

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An Endocrine Society Clinical Practice Guideline

- In postmenopausal women at high risk of fractures, we recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk.
- In postmenopausal women with osteoporosis who are taking bisphosphonates, we recommend that fracture risk be reassessed after 3 to 5 years, and women who remain at high risk of fractures should continue therapy, whereas those who are at low-to-moderate risk of fractures should be considered for a “bisphosphonate holiday.”
  - Reassess fracture risk at 2- to 4-year intervals
    - BMD
    - Bone turnover markers
      - Serum C-terminal or procollagen type 1 N-terminal

Pharmacological Management of Osteoporosis in Postmenopausal Women:

ENDO2019

An Endocrine Society Clinical Practice Guideline

- Denosumab as an alternative initial treatment.
  - When stop to be follow by bisphosphonates, hormone therapy, or selective estrogen receptor
- In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe or multiple vertebral fractures, we recommend teriparatide or abaloparatide treatment for up to 2 years for the reduction of vertebral and nonvertebral fractures.
- In postmenopausal women with osteoporosis who have completed a course of teriparatide or abaloparatide, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone density gains.

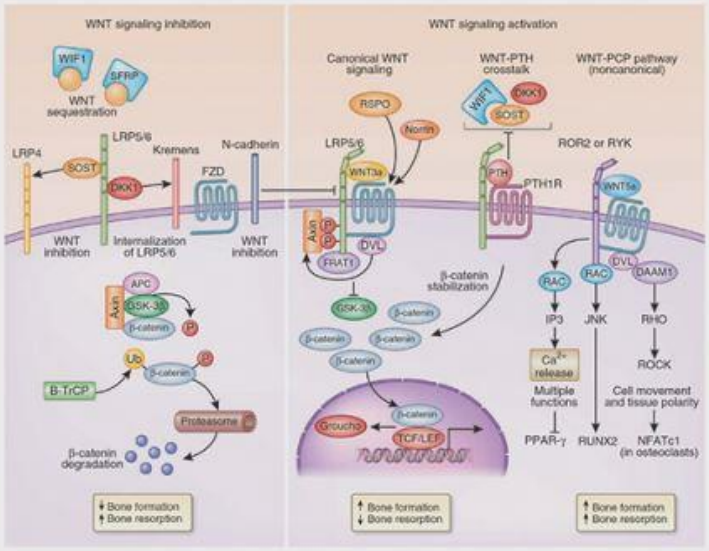
Year in Osteoporosis Healthcare Delivery: Science and Breakthroughs

Joy Wu, MD, PhD
Division of Endocrinology
@JoyYWu

Stanford MEDICINE

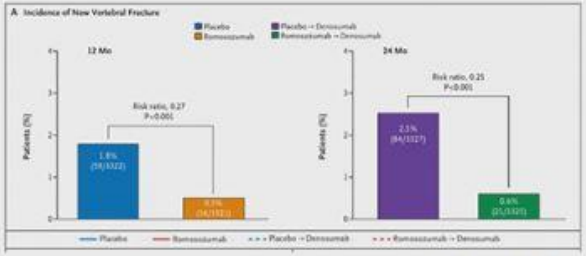
ENDO 2019
March 23, 2019

Wnt signaling regulates bone formation

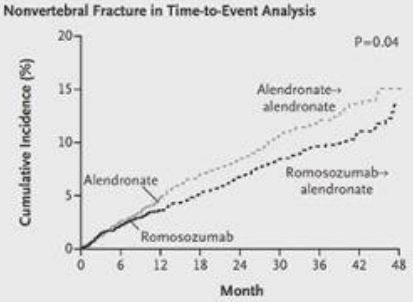


Baron, Nature Medicine 2013

Clinical efficacy of romosozumab:



Cosman, NEJM 2016



Saag, NEJM 2017

Romosozumab for osteoporosis

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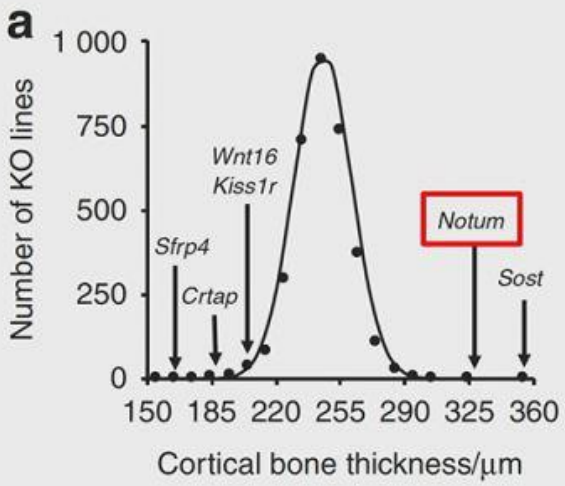
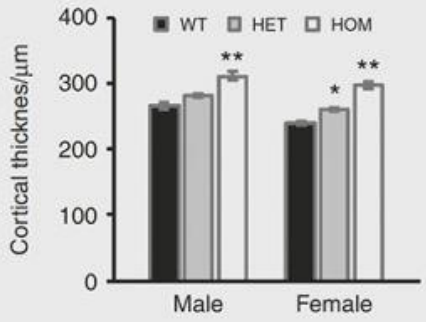
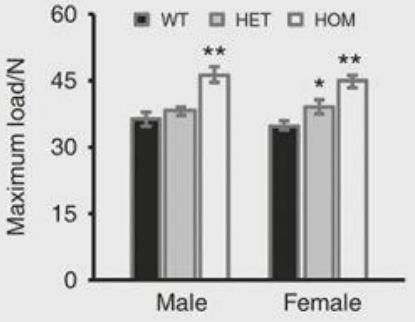
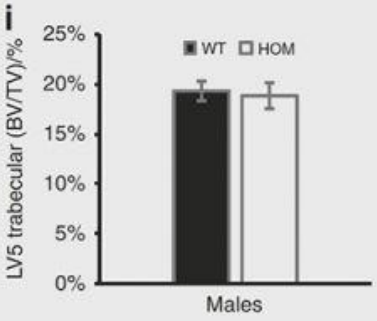
- A humanized monoclonal antibody to sclerostin.
- Works by binding and inhibiting the activity of the protein sclerostin and, as a result, has a dual effect on bone, both increasing bone formation and decreasing bone breakdown.
- Dose: two injections monthly for twelve months.
- To maintain benefit on the second year has to be followed by denosumab or alendronate.
- Approved by FDA on April 9, 2019
  - Boxed warning: may increase risks for myocardial infarction, stroke and CV death and should not be taken by patients who experienced a CV event within the previous year.

NOTUM is a Wnt lipase that regulates cortical bone formation

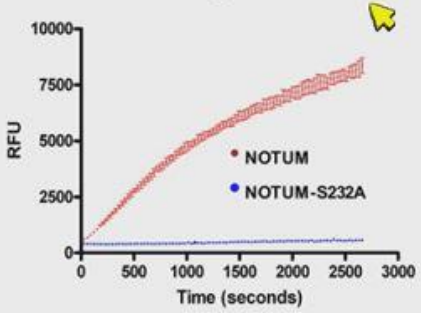








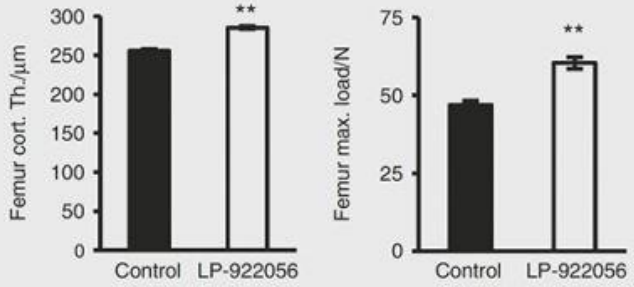
OPTS cleavage

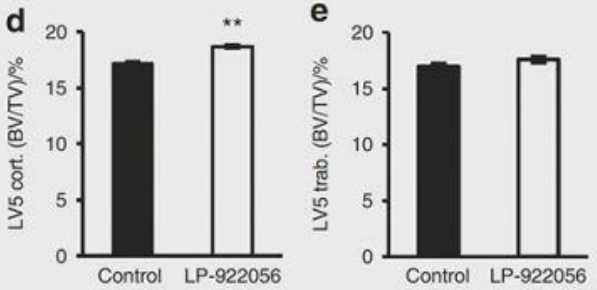


Brommage, Bone Res 2019

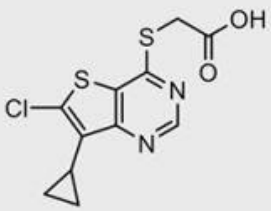
16 weeks

An orally active NOTUM inhibitor increases cortical bone thickness and strength

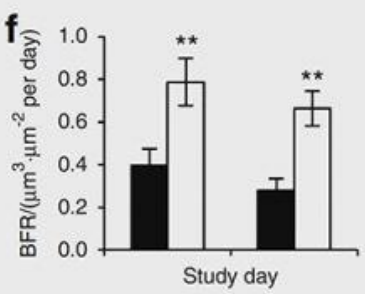


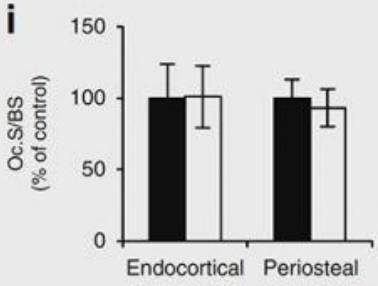


16 weeks (treated for 4 weeks)



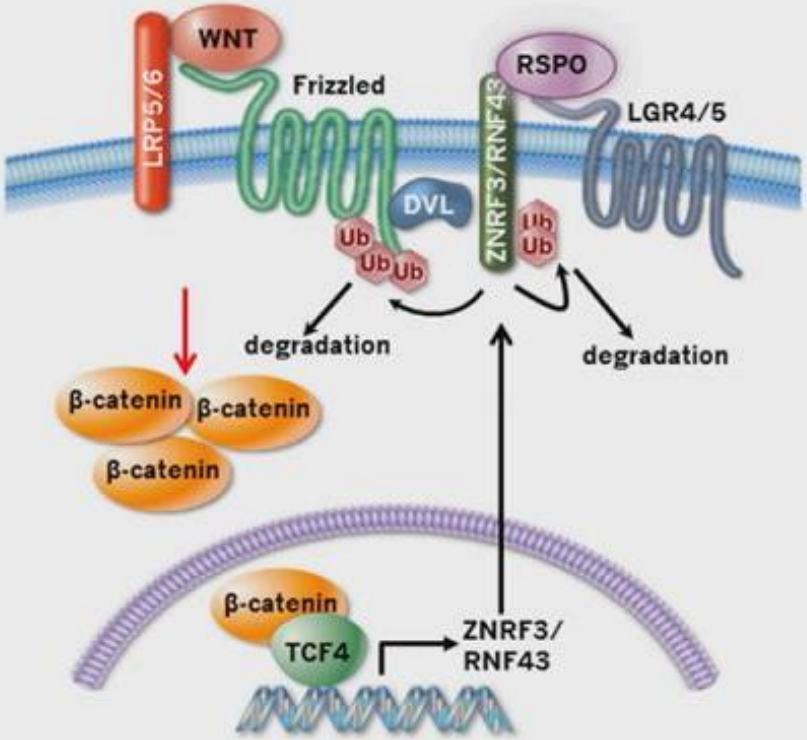
LP-922056





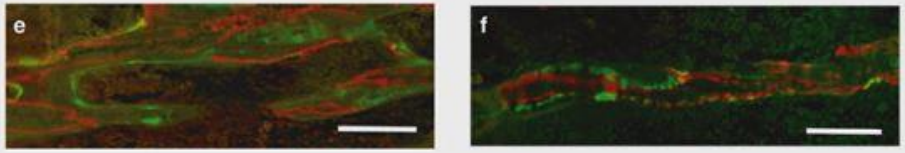
Brommage, Bone Res 2019

R-spondins potentiate Wnt signaling

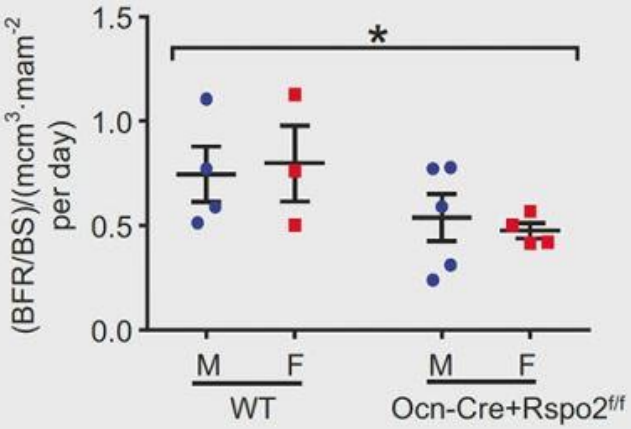


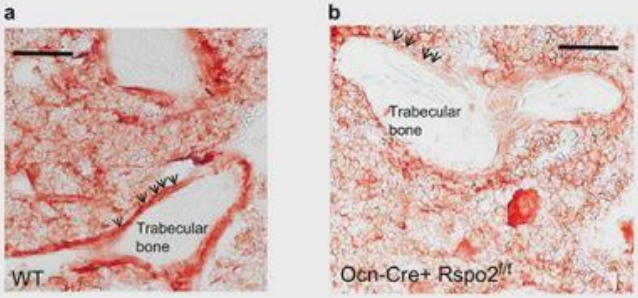
Hao, Cancers 2016

R-spondin-2 deficiency decreases bone formation and active β-catenin levels

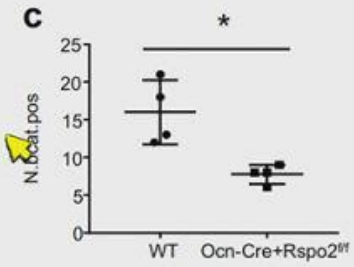


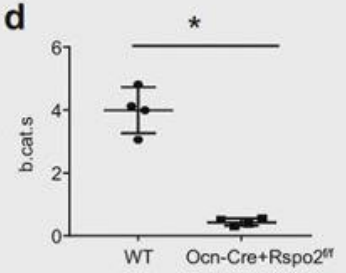
1 month





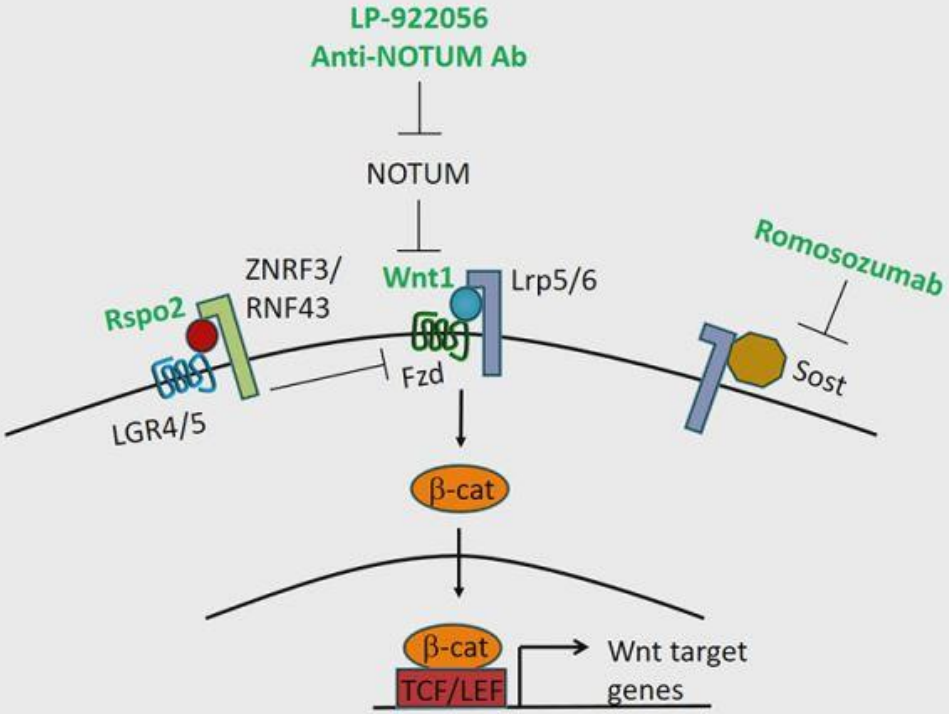
3 months





Knight, Bone Res 2017

Wnt signaling summary



Cushing Syndrome
Cushing Disease

Subclinical Cushing Syndrome

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- John Newell-Price, MD, PhD
- Martin Fassnacht, MD
- Irina Bancos, MD
- Barbra S Miller, MD
- Ahmed Iqbal, MBBS

Subclinical Cushing Syndrome

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- May be difficult to recognize, especially when it is mild, and the presenting features are common in the general population.
  - Patients presenting at an early age with weight gain, pre-diabetes and hypertension associated to:
    - Pulmonary embolism
    - Multiple vertebral fracture
  - Young woman with polycystic ovarian disease and new depression, easy bruising, and memory problems
  - Patient with severe signs and symptoms of the syndrome that occur concurrently within a few months
  - Patient who acquire more and more signs and symptoms over a period of time

Subclinical Cushing Syndrome

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- If the tests are normal and there is suspicious of diagnosis
  - Follow the patient and repeat the test 6 month to 1 year
  - Review clinical history and rule out exogenous PO, topical or subcutaneous or intramuscular steroids

Challenges in the Diagnosis and Management: Cushing Disease

- Mark E Molitch, MD
- Garni Barkhoudarian, MD
- James W Findling, MD

Challenges in the Diagnosis and Management: Cushing Disease

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- Screening test for diagnosis (2 required for diagnosis)
  - 24-hour urine free cortisol (UFC) excretion
  - late night/bedtime salivary cortisol levels
  - 1 mg overnight dexamethasone suppression test

Challenges in the Diagnosis and Management: Cushing Disease

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- After the diagnosis of Cushing's syndrome is established, ACTH is measured as a first step to determine the cause.
- Those patients with low/undetectable values should next undergo:
  - Adrenal gland imaging with computed tomography and/or magnetic resonance imaging (MRI) to identify unilateral masses with adjacent and contralateral atrophy or bilateral disease.
- Normal or elevated ACTH values should undergo:
  - Pituitary MRI
  - Inferior petrosal sinus sampling
  - Corticotropin releasing hormone
  - 8 mg dexamethasone suppression

Challenges in the Diagnosis and Management: Cushing Disease

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- Optimal treatment of Cushing's syndrome involves identification and subsequent resection of abnormal ACTH- or cortisol-producing tissue/tumor

Challenges in the Diagnosis and Management: Cushing Disease

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- Alternatives to surgical resection of tumor
- Agents that block adrenal steroidogenesis at various enzymatic steps
  - Metyrapone (11β-hydroxylase)
  - Ketoconazole (side chain cleavage, 17-hydroxylase and 17,20-lyase, 11β-hydroxylase and aldosterone synthase)
  - Mitotane (11β-hydroxylase and cholesterol side chain cleavage)
  - Glucocorticoid receptor antagonists provide a different mechanism of action to reduce cortisol action. *Korlym*
- Agents in development
  - LCI699 (osilodrostat), acts on 11β-hydroxylase
  - Fluconazole
- Above agent effect 40% - 50% decrease in cortisol

Challenges in the Diagnosis and Management: Cushing Disease

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- Agents that target proopiomelanocortin (POMC) transcription factors – 40% normalized UFC
  - Somatostatin analog pasireotide
  - Dopamine analog cabergoline
  - Retinoic acid
- Severe hypercortisolism carries a high risk for infections and thrombotic phenomena and may be life-threatening.

Molecular Markers Guiding Intervention and Treatment

Sarah Mayson, MD

When to consider molecular testing

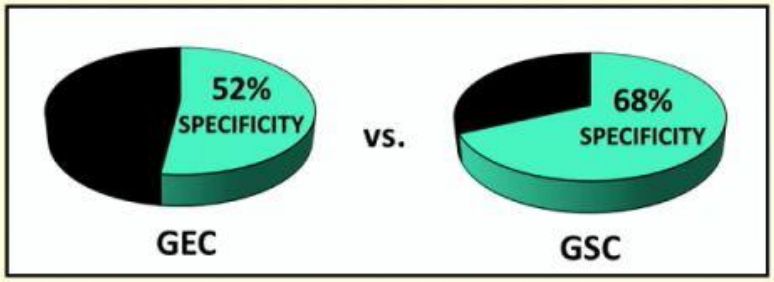
TBSRTC– 2017 update

FNAB Cytology Diagnosis	Risk of CA/NIFTP	Usual Management
I. Nondiagnostic	5-10%	Repeat FNA w/ US guidance
II. Benign	0-3%	Clinical and US follow up
III. AUS/FLUS	10-30%	Repeat FNA, molecular testing or lobectomy
IV. FN/SFN	25-40%	Molecular testing, lobectomy
V. Suspicious for malignancy	50-75%	NTT or lobectomy, ?Molecular testing to determine extent of surgery
VI. Malignant	97-99%	NTT or lobectomy

Cibas and Ali. Thyroid. 2017

Specificity of Afirma GSC is improved vs. GEC

- Blinded multicenter clinical validation study
- Used existing samples from GEC validation
- 191 of 210 Bethesda III/IV nodules

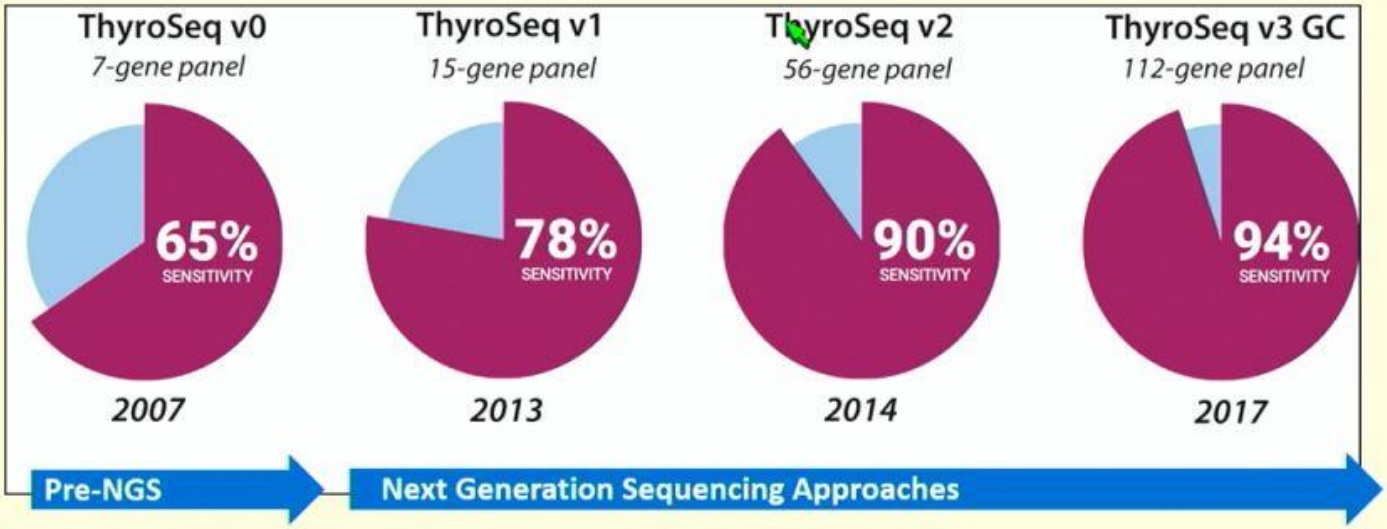


Test	Sensitivity	Specificity	CA (%)	NPV	PPV
GEC	92%	52%	32%	93%	47%
GSC	91%	68%	24%	96%	47%

Alexander EK, et al, *NEJM* 2012
Patel KN, *JAMA Surg.* 2018

Molecular Markers Guiding Intervention and Treatment - Sarah Mayson, MD

ThyroSeq Test Evolution



Sensitivity	Specificity	CA/NIFTP	NPV	PPV
94%	82%	28%	97%	66%

- Prospective double-blinded
- 10 clinical sites
- 232 Bethesda III/IV nodules

Steward DL, et al. *JAMA Oncology.* 2018.
http://thyroseq.inmotionapptest.net/physicians/test-details/test-description

Molecular Markers Guiding Intervention and Treatment - Sarah Mayson, MD

CLINICAL HISTORY
FNA cytology: FN/SFN (Bethesda IV), FN/SFN (Bethesda IV)

THYROSEQ® GC RESULTS SUMMARY

RIGHT INFERIOR THYROID FNA

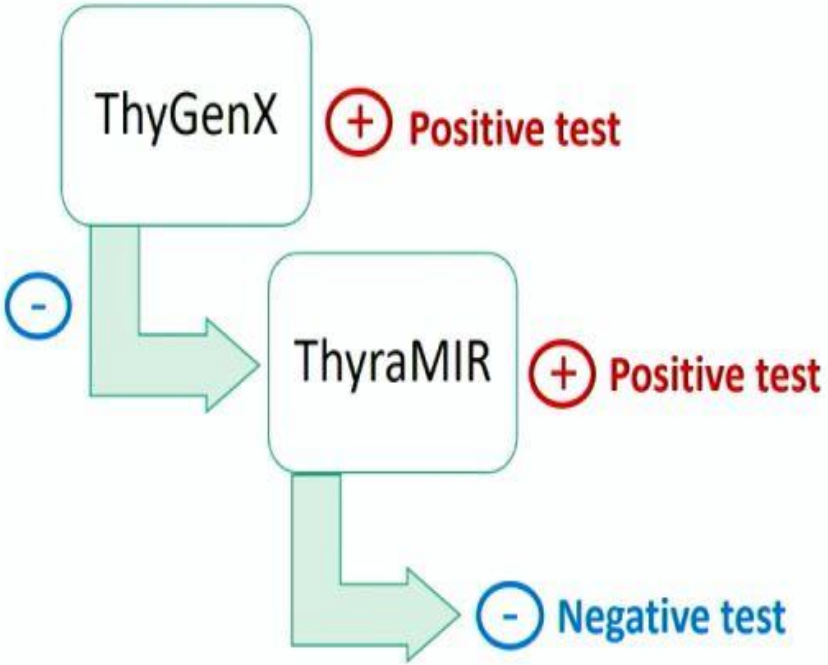
Test Result	Probability of Cancer or NIFTP	Potential Management
POSITIVE	High (>95%)	Surgical excision* *See interpretation below for details*

INTERPRETATION

- Mutations in the NRAS and TERT genes were identified.
- RAS mutations are early oncogenic events in follicular-type thyroid tumors (follicular variant PTC, follicular carcinoma, NIFTP), whereas TERT mutations are typically late events associated with more invasive tumors and higher risk of distant metastases.
- Co-occurrence of RAS and TERT mutations confers >95% risk of cancer and increases likelihood of more aggressive disease.
- Because of the molecular signature of high-risk cancer, total thyroidectomy could be considered for many of these patients.
- Patient management decisions must be based on the independent medical judgment of the treating physician. Molecular test results should be taken into consideration in conjunction with all relevant imaging and clinical findings, patient and family history, as well as patient preference.

99% Positive for BRAF & 50% Positive for RAS for malignancy

ThyGenX/ThyraMIR



- Step 1: ThyGenX
  - 8-gene panel (5 mutations and 3 gene fusions)
- Step 2: ThyraMIR
  - expression of 10 miRNA genes
  - Short single-stranded noncoding RNA segments

NPV – 97%
PPV – 68%

Labourier et al. *J Clin Endocrinol Metab*. 2015; 100: 2743

Molecular testing

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- RosettaGX Reveal has a 99% negative predictive value and 60% positive predictive value, and is the first thyroid test that works on stained fine-needle aspiration smears.

Summary/Key Points

- The current generation of molecular tests function reasonably well as "rule-out" tests for thyroid cancer, but NPV must be calculated in a site-specific manner given differences in population prevalence of malignancy
- Post-validation studies of the new tests are critical to confirming their performance in a "real-world" setting
- Clinical follow up studies of Afirma GEC benign nodules are reassuring; long-term follow up of ITNs with negative testing also needed for other molecular tests
- Any decision whether or not to use molecular testing should take into context the patient's clinical risk factors, US findings, cytology, and personal preferences