



Guida all'Iperparatiroidismo

Danno d'organo: Rene

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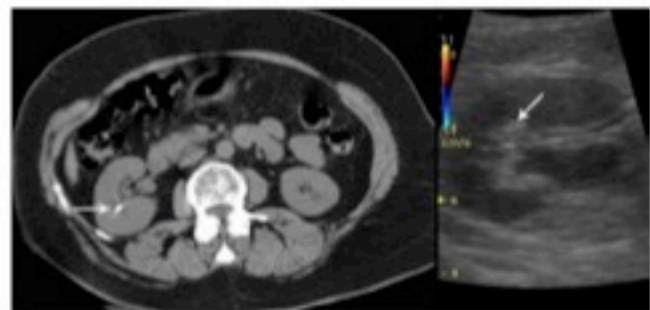
Roma, 9-12 novembre 2017

# Conflitti di interesse



Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Eli-Lilly Italia, Abiogen



## Calcolosi renale sintomatica

**10-20%** dei pz

Coliche ricorrenti

Uropatia ostruttiva

Renella, Pielonefriti

**Ridotto eGFR/IRC**

**< 60ml/min/1.73m<sup>2</sup>**

**13-19%** dei pz

## Calcolosi renale asintomatica

**25-55%** dei pz

Microlitiasi

Calcoli a stampo

Calcificazioni interstiziali  
(ossalato di calcio)

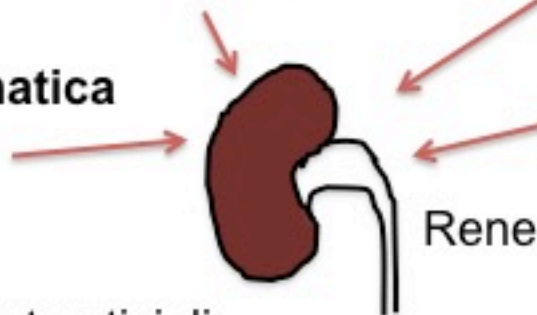
Calcificazioni intratubulari  
(fosfato di calcio)

**Nefrocalcinosi**

**Ipercalciuria**

**>4 mg/kg/24h**

**65-75%** dei pz



# Nefrolitiasi in PHPT



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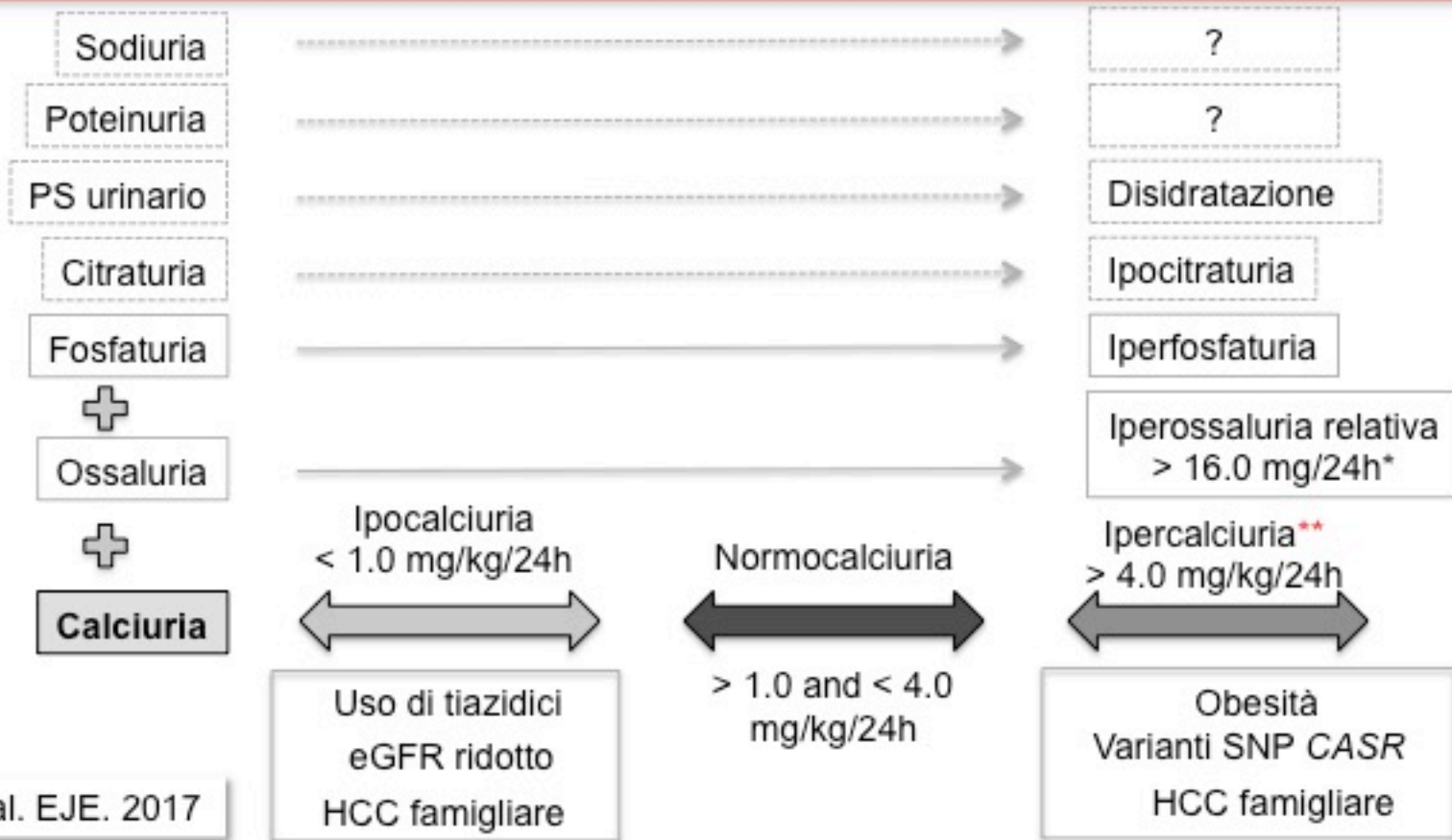


- Nephrolithiasis (detected by imaging or history of passing stones) was **more frequent in men** (50.5% vs. 33% in women,  $p = 0.003$ )
- Kidney stones were **less frequent** and osteoporosis more frequent **in postmenopausal-female** than in premenopausal-female PHPT patients (28.1% vs. 59.2% and 58.9% vs. 18.5%, respectively).

# Profilo litogenico nelle urine dei pazienti con PHPT



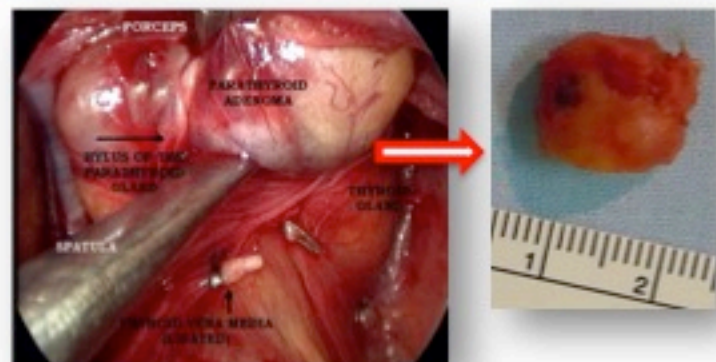
Roma, 9-12 novembre 2017



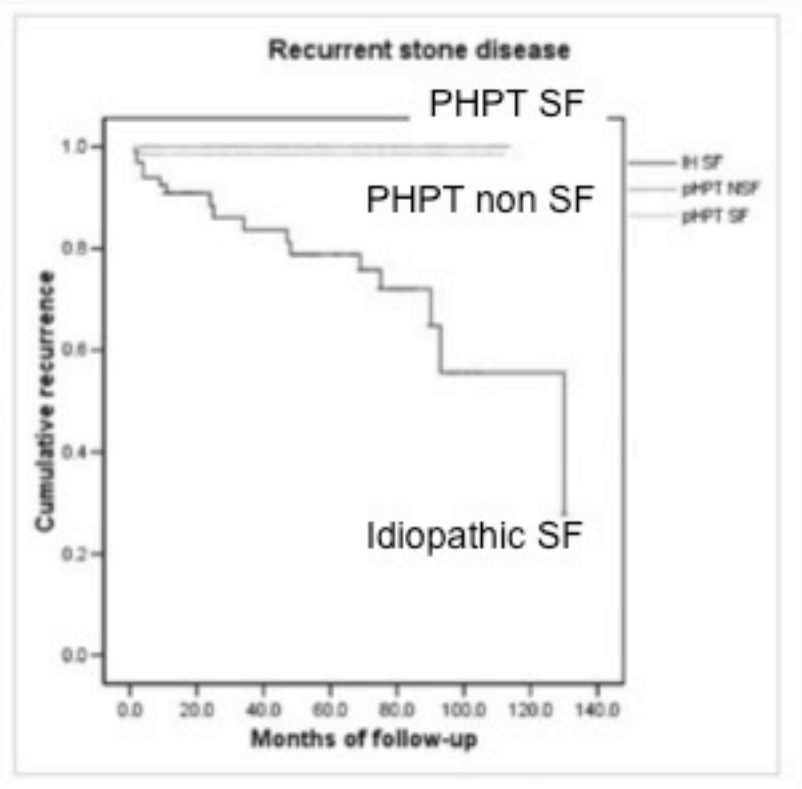
Verdelli et al. EJE. 2017

# Effetto della paratiroidectomia sulla calcolosi renale

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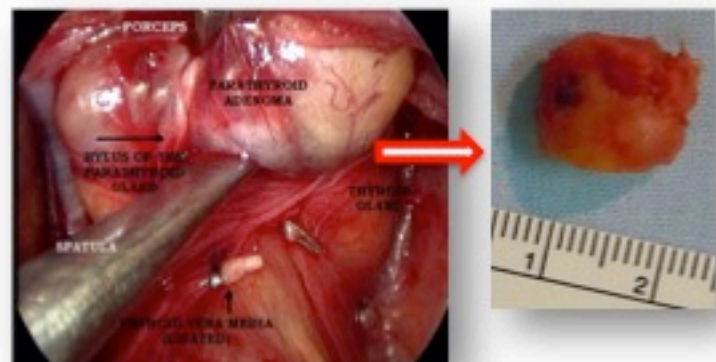


Median 5-year recurrence of symptomatic stone disease in idiopathic SF was just over 20% compared with **1.5%** in SF with PHPT undergoing surgery ( $p < 0.001$ )

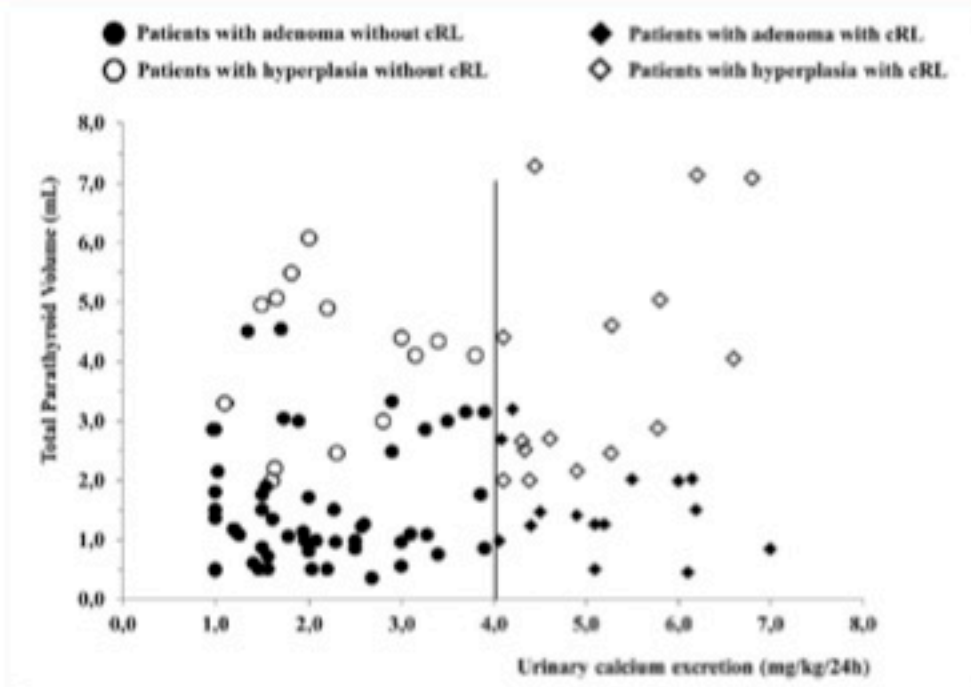


# Effetto della paratiroidectomia sull'ipercalciuria

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- Hypercalciuria is present in **30%** of patients with PHPT after successful surgery,
- It is associated with parathyroid **hyperplasia** before surgery
- It **lacks of improvement in BMD** after surgery.





# Effetto della terapia medica su calcolosi renale e ipercalcemia



## Calcolosi renale

### Cinacalcet

No dati

### Colecalciferolo

Nessun effetto

## Ipercalcemia

### Cinacalcet

Nessun effetto! (Riccardi 2016)

### Colecalciferolo

In pazienti PHPT e deficit di 25OHD: nessun effetto

### Tiazidici

Riducono ipercalcemia  
No modificazioni di calcemia e PTH  
(Riss 2016, Tsvetov 2017)



**Table 3** Prevalence of reduced kidney function in PHPT patients.

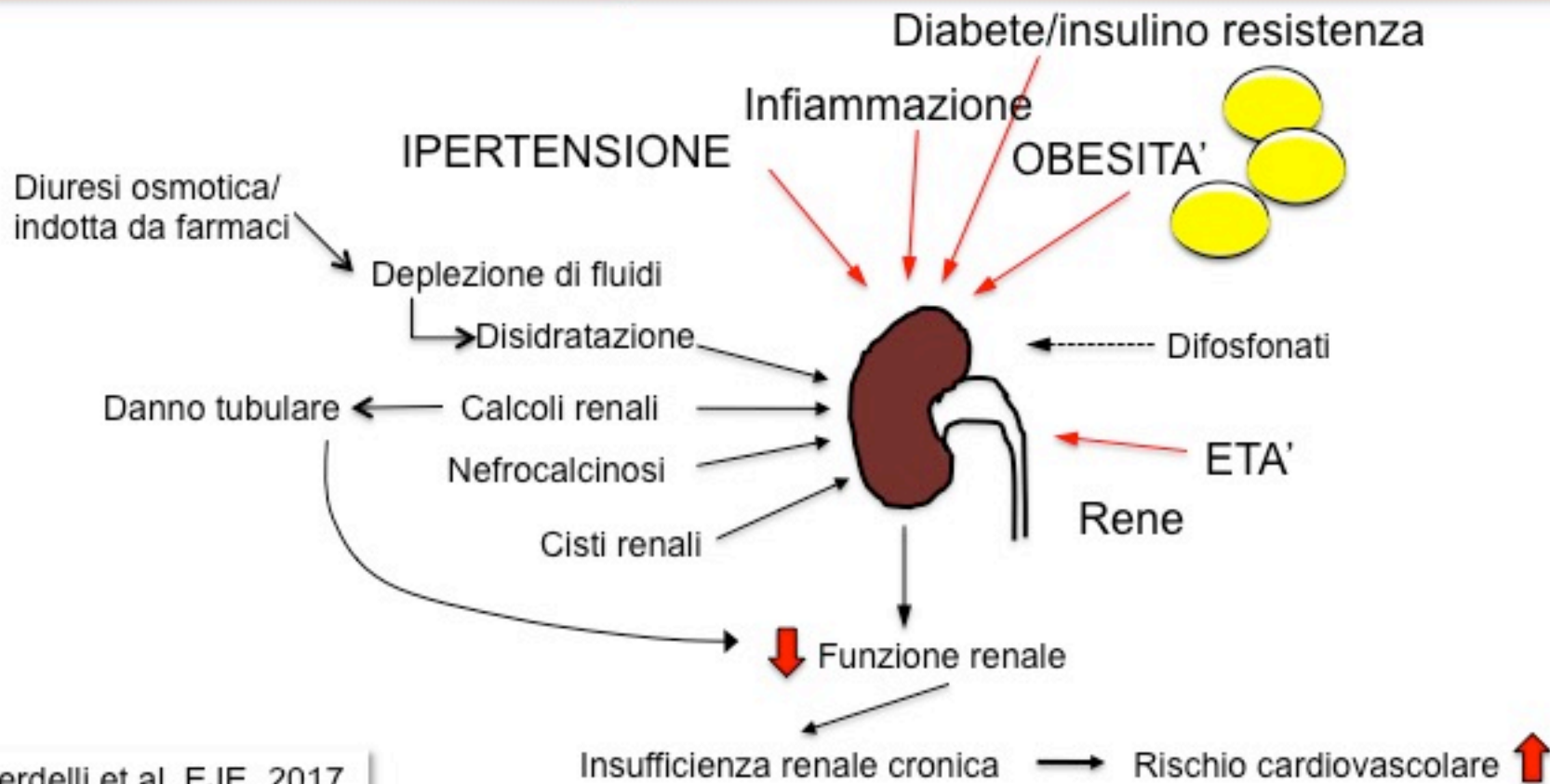
	Patients (n)	Period	Origin	Kidney stones (%)	Equation	eGFR (mL/min/1.73 m <sup>2</sup> )			
						>90	89-60	30-59	<30
Walker 2012	138	1984-1991	USA	16	MDRD#	84%		15%	1%
Walker 2014	114	2005-2013	USA	10	MDRD#	85%		15%	0%
Walker 2014	114	2005-2013	USA	10	CKD-EPI*	81%		19%	0%
Tassone 2009	294	1993-2007	Italian	nr	MDRD#	52%	31%	15%	2%
Tassone 2015	109	1995-2012	Italian	nr	CKD-EPI*	87%		13%	
Ermetici 2015	190	2005-2010	Italian	54	CKD-EPI**	47%	39%	13%	1%

**Table 2** GFR categories.

GFR category	GFR (mL/min/1.73 m <sup>2</sup> )	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

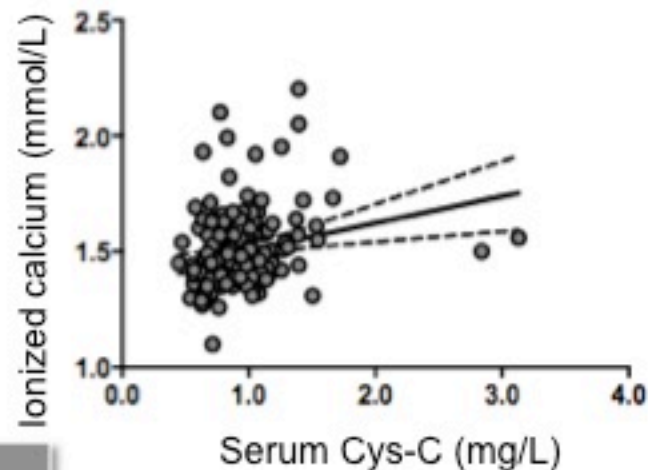
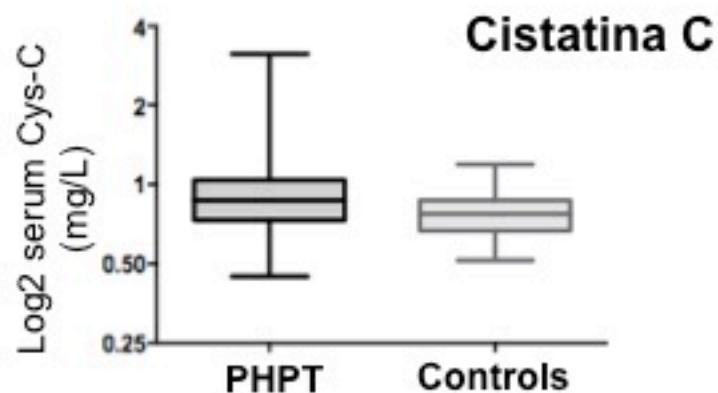


# Fattori di rischio per ridotta funzione renale nei pazienti con PHPT





# eGFR in PHPT

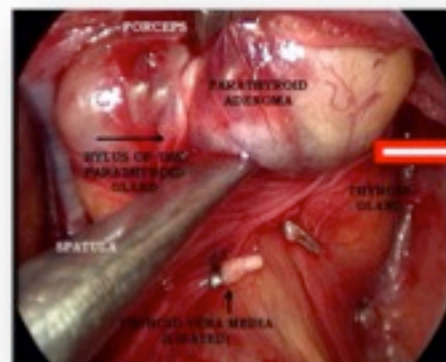


Parameter	$\beta$	<i>P</i>
<b>eGFRcr-cys CKD-EPI</b>		
Hypertension	0.218±0.077	0.0001
HOMA-IR	0.126±0.119	0.04
Cardiovascular diseases	-0.005±0.002	0.011

# Caratteristiche cliniche dei pazienti PHPT con ridotto eGFR

	PHPT patients with eGFRcr-cys		p
	<60 ml/min/1.73m <sup>2</sup>	>60 ml/min/1.73m <sup>2</sup>	
n	25	161	
Age (yrs)	70.0±1.9	58.8±1.1	0.0002
Sex (males/ females)(% males)	10/15 (40)	32/129 (20)	0.047
BMI (kg/m <sup>2</sup> )	27.3±0.9	25.3±0.4	0.041
Ionized calcium (mmol/L)	1.59±0.04	1.48±0.01	0.003
Serum Calcium (mg/dl)	11.6±0.23	11.0±0.07	0.005
Serum Phosphate (mg/dl)	2.5±0.10	2.4±0.04	0.778
Serum PTH (pg/ml)	300.3±46.5	166.0±10.7	0.0001
Calcium excretion (mg/kg/24h)	3.4±0.4	4.8±0.2	0.019
Phosphate excretion (g/24h)	0.72±0.05	0.75±0.04	0.690
Serum 25OHD (ng/ml)	22.3±4.9	20.3±1.7	0.690
Glucose (mg/dl)	96.2±4.5	90.8±1.3	0.186
Serum insulin (mU/L)	15.6±3.3	9.4±0.7	0.010
HOMA-IR	4.1±1.0	2.2±0.2	0.003
Total-cholesterol (mg/dl)	203.9±7.6	209.4±3.4	0.564
HDL-cholesterol (mg/dl)	51.7±4.2	60.4±1.4	0.044
LDL-cholesterol (mg/dl)	129.3±8.9	127.7±2.9	0.853
Triglycerides (mg/dl)	139.0±12.9	127.7±5.0	0.061
Diabetes (%)	12.0	11.2	0.819
Hypertension (%)	84.0	47.5	0.001
Kidney stones (%)	48.0	53.0	0.764
Kidney cysts (%)	65.0	28.1	0.033

# Effetto della paratiroidectomia sulla funzione renale



In pazienti **PHPT asintomatici**:  
Nessun effetto su eGFR

In pazienti **PHPT sintomatici**:

Estimated GFR categories before and after parathyroidectomy.

Group	G-1 >90	G-2 60-89	G3a 49-59	G3b	G4	G5	Total
Before Operation	55 [37.9%]	47 [32.4%]	21 14.5%	12 8.3%	10 6.9%	0	145
After operation	42 29%	58 40%	27 18.5%	9 5.5%	7 4.8%	1 0.7%	144 <sup>2</sup>

<sup>2</sup> One patient expired.

# Effetto della paratiroidectomia sulla funzione renale



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**Table 2.** Pre- and Post-PTX Data in Patients Subdivided According to eGFR

Tassone 2016	Group 1 (eGFR $\geq$ 60 mL/min/1.73 m <sup>2</sup> ) (n = 95)		Group 2 (eGFR < 60 mL/min/1.73 m <sup>2</sup> ) (n = 14)	
	Pre-PTX	Post-PTX	Pre-PTX	Post-PTX
Age, y	56.6 $\pm$ 10.8	58.9 $\pm$ 11.2	68.4 $\pm$ 10.4	70.8 $\pm$ 11.0
BMI, kg/m <sup>2</sup>	25.9 $\pm$ 4.8	26.9 $\pm$ 5.2	26.4 $\pm$ 4.8	27.1 $\pm$ 5.76
SBP, mm Hg	140.3 $\pm$ 19.5	144.8 $\pm$ 20.1	148.3 $\pm$ 16.0	141.5 $\pm$ 23.8
DBP, mm Hg	86.2 $\pm$ 9.2	87.3 $\pm$ 9.7	87.9 $\pm$ 11.6	87.5 $\pm$ 10.3
PTH, pg/mL <sup>2</sup>	140 (95–250)	48 (34–66)	248 (120–597)	57 $\pm$ 35
Calcium, mg/dL	11.4 $\pm$ 1.5	9.4 $\pm$ 0.61	11.6 $\pm$ 1.3	9.16 $\pm$ 0.63
Ionized calcium, mmol/L	1.5 $\pm$ 0.2	1.19 $\pm$ 0.08	1.55 $\pm$ 0.22	1.16 $\pm$ 0.08
Creatinine, mg/dL	0.82 $\pm$ 0.16	0.87 $\pm$ 0.19	1.32 $\pm$ 0.45	1.41 $\pm$ 0.60
25(OH)D3, ng/mL	31.7 $\pm$ 24.0	49.2 $\pm$ 31.8	35.0 $\pm$ 30.9	33.5 $\pm$ 25.7
CKD-EPI-eGFR, mL/min/1.73 m <sup>2</sup>	86.8 (73.5–98.2)	81.6 (69.5–91.6)	52.6 (48.7–57)	50.2 (37.0–53.0)

- PTX prevents further deterioration of renal function in PHPT patients with a coexisting renal impairment.
- Presurgical eGFR and SBP are independently associated with the variation in eGFR after PTX.

Independent Variables	$\beta$	P
Age, y	0.08	.054
SBP, mm Hg	0.24	.019
Serum calcium, mg/dL	-0.096	.314
Serum creatinine, mg/dL	0.07	.679
Baseline CKD-EPI-eGFR, mL/min/1.73 m <sup>2</sup>	0.487	.025



# Effetto della terapia medica sulla funzione renale



## **Cinacalcet**

Nessun effetto

(Shoback 2003, Peacock 2011)

## **Colecalciferolo**

In donne PHPT

25OHD correla inversamente  
con eGFR (Viccica 2016)  
No studi di intervento

## **Bisfosfonati**

Alendronato per PHPT-relata osteoporosi: nessun effetto

Zoledronato per ipercalcemia severa: controindicato se eGFR < 30 ml/min

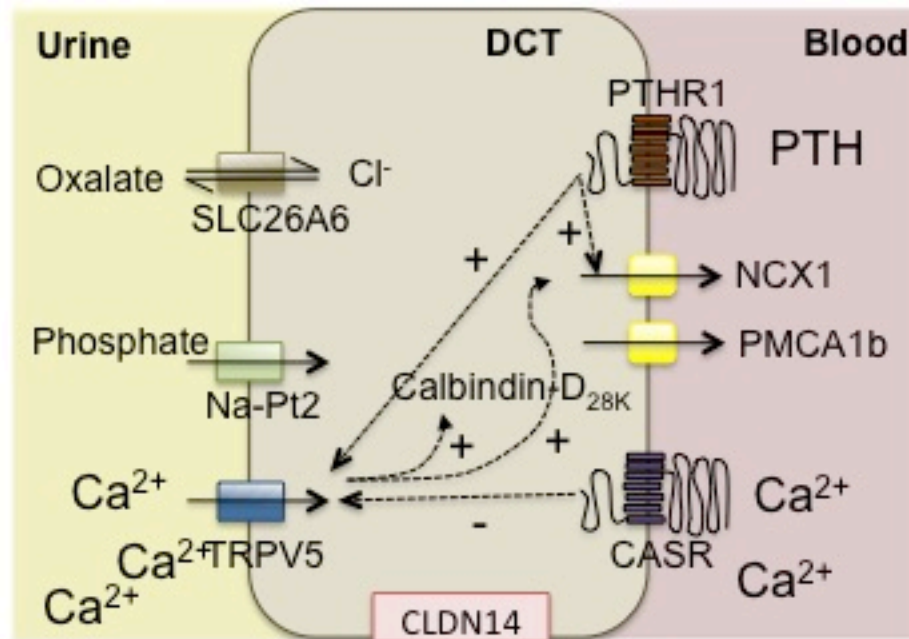
Denosumab in alternativa



# Aspetti genetici



Molecules involved in the calcium, oxalate and phosphate handlings at the distal convolute (DCT) and connecting tubules levels





# Effetto delle varianti polimorfiche del gene CASR sul danno renale in PHPT



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CASR SNPs	Accession number	Substitution	Minor Allele	Minor allele activity	PHPT population	Minor allele frequency in PHPT vs HC	Association with PHPT clinical and/or biochemical phenotypes
A986S	rs1801725	G>T	S	nd	Italian Italian Italian German	40% vs 30% 38% vs 34% 26.4% vs 19.6% 40% vs 28%	None
R990G	rs1042636	A>G	G	Increased	Italian Italian German Italian	12% vs 6.5% 4.0% vs 5.0% 8.0% vs 13.7% 5.8% vs 8.8%	Kidney stones Hypercalciuria Lower serum PTH Lower serum P
Q1011E	rs1801726	C>G	E	nd	Italian Italian German Italian	5% vs 10% 3.0% vs 3.5% 14% vs 9% 2.0% vs 5.5%	None
NCRR	rs7652589 in 5'-UTR	G>A	A	Increased	Italian	32.2% vs 33.4%	Kidney stones Higher serum Ca <sup>2+</sup> Higher serum PTH
NCCR	rs1501899 in intron 1	G>A	A	Increased	Italian	32.1% vs 31.5%	Kidney stones Higher serum Ca <sup>2+</sup> Higher serum PTH



# Effetto delle varianti polimorfiche di geni associati al CASR sui livelli di PTH



Common genetic variants located near genes involved in **vitamin D metabolism** and **calcium and renal phosphate transport** associated with differences in circulating PTH concentrations.

Robinson-Cohen 2017

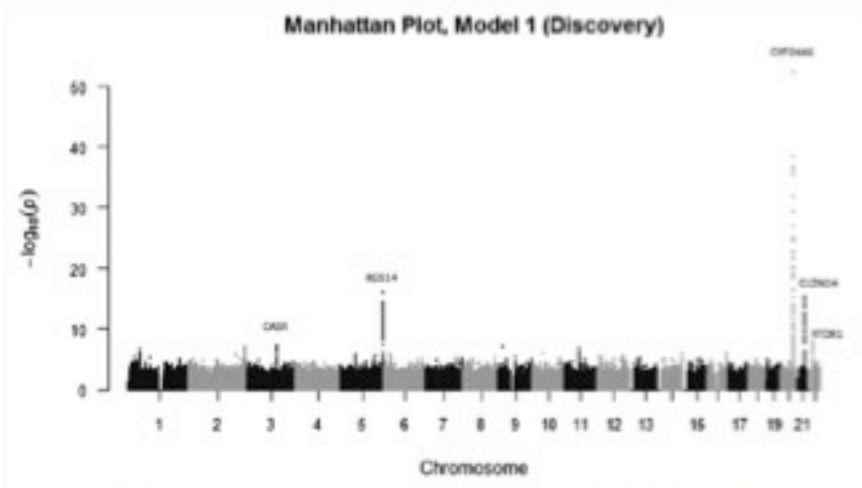


Table 3. Associations of top single nucleotide polymorphisms with ln-transformed serum PTH concentrations among individuals of black descent ( $n=4279$ )

SNP	Nearest Gene	Chr	Position	PTH-Increasing Allele	Other Allele	PTH-Increasing Allele Frequency <sup>a</sup>	$\beta$ (SEM) <sup>b</sup>	P Value	Fst <sup>c</sup>
rs6127099	<i>CYP24A1</i>	20	52,731,402	T	A	0.21	+0.03 (0.0136)	0.0363	0.020
rs4074995	<i>RGS14</i>	5	176,797,343	G	A	0.92	-0.04 (0.0160)	0.0059	0.057
rs219779	<i>CLDN14</i>	21	37,833,751	G	A	0.69	-0.01 (0.0096)	0.5337	0.102
rs4443100	<i>RTDR1</i>	22	23,372,864	C	G	0.80	-0.02 (0.0106)	0.05366	0.100
rs73186030	<i>CASR</i>	3	122,013,465	T	C	0.01	NA	NA	0.055

# Fattori da considerare per la gestione chirurgica vs medica



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## Opzione chirurgica

**Symptomatic PHPT** patients for kidney stones should not experience delay in the diagnosis and surgical treatment of PHPT

**Asymptomatic PHPT** patients are recommended to receive an extensive diagnostic workout aimed to define kidney involvement

**Asymptomatic PHPT patients with eGFR below 60 mL/min/1.73 m<sup>2</sup>** should be subject to surgery as part of the goal aimed to remove all the factors associated with the further decline in eGFR

## Opzione medica

Diagnosis and treatment of all the **concomitant risk factors of CKD**: hypertension, obesity, diabetes/insulin resistance and previous kidney damages

Modification of lithogenic profile of urine

Monitoring and management of **PHPT patients with established CKD** can be a challenge: CKD-related biochemical and clinical alterations alter the classic clinical presentation of PHPT and prevent the use of bisphosphonates to control hypercalcemia



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