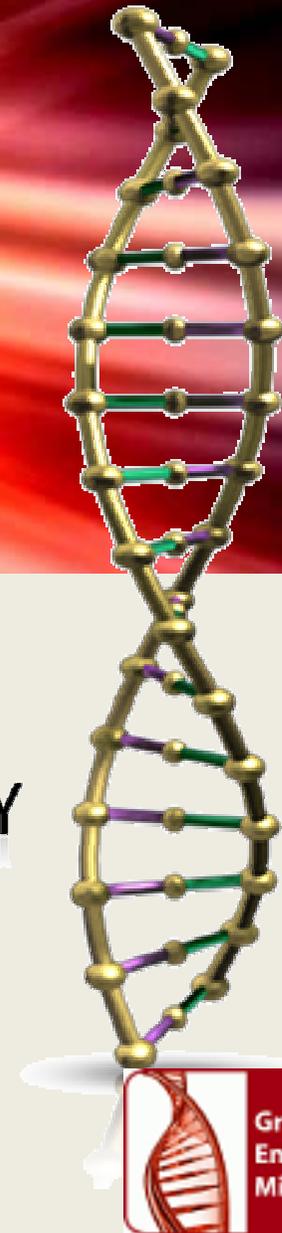




SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA

LA VISIÓN GLOBAL DE LA PERSONA ENFERMA



UTILIDAD DE LA CISTATINA C Y NT-proBNP EN LA ENFERMEDAD DE ANDERSON-FABRY

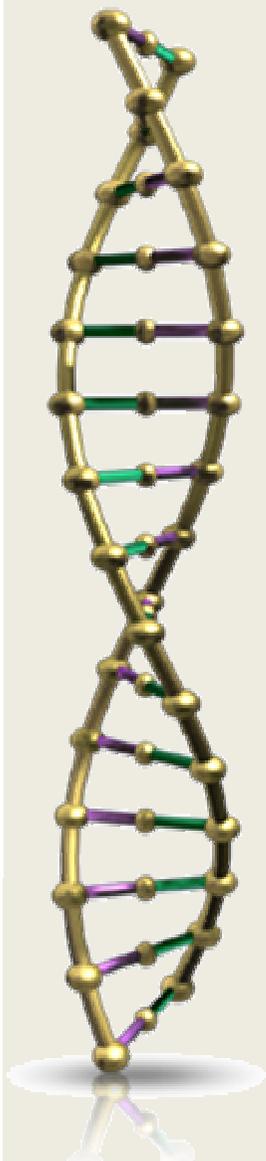
Susana Olivera González

Medicina Interna. Hospital de Denia (Alicante)

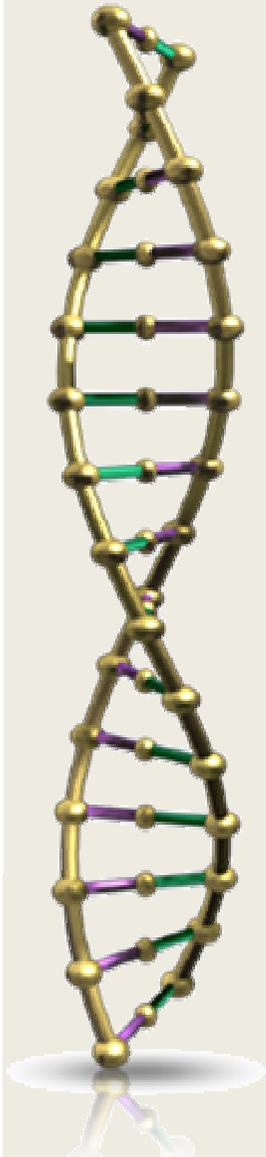


ENFERMEDAD DE FABRY

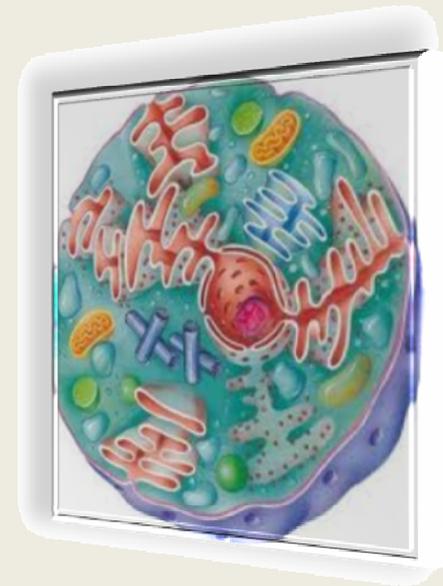
ENFERMEDAD DE FABRY



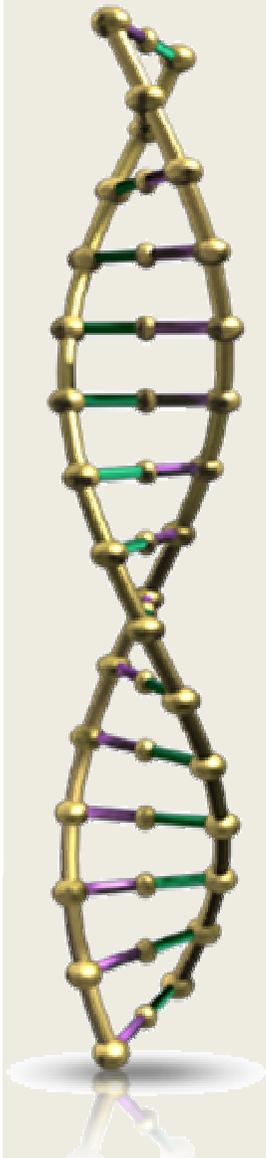
ENFERMEDAD DE FABRY: DEFINICIÓN



- Enfermedad por depósito lisosomal
- Déficit alfa galactosidasa A
- Acúmulo globotriaosilceramida (GL3)

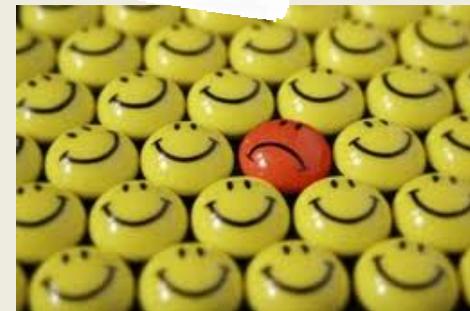


ENFERMEDAD DE FABRY: DEFINICIÓN



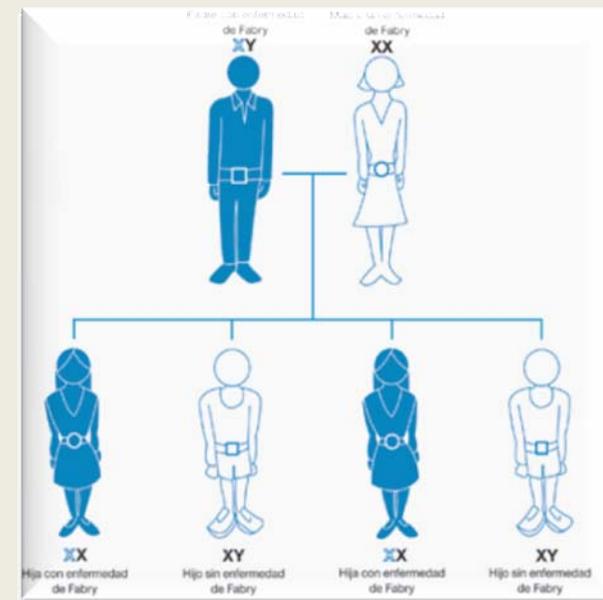
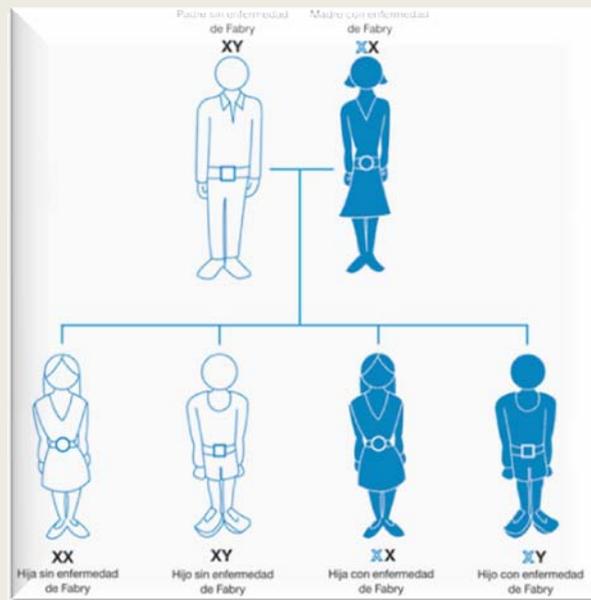
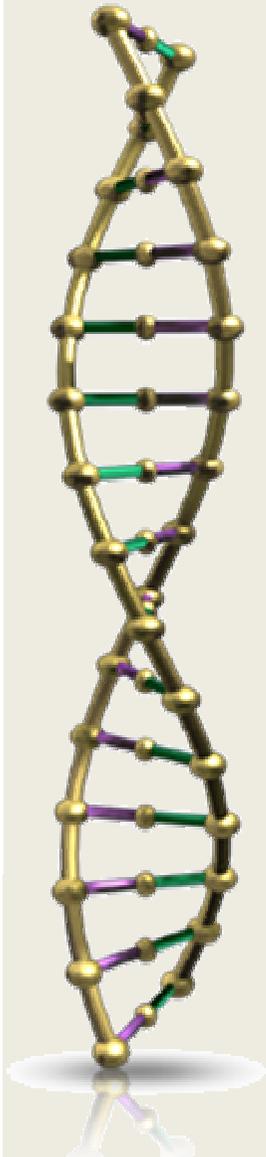
- V...son y Joha... (1898)

- Enfermedad infradiagnosticada



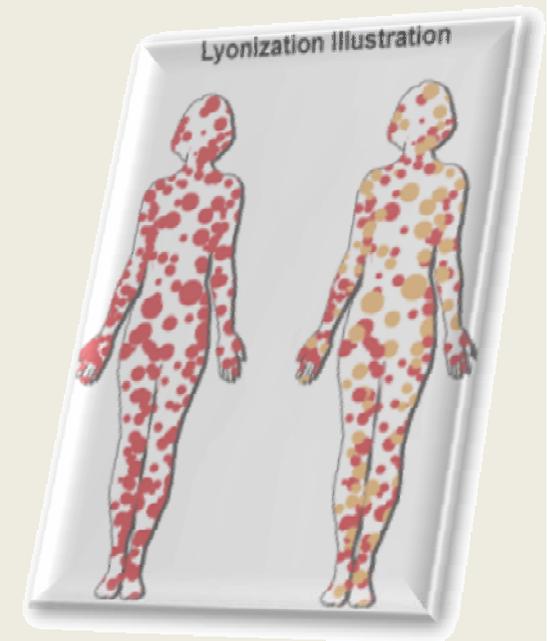
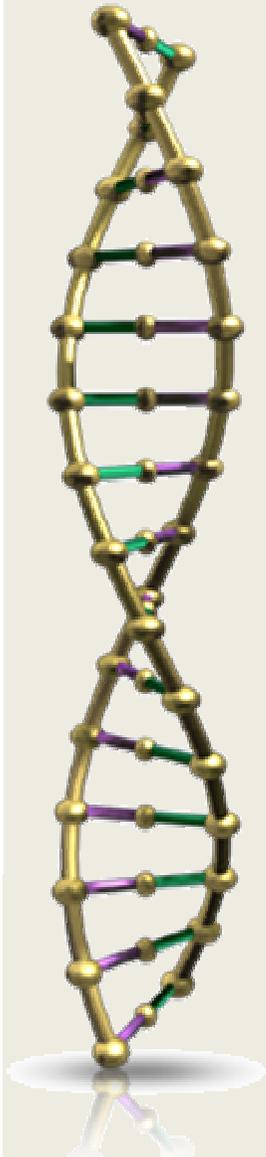
ENFERMEDAD DE FABRY: DEFINICIÓN

- Herencia “recesiva ligada al cromosoma X”
 - Mujeres portadoras

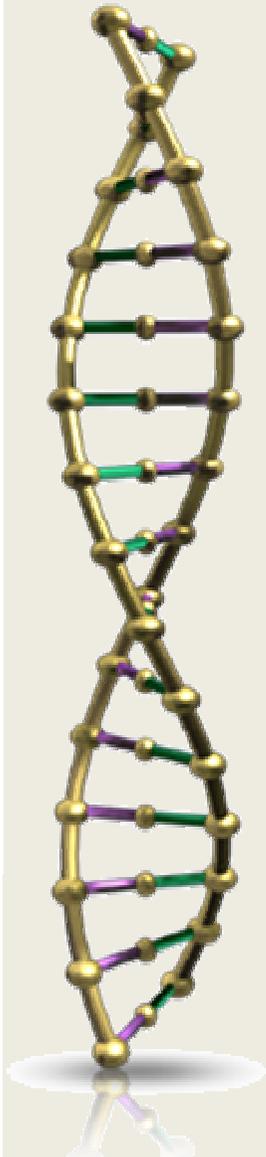


ENFERMEDAD DE FABRY: DEFINICIÓN

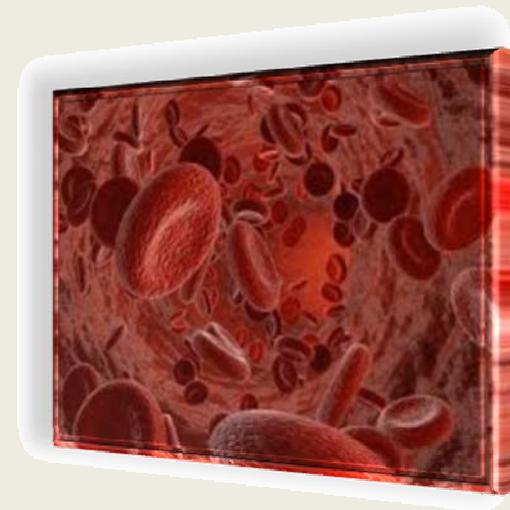
- Fenómeno de “lionización”
- Inactivación no randomizada del cromosoma X



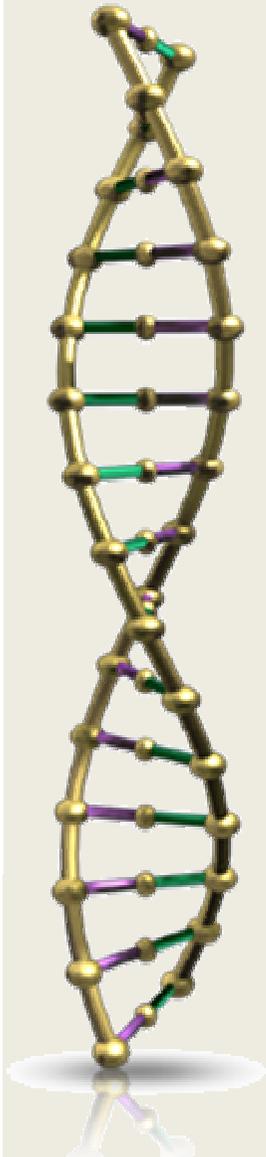
ENFERMEDAD DE FABRY: FISIOPATOLOGÍA



- Acúmulo de globotriaosilceramida en el endotelio vascular
- Disfunción endotelial
- Fallo de los distintos órganos



ENFERMEDAD DE FABRY: CLÍNICA

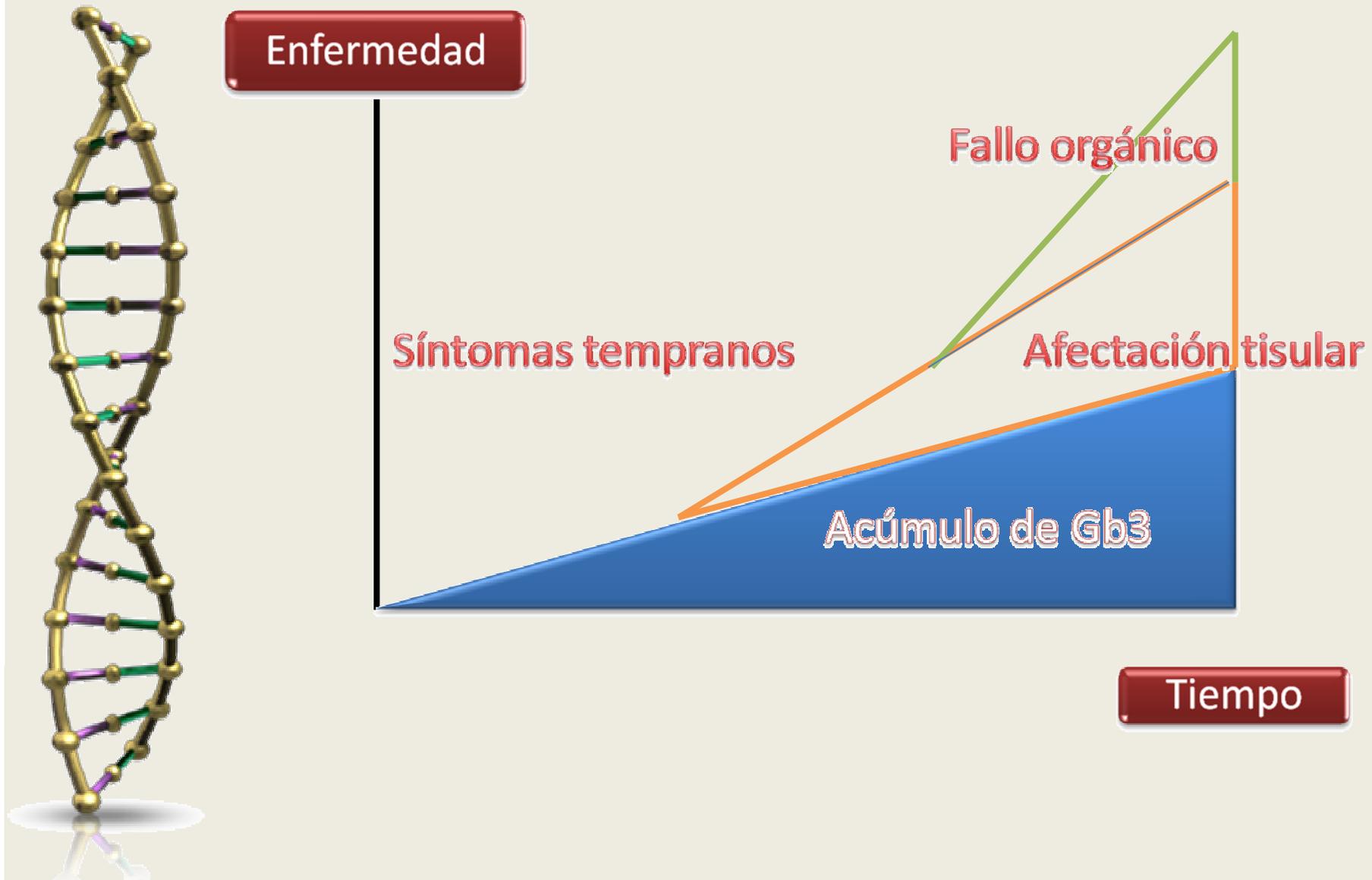


Infancia: crisis de dolor, hipohidrosis, episodios de fiebre recurrente

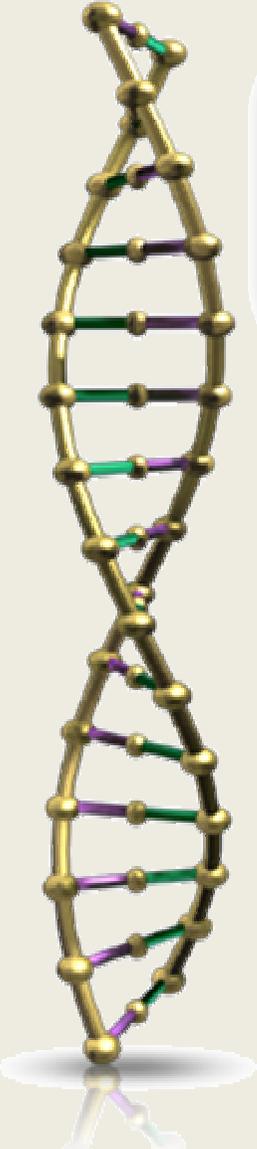
Adolescencia: lesiones dérmicas, crisis de dolor abdominal

Adultos: complicaciones, cerebrovasculares, renales, y cardíacas

ENFERMEDAD DE FABRY: CLÍNICA



ENFERMEDAD DE FABRY: DIAGNÓSTICO



Sospecha clínica

- × Angioqueratoma en traje de baño
- × Hipo/anhidrosis
- × Intolerancia al ejercicio físico

Diagnóstico bioquímico

Disminución de la actividad de la α -galactosidasa A

Diagnóstico molecular

Mutaciones en el gen GLA

ENFERMEDAD DE FABRY: TRATAMIENTO

Tratamiento no enzimático

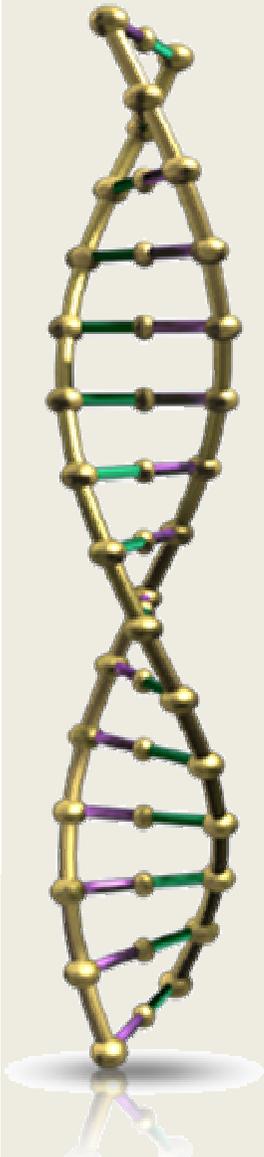
- IECAs/ARAII.
- Antiagregantes.
- Estatinas.
- Tratamiento del dolor.
- Diálisis.



Tratamiento enzimático sustitutivo

- Agalsidasa alfa (Replagal®).
- Agalsidasa beta (Fabrazyme®).

Otras terapias



AFECTACIÓN RENAL

- **AFECTACIÓN RENAL**

- Filtrado glomerular renal (FGR): función renal

- Estimación del FGR

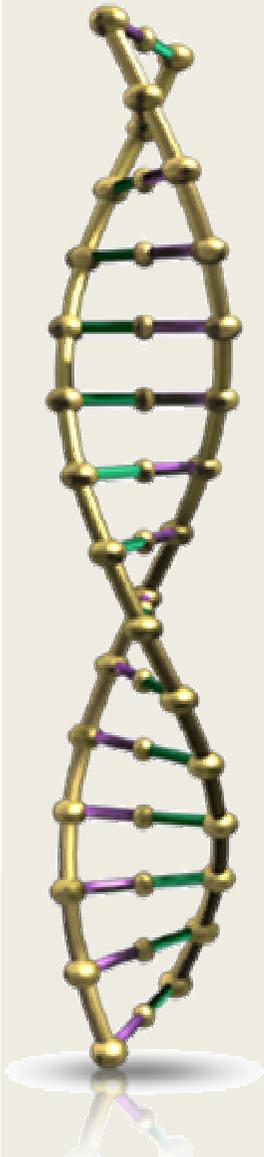
- Gold standard: aclaramiento de inulina, isótopos, etc.

- Aclaramiento de creatinina

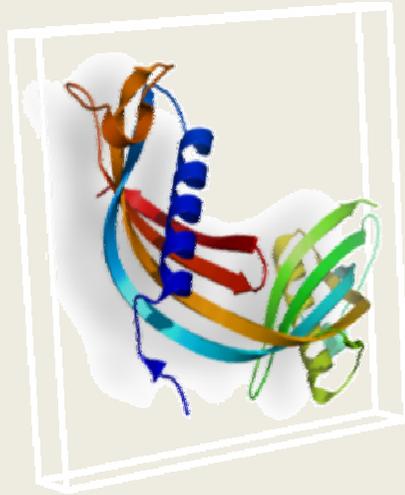
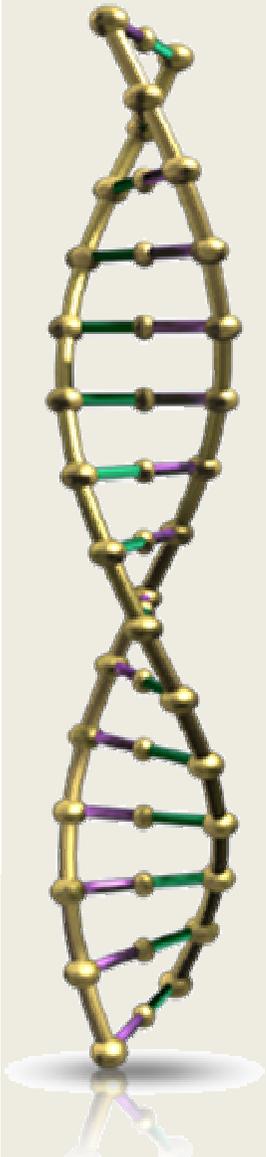
- Fórmula de Cockcroft-G

- Fórmula MDRD

- Cistatina C



CISTATINA C



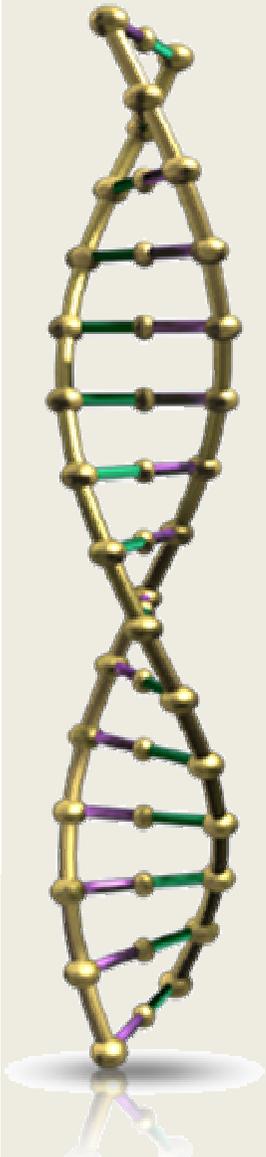
CISTATINA C

- Cistatina C y enfermedad renal crónica
- Cistatina C y riesgo cardiovascular
- Valor en la edad pediátrica

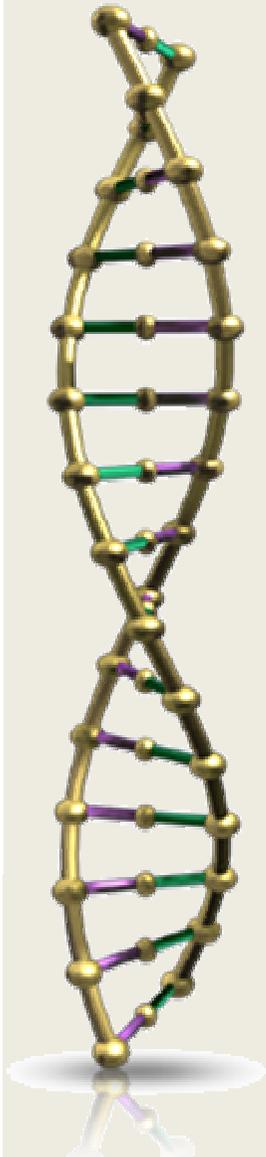
AFECTACIÓN CARDÍACA

- **AFECTACIÓN CARDIOVASCULAR**

- Hipertrofia del ventrículo izquierdo y disfunción diastólica
- Ecocardiograma y RM
- NT-proBNP



NT-proBNP



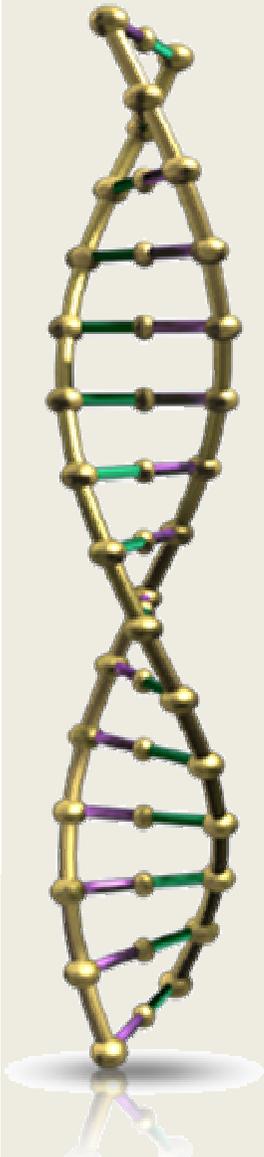
NT-proBNP



- Desventajas: edad y aclaramiento renal
- Utilidad en la clínica

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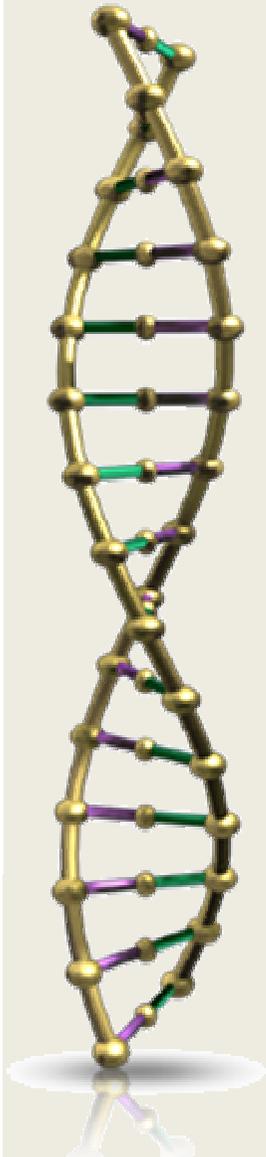


- Presencia o gravedad de la enfermedad
- Incógnitas acerca del tratamiento
 - Inicio
 - Dosis
 - Respuesta al tratamiento
- Otras enfermedades de depósito



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Actividad de la alfa-galactosidasa A

- No orienta en el pronóstico ni inicio del TES
- No se correlaciona con la gravedad de las lesiones

Mutación

- No tiene correlación con el fenotipo

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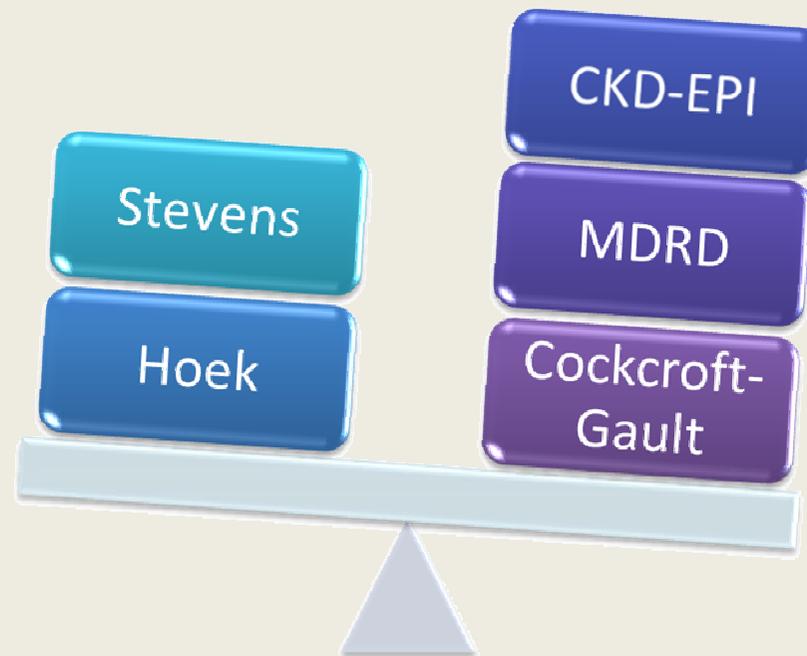
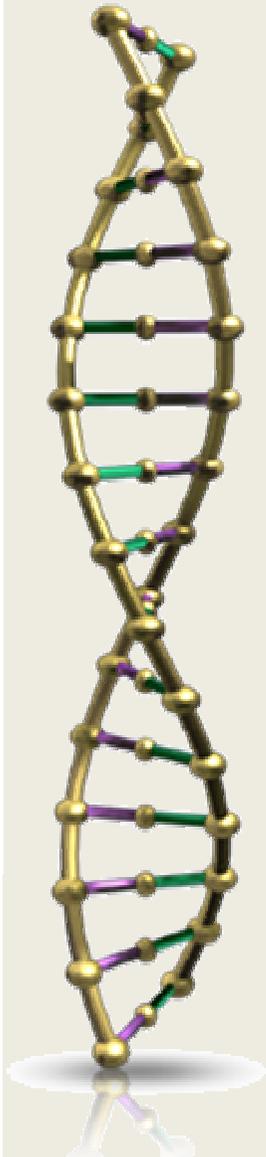
Nephrol Dial Transplant (2010) 25: 2549–2556

doi: 10.1093/ndt/gfq108

Advance Access publication 9 March 2010

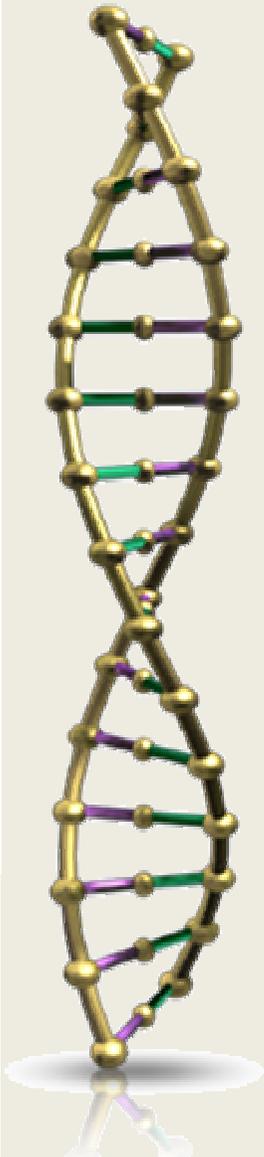
The value of estimated GFR in comparison to measured GFR for the assessment of renal function in adult patients with Fabry disease

Saskia M. Rombach^{1,*} and Marije C. Baas^{2,*}, Ineke J. M. ten Berge², Raymond T. Krediet², Frederike J. Bemelman², Carla E. M. Hollak¹



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Proteínas plasmáticas:

- PCR
- Mieloperoxidasa
- Metaloproteinasa 9
- Quitotriosidasa

Disfunción endotelial y plaquetaria:

- Alfa2-antiplasmina

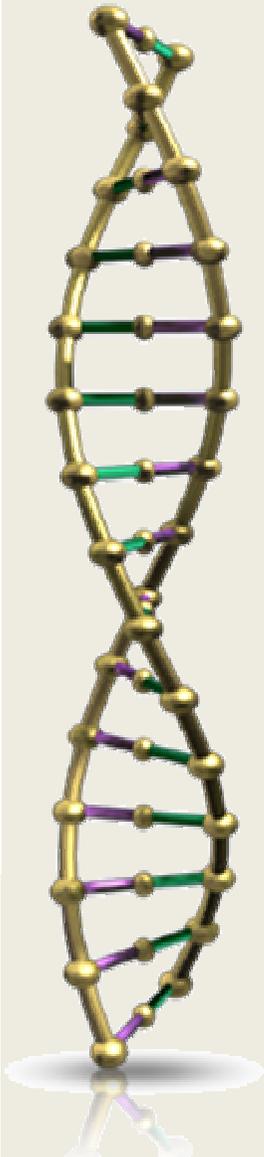
Otros marcadores:

- Uromodulina
- KIM-1
- Alfa1microglobulina

Vedder AC et al. J Inherit Metab Dis 29:106-111
Moore DF et al. J Neurol Sci 257;258-63.

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Globotriaosilceramida (Gb3)

- Elevada en plasma y orina
- Utilidad: mujeres asintomática con mutación con consecuencia desconocidas
- No sirve para el seguimiento
- No correlación con el acúmulo

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Arteriosclerosis, Thrombosis, and Vascular Biology

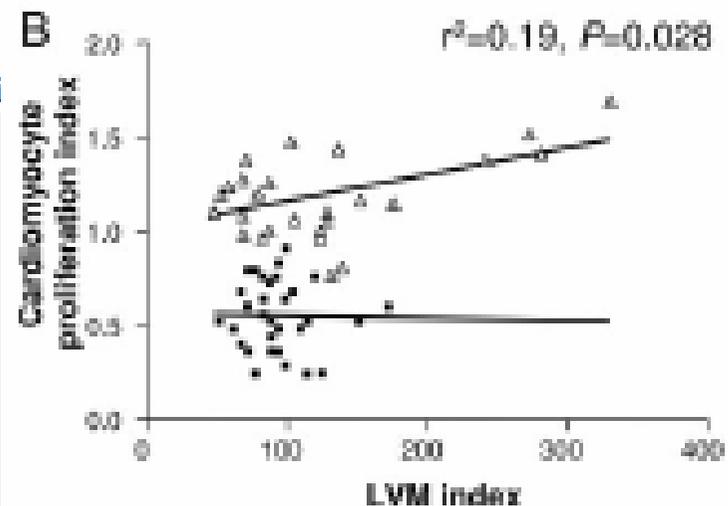
JOURNAL OF THE AMERICAN HEART ASSOCIATION



Cardiac and Vascular Hypertrophy in Fabry Disease : Evidence for a New Mechanism Independent of Blood Pressure and Glycosphingolipid Deposition

Frédéric Barbey, Nouredine Brakch, Ales Linhart, Nathalie Rosenblatt-Velin, Xavier Jeanrenaud, Salah Qanadli, Beat Steinmann, Michel Burnier, Tomas Palecek, Jan Bultas and Daniel Hayoz

Arterioscler Thromb Vasc Biol. 2006;26:839-844; on

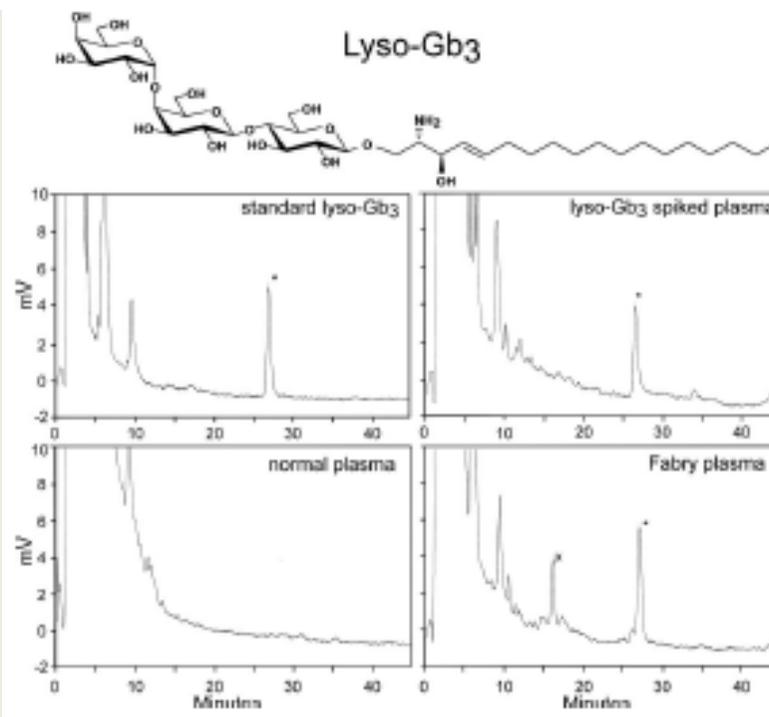


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Elevated globotriaosylsphingosine is a hallmark of Fabry disease

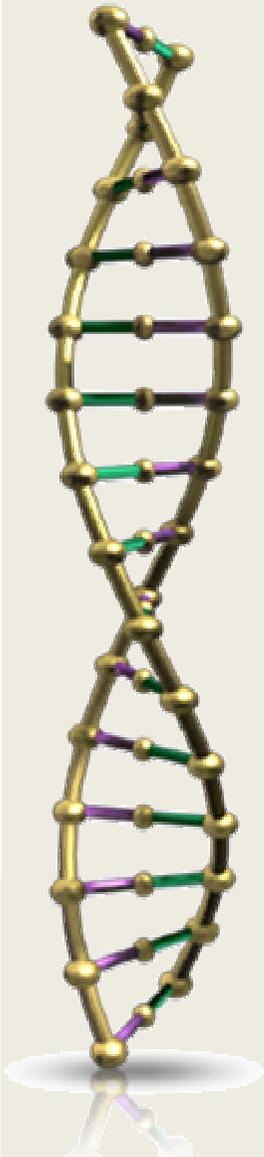
Johannes M. Aerts^{1,2}, Johanna E. Groener², Sijmen Kuiper², Wilma E. Donker-Koopman², Anneke Strijland², Roelof Ottenhoff², Cindy van Roomen², Mina Mirzalian², Frits A. Wijburg², Gabor E. Linthorst², Anouk C. Vedder², Saskia M. Rombach², Josanne Cox-Brinkman², Pentti Somerharju², Rolf G. Boot², Carla E. Hollak², Roscoe O. Brady^{1,3}, and Ben J. Poorthuis²



February 26, 2008 | vol. 105 | no. 8

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- LysoGb3 plasmática elevada en el nacimiento
- Mujeres: baja en el momento del nacimiento, y se eleva progresivamente
- Se correlaciona con aumento de enfermedad cerebrovascular en varones

Rombach SM et al. Biochim Biophys Acta 1802:741–748

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Nephrol Dial Transplant (2011) 26: 1797–1802

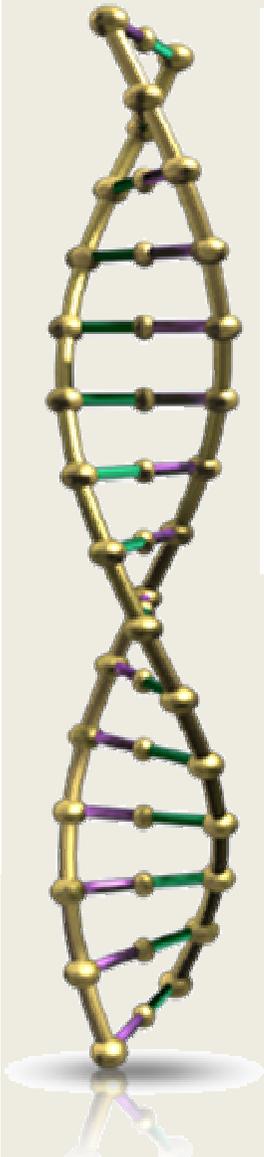
doi: 10.1093/ndt/gfq306

Advance Access publication 26 May 2010

Globotriaosylsphingosine actions on human glomerular podocytes: implications for Fabry nephropathy

Maria D. Sanchez-Niño¹, Ana B. Sanz², Susana Carrasco¹, Moin A. Saleem³, Peter W. Mathieson³, José M. Valdivielso⁴, Marta Ruiz-Ortega¹, Jesus Egido¹ and Alberto Ortiz¹

Demostración del papel patogénico de la lysoGb3 en el daño glomerular, por la liberación de mediadores secundarios de este daño renal



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Clinica Chimica Acta 411 (2010) 1906–1914



Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim



How well does urinary lyso-Gb₃ function as a biomarker in Fabry disease?

Christiane Auray-Blais ^{a,*}, Aimé Ntwari ^a, Joe T.R. Clarke ^a, David G. Warnock ^b, João Paulo Oliveira ^c, Sarah P. Young ^d, David S. Millington ^d, Daniel G. Bichet ^e, Sandra Sirrs ^f, Michael L. West ^g, Robin Casey ^h, Wuh-Liang Hwu ⁱ, Joan M. Keutzer ^j, X. Kate Zhang ^j, René Gagnon ^a

Table 5

Statistical data of urine lyso-Gb₃/creatinine and Gb₃/creatinine for different variables.

	Gb ₃ ($\mu\text{g}/\text{mmol creat}$)	Serum creatinine (mg/dl)	MDRD eGFR ($\text{ml}/\text{min}/1.73 \text{ m}^2$)	Urinary proteins (mg/dl)	Urinary albumin (mg/l)	UCPR (g/g)	ACR (mg/g)	Urinary creatinine (mg/dl)	Hemoglobin (g/dl)
<i>Lyso-Gb₃ (pmol/mmol creat)</i>									
Pearson correlation coefficients	0.84505	0.54438	-0.33047	0.73792	0.73571	0.74488	0.72732	-0.23159	0.07345
Prob> r under H ₀ : Rho = 0 p	<.0001	0.0239	0.1951	0.0007	0.0008	0.0213	0.0171	0.3711	0.7794
Number of patients	17	17	17	17	17	9	10	17	17
<i>Gb₃ ($\mu\text{g}/\text{mmol creat}$)</i>									
Pearson correlation coefficients		0.77863	-0.52364	0.87632	0.89858	0.87946	0.89647	-0.123	0.11659
Prob> r under H ₀ : Rho = 0 p		0.0002	0.031	<.0001	<.0001	0.0018	0.0004	0.6381	0.6559
Number of patients	17	17	17	17	17	9	10	17	17

UPCR: urine protein/creatinine ratio. ACR: urine albumin/creatinine ratio.

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Mutant α -galactosidase A with M296I does not cause elevation of the plasma globotriaosylsphingosine level

Sayuri Mitobe ^a, Tadayasu Togawa ^b, Takahiro Tsukimura ^b, Takashi Kodama ^a, Toshie Tanaka ^c, Kent Doi ^d, Eisei Noiri ^d, Yasuhiro Akai ^e, Yoshihiko Saito ^e, Makoto Yoshino ^f, Toshihiro Takenaka ^g, Seiji Saito ^h, Kazuki Ohno ⁱ, Hitoshi Sakuraba ^{a,c,*}

Molecular Genetics and Metabolism 107 (2012) 623–626

Clinical and biochemical findings of Fabry patients with the M296I enzyme.

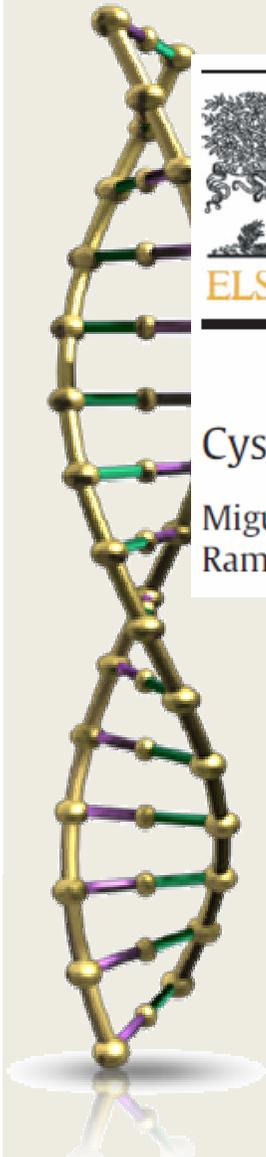
a. Clinical manifestations.

Case no.	Age (year)	Sex	Status	Clinical manifestations					
				Pain	Angiokeratoma	Hypohidrosis	Renal involvement	Cardiac involvement	Cerebrovascular involvement
1	2	Male	He mizygote	–	–	–	–	–	–
2	11	Male	He mizygote	–	+	+	–	–	–
3	54	Male	He mizygote	–	–	–	+	+	–
4	61	Male	He mizygote	–	–	–	+	+	–
5	31	Fe male	He terozygote	+	–	+	+	–	–
6	31	Fe male	He terozygote	–	–	–	–	–	–
7	33	Fe male	He terozygote	–	–	–	–	–	–

b. GLA activities in plasma and leukocytes, and lyso-Gb3 and Gb3 levels in plasma.

Subject	GLA activity		Plasma lyso-Gb3 (nmol/l)	Plasma Gb3 (μ g/ml)
	Plasma (nmol/h/ml)	Leukocytes (nmol/h/mg protein)		
Case 1	1	2	<2	3.1
Case 2	1	2	<2	5.9
Case 3	2	2	<2	5.7
Case 4	3	1	<2	4.0
Case 5	4	22	<2	2.1
Case 6	3	28	<2	4.1
Case 7	6	30	<2	6.1
Classic Fabry male	0 \pm 0 [24] *	0 \pm 0 [36] *	100 \pm 48 [15] *	13.5 \pm 6.8 [15] *
Later-onset Fabry male	1 \pm 1 [5] *	5 \pm 4 [5] *	35 \pm 25 [5] *	4.6 \pm 1.1 [5] *
Fabry female	3 \pm 1 [15] *	35 \pm 19 [18] *	17 \pm 10 [9] *	4.3 \pm 1.0 [9] *
Normal subject	8 \pm 2 [63] *	49 \pm 15 [33] *	<2 [20]	4.6 \pm 1.6 [18] *

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Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme



Cystatin C and NT-proBNP as prognostic biomarkers in Fabry disease

Miguel-Ángel Torralba-Cabeza ^{a,*}, Susana Olivera ^{a,1}, Derralynn A. Hughes ^b, Gregory M. Pastores ^c,
Ramón Nuviala Mateo ^d, Juan-Ignacio Pérez-Calvo ^a



CISTATINA C

JNephrol 2007; 20: 437-443

Cystatin C as a marker of early changes of renal function in Fabry nephropathy

Sandro Feriozzi¹, Dominique P. Germain²,
Raffaele Di Vito³, Alain Legrand⁴, Roberta Ricci⁵,
Frédéric Barbey⁶

¹ Nephrology and Dialysis Unit, Ospedale Belcolle, Viterbo - Italy

² Centre de reference pour la maladie de Fabry et les maladies héréditaires du tissu conjonctif, AP-HP, Paris - France

³ Nephrology and Dialysis Unit, Ospedale "Bernabeo", Ortona, Chieti - Italy

⁴ Department of Biochemistry, CHU Kremlin Bicêtre Cedex-France

⁵ Institute of Clinical Pediatrics, Università Cattolica S. Cuore, Rome - Italy

⁶ Department of Nephrology, Lausanne University Hospital, Lausanne - Switzerland

EFFECTS OF 3 YEARS OF ENZYME REPLACEMENT THERAPY (ERT) ON RENAL FUNCTION IN 21 PATIENTS

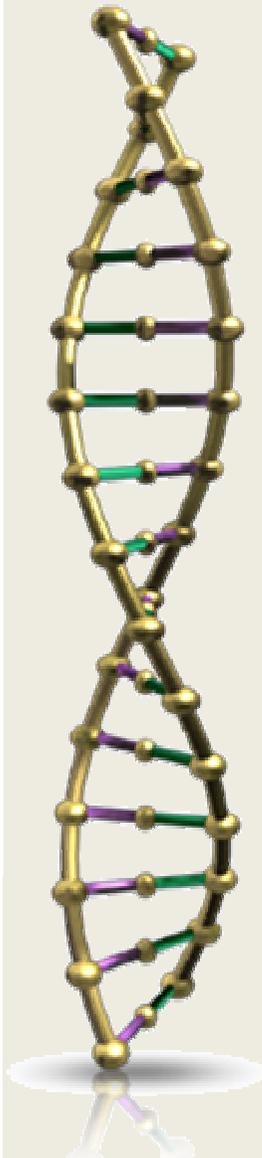
	Baseline	1 year ERT	2 year ERT	3 year ERT	p ANOVA
Serum creatinine (mg/dL)	1.01 ± 0.2	0.97 ± 0.2	1 ± 0.3	1.07 ± 0.4	NS
Cystatin C (mg/L)	0.83 ± 0.25	0.95 ± 0.31 [†]	0.97 ± 0.32	1.03 ± 0.43	0.008
MDRD (ml/min)	88.3 ± 21	95.2 ± 30.3	95.1 ± 36.5	92.4 ± 28	NS
C&G (ml/min)	99.9 ± 32	107.3 ± 37	107.7 ± 50	100.5 ± 32	NS
Cystatin C clearance* (ml/min)	94.9 ± 34	82.8 ± 28 [‡]	81.6 ± 30	78.7 ± 28	0.02

MDRD = Modification of Diet in Renal Disease formula; C&G = Cockcroft-Gault formula; NS = not significant.

*Estimated using the Hoek formula.

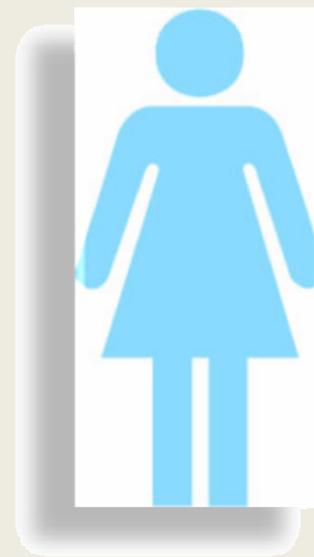
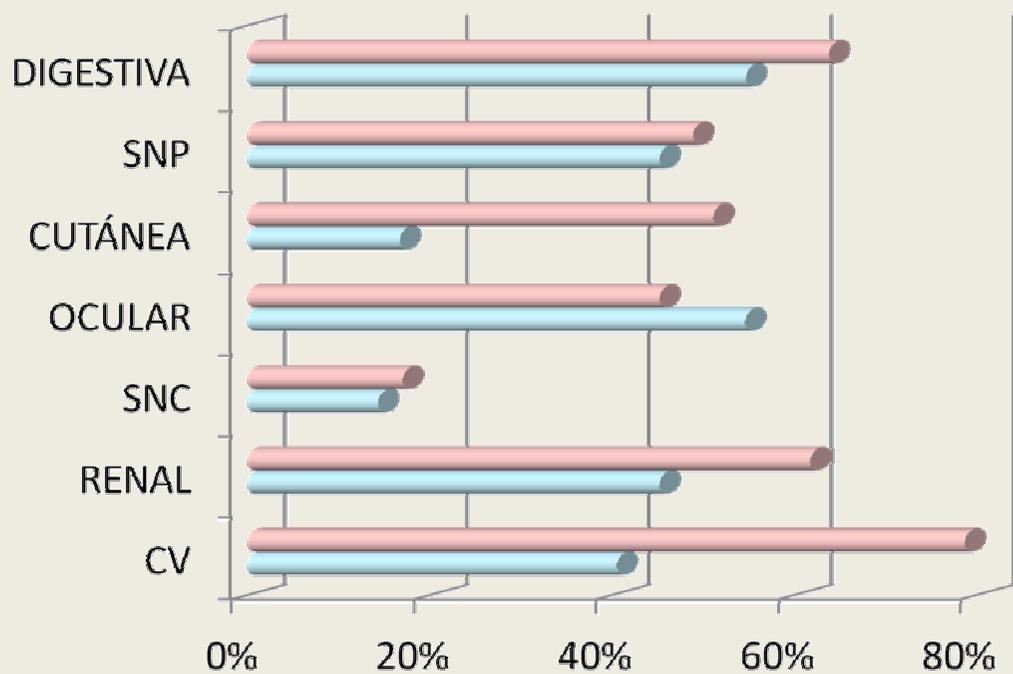
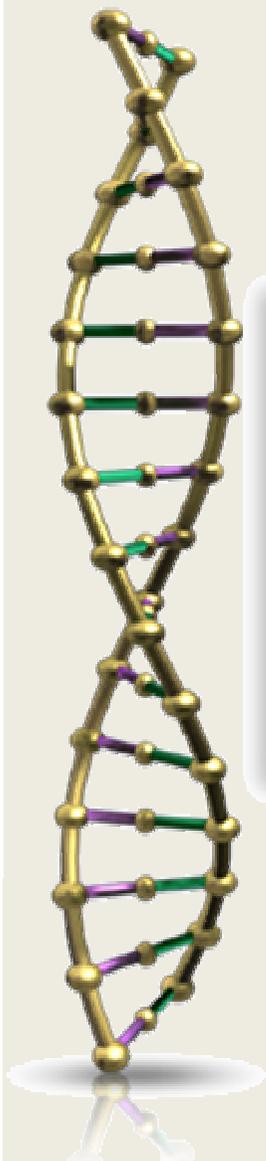
[†]p= 0.02, 1 year ERT vs. baseline.

[‡]p=0.07, 1 year ERT vs. baseline.

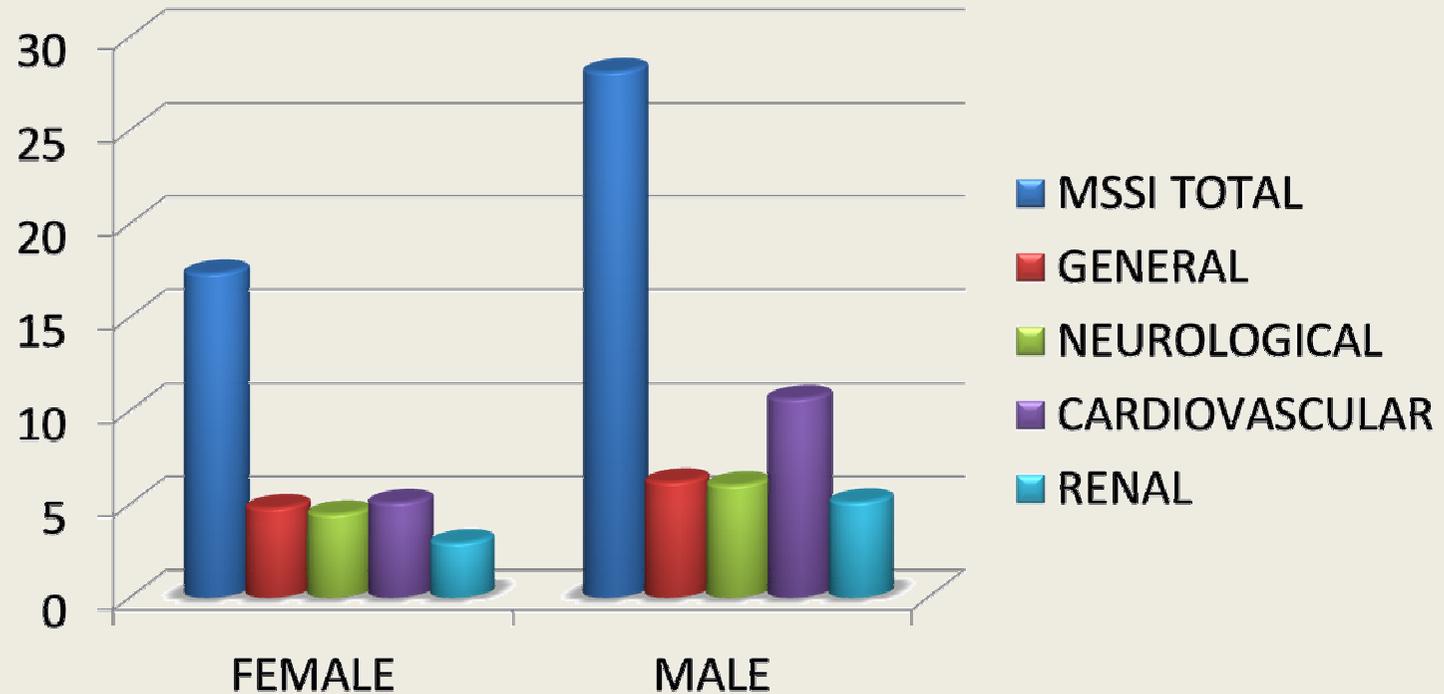
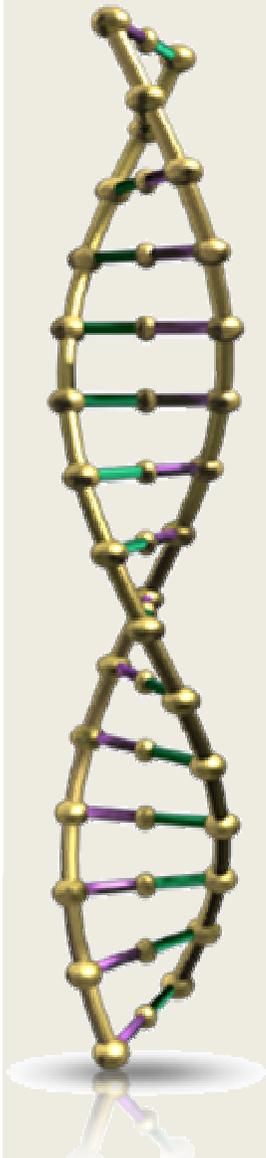


RESULTADOS: CLÍNICA

RESULTADOS: CLÍNICA

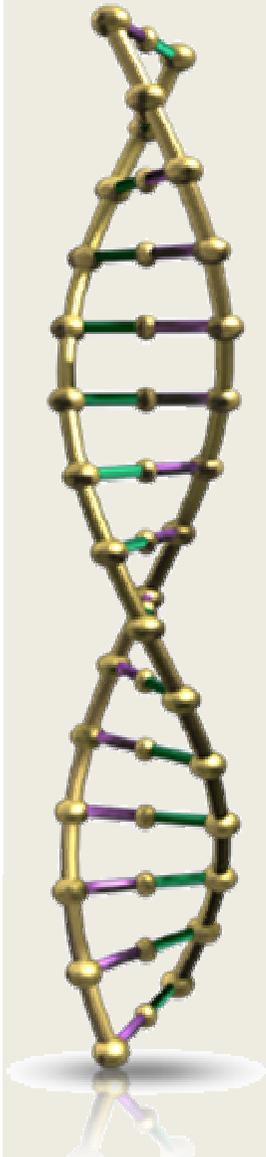


RESULTADOS: INDICE DE MAINZ



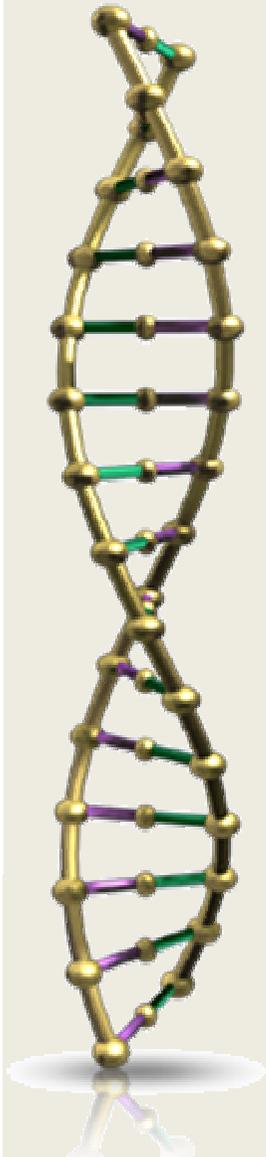
	MSSI TOTAL	GENERAL	NEUROLÓGICO	CARDIO-VASCULAR	RENAL
MUJERES	17,35	4,8	4,47	5,08	2,93
HOMBRES	28,13	6,19	6,02	10,64	5,11

RESULTADOS: COEFICIENTE DE CORRELACIÓN

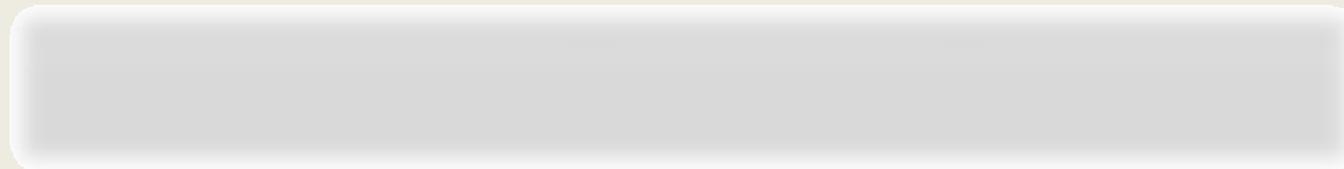


	Cistatina C	NT-proBNP
MSSI Total	0,558	0,526
General	0,147	0,214
CV	0,373	0,656
Renal	0,644	0,499
Neurológico	0,466	,0,404
FGR	0,713	0,557

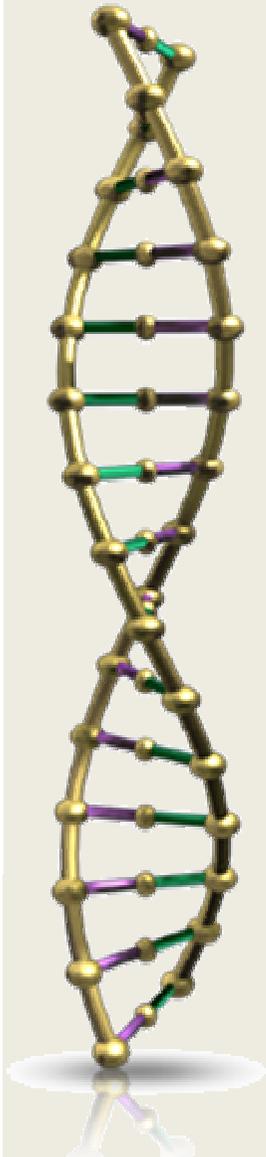
RESULTADOS: COEFICIENTES DE CORRELACIÓN



	HOMBRES	MUJERES
CsC-MSSI Renal	0.642	0.601
NTproBNP-MSSI CV	0.457	0.747
CsC-FGR	0.409	0.685



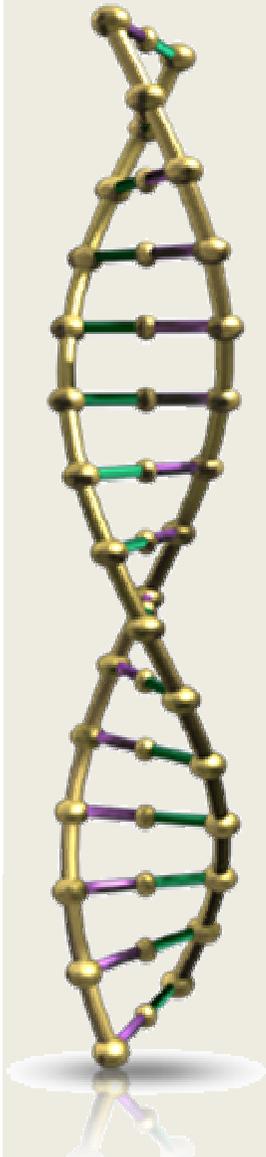
RESULTADOS: AREA BAJO LA CURVA



DAÑO CV	AUC	CI 95%
Creatinina	0,704	0,571-0,799
Cistatina C	0,724	0,613-0,835
NT-proBNP	0,740	0,637-0,844



RESULTADOS: AREA BAJO LA CURVA



DAÑO RENAL	AUC	CI 95%
Creatinina	0,698	0,585-0,811
Cistatina C	0,717	0,725-0,902
NT-proBNP	0,813	0,611-0,823



ESTUDIOS POSTERIORES

The American Journal of Cardiology (www.ajconline.org)

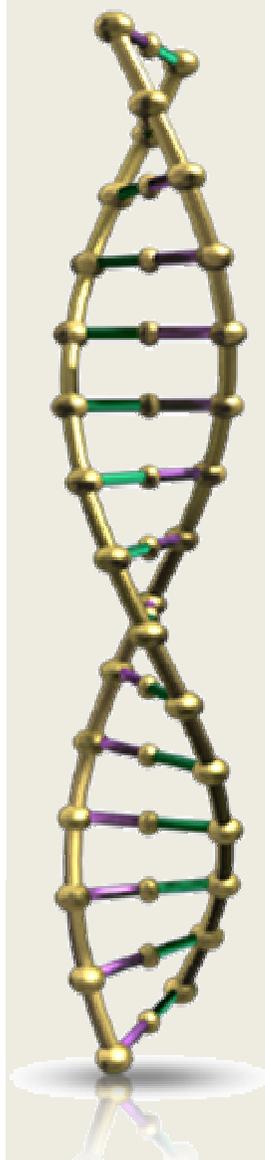
Role of Serum N-Terminal Pro-Brain Natriuretic Peptide Measurement in Diagnosis of Cardiac Involvement in Patients With Anderson-Fabry Disease

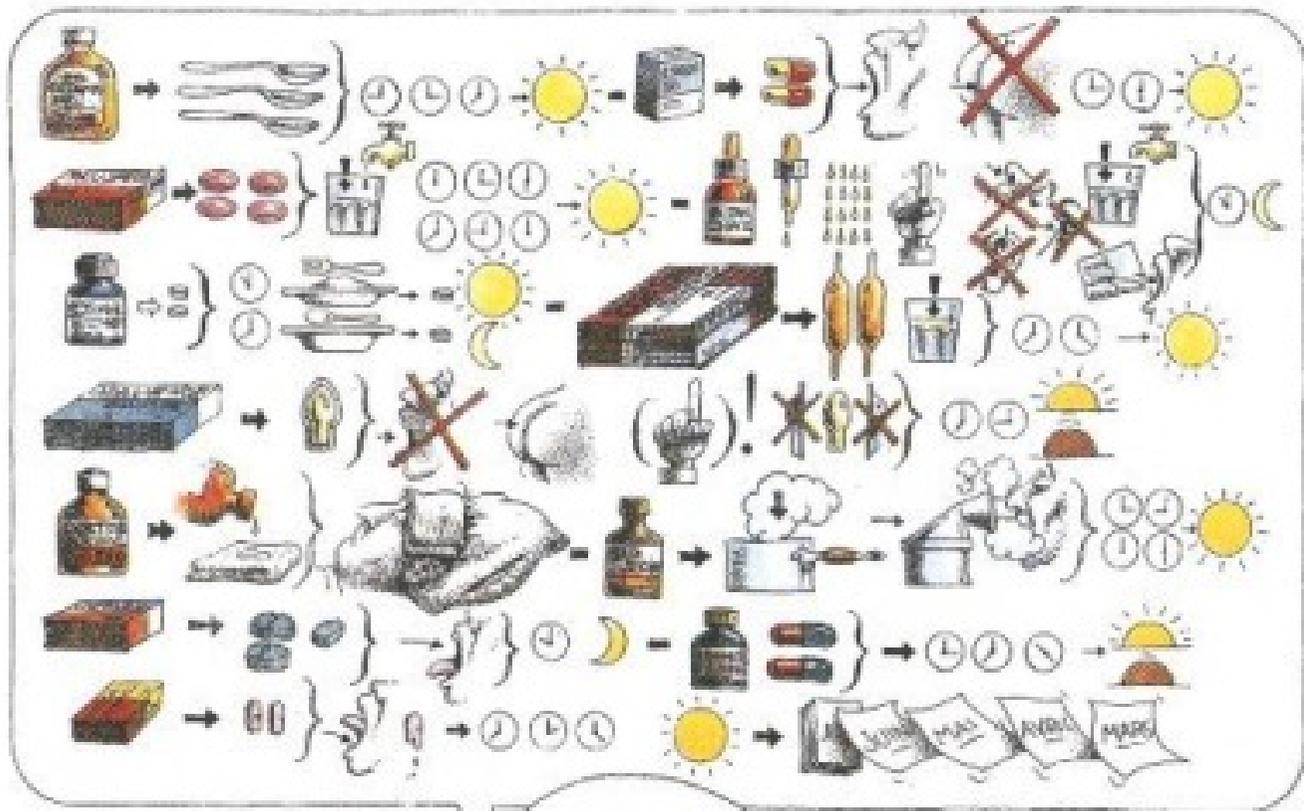
Caroline J. Coats, MBBS^{a,*}, Valentina Parisi, MD^a, Monica Ramos, MD^a, Kalaiarasi Janagarajan, MSc^a, Constantinos O'Mahony, MBBS^a, Anne Dawnay, PhD^b, Robin H. Lachmann, FRCP^c, Elaine Murphy, MBBCh^c, Atul Mehta, MD^d, Derralynn Hughes, DPhil^d, and Perry M. Elliott, MD^a

Operating characteristics of N-terminal pro-brain natriuretic peptide (NT-proBNP) thresholds in Anderson-Fabry disease (AFD) (n = 117)

NT-proBNP (pmoVL)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Ability to predict cardiac involvement*					
≥5	90.7	29.0	81.9	46.8	77.1
≥20	68.6	93.5	99.7	9.2	69.4
≥50	53.5	96.8	99.9	4.4	54.4
≥100	31.4	100.0	100.0	0.0	31.4
Ability to predict abnormal echocardiographic findings					
≥5	96.7	26.8	65.5	84.9	68.0
≥20	83.6	82.1	96.0	49.5	83.4
≥50	67.2	89.3	97.7	29.0	70.1
≥100	42.6	98.2	99.8	6.4	44.7

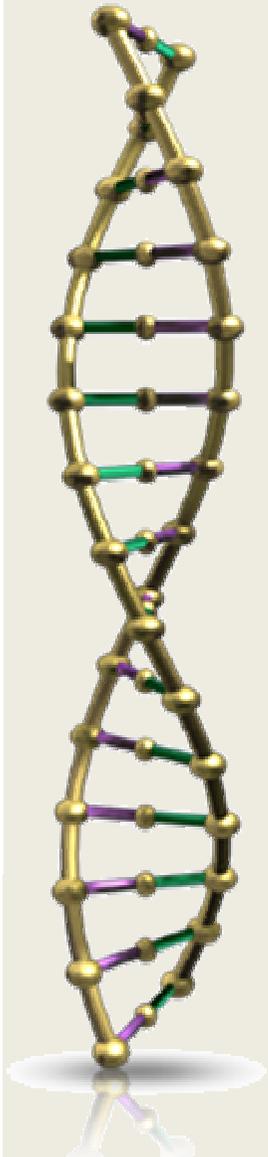
* Echocardiographic or electrocardiographic findings.





BIOMARCADORES

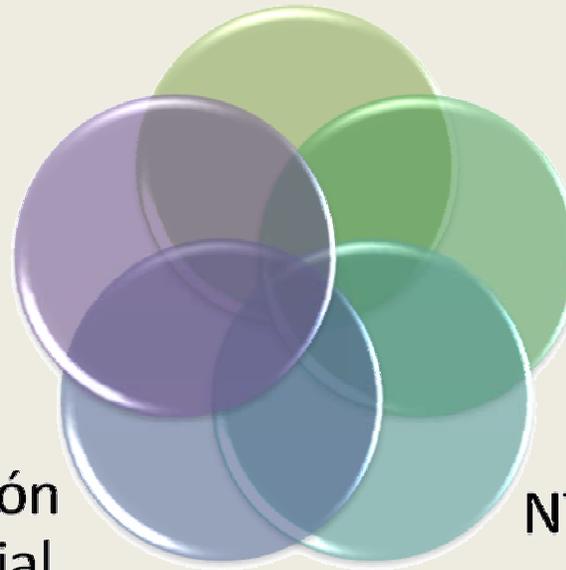
BIOMARCADORES



?????

LysoGb3

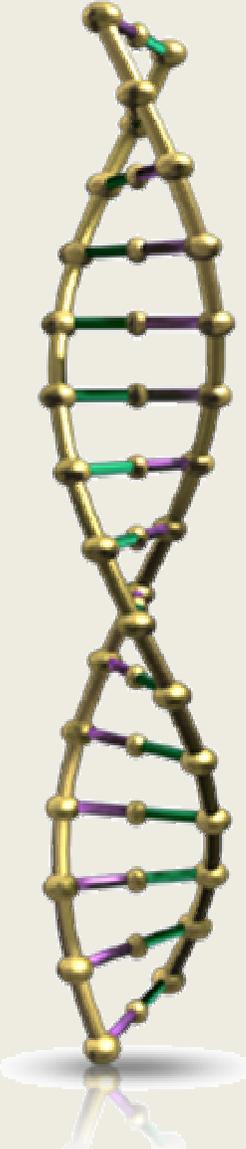
Disfunción
endotelial



Cistatina C

NT-proBNP

CONCLUSIONES



Inicio precoz del TES

Mujeres pueden padecer la enfermedad en la misma medida que los hombres

No existe un marcador biológico óptimo

La cistatina C y el NT-proBNP podrían ser biomarcadores útiles en la enfermedad de Fabry

Ningún mar en calma hizo experto a un marinero
Anónimo



"La costa salvaje de Belle-Ille", Jean Claude Monet