

METHOD FOR PREDICTING THE EARLY ONSET AND SEVERITY OF LEVODOPA INDUCED DYSKINESIA (LID) IN SUBJECTS DIAGNOSED OF PARKINSON'S DISEASE

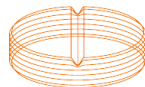


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Biomèdiques
August Pi i Sunyer

Madrid, 14 de noviembre de 2017



MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

1. THE TEAM AND THE INSTITUTIONS BEHIND

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BARCELONA



Dr. Rubén Fernández
Santiago - geneticist



Núria Martín-Flores
- biologist



Dr. Mario Ezquerro
Travalón - geneticist



Dr. Cristina Malagelada
Grau - biochemist



Dr. Maria Josep Martí
Domènech - neurologist

2. THE PRODUCT

2.1. TARGET INDICATIONS

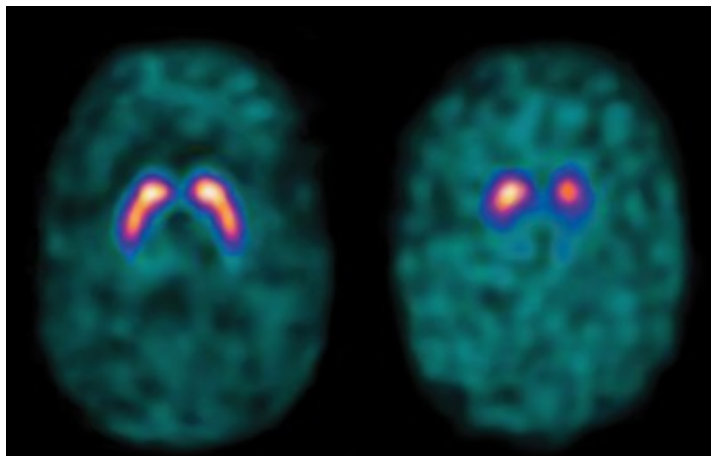
PARKINSON'S DISEASE (PD)

- ▶ UNKNOWN CAUSE: COMBINATION OF GENETIC (other family member with PD) AND ENVIRONMENTAL FACTORS (pesticides, well water, rural living etc...)

DaTScan diagnosis

Control

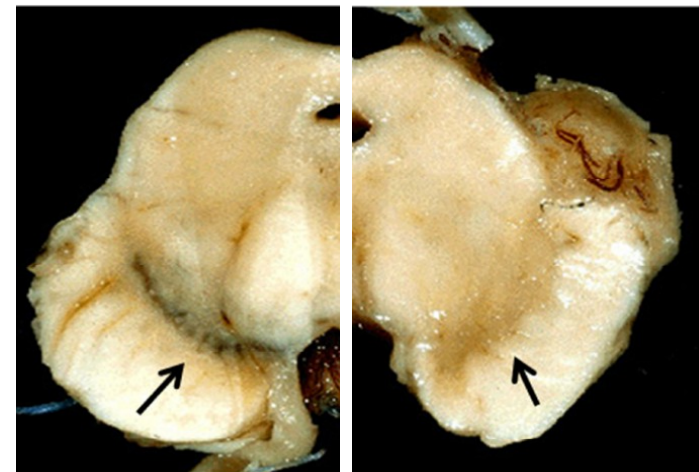
PD



Post-mortem confirmation

Control

PD



2.1. TARGET INDICATIONS

PARKINSON'S DISEASE (PD)

Epidemiology figures (estimations)

Incidence: 4.5 – 21 cases/100,000 population

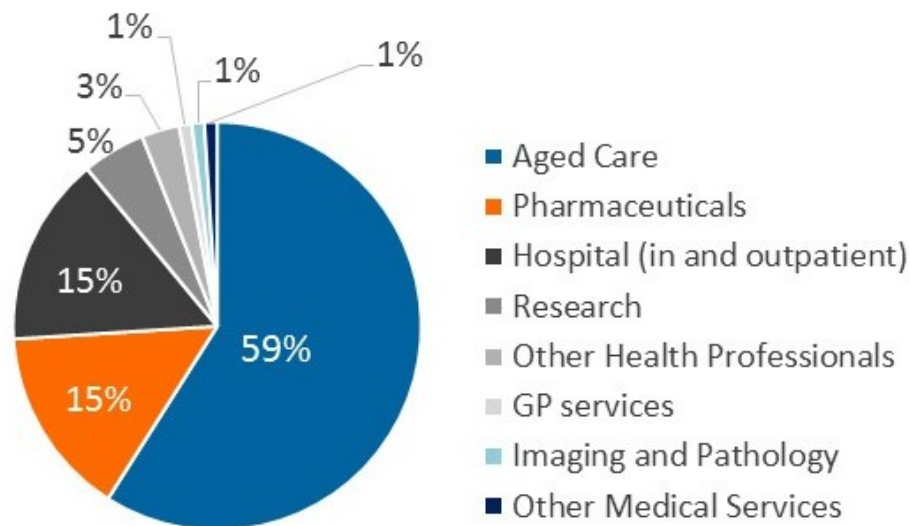
Prevalence: 18 – 328 cases/100,000 population

Most studies yield prevalence of 120 cases per 100,000 population

► The annual European estimated cost of the disease is €13,9 billion¹, being health system costs 62% of the total

Source: Medscape (2017) <http://bit.ly/17axmSp>

Health System costs components (2011)

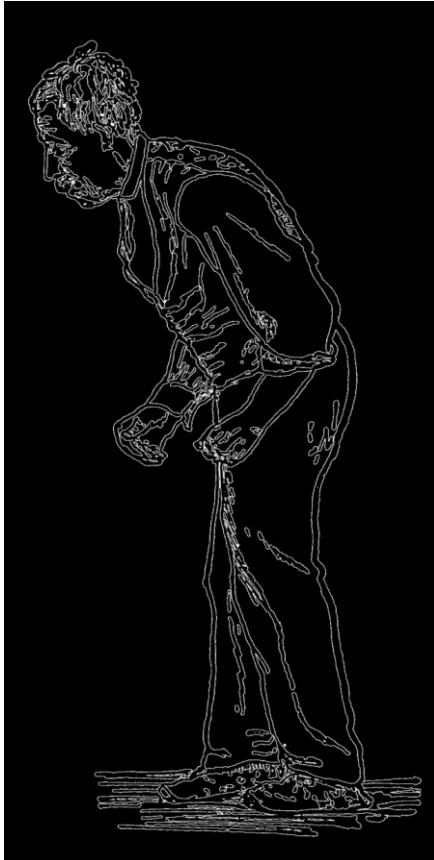


Source: internal

¹ Gustavsson, A. et al., Cost of disorders of the brain in Europe 2010 Eur Neuropsychopharmacol. 2011 Oct;21(10):718-79.

2.1. TARGET INDICATIONS

PARKINSON'S DISEASE (PD)



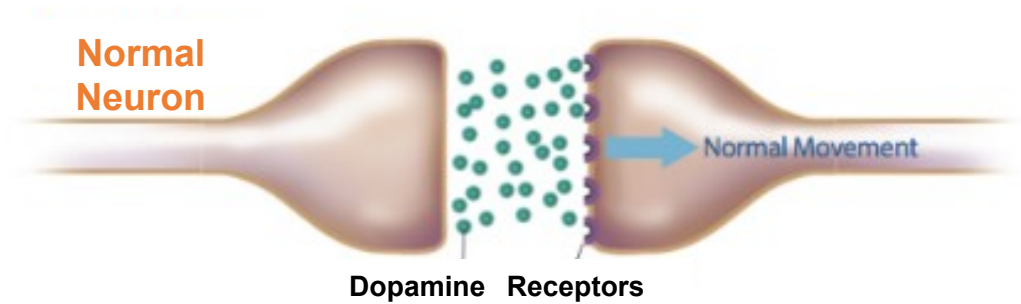
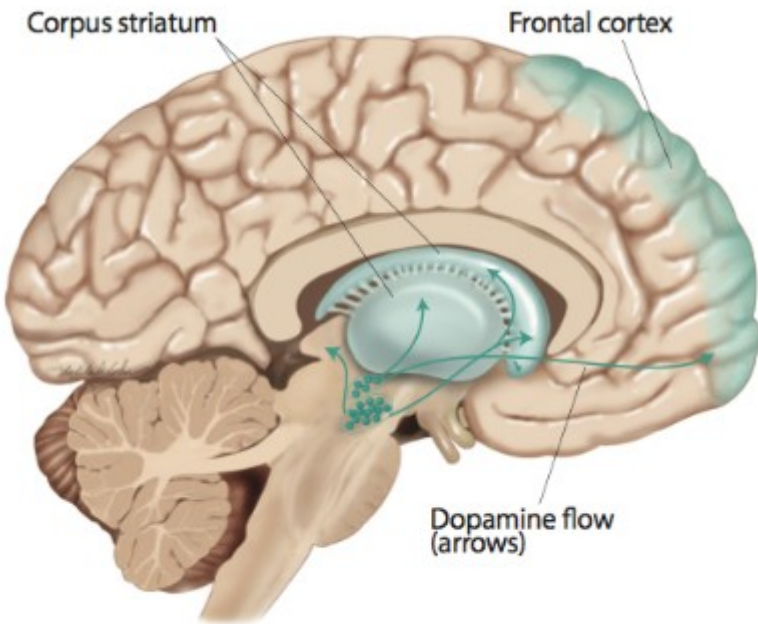
Motor symptoms

- Rigidity and tremor of extremities and head
- Slowness of movement (bradykinesia)
- Postural instability
- Loss of facial expression
- Slow, monotonous speech

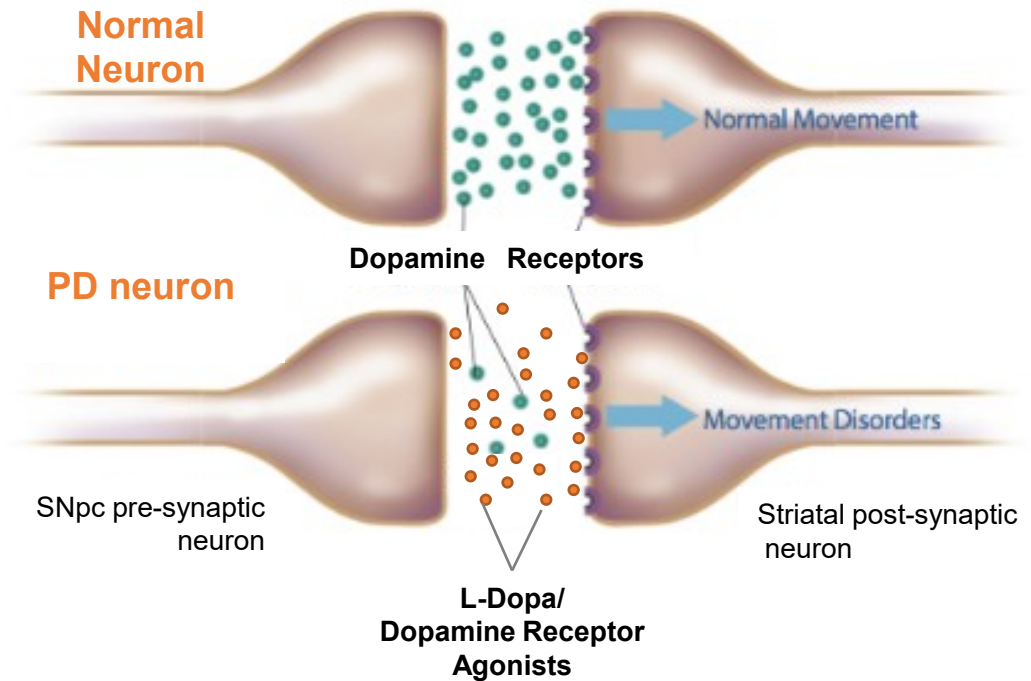
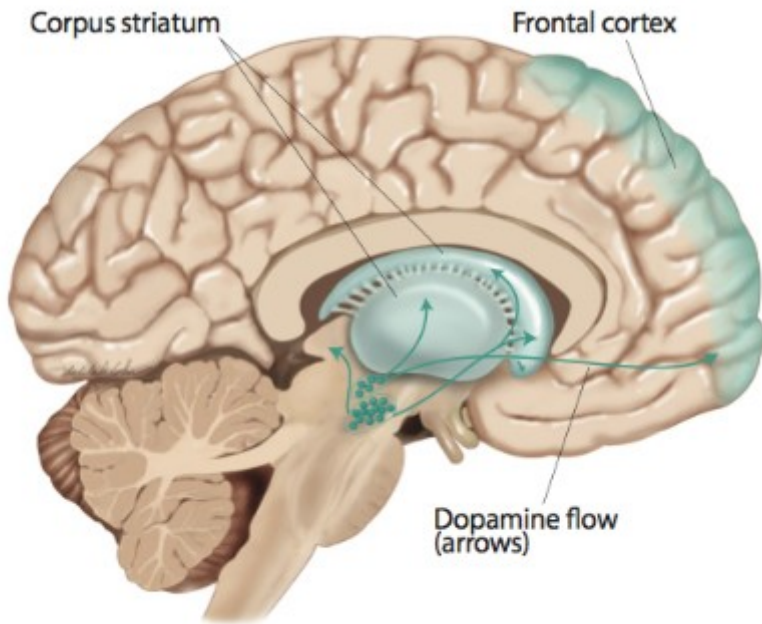
Non-Motor symptoms

- Sleep disturbances
- Constipation
- Depression, fear and anxiety
- Cognitive decline (dementia)

2.1. TARGET INDICATIONS

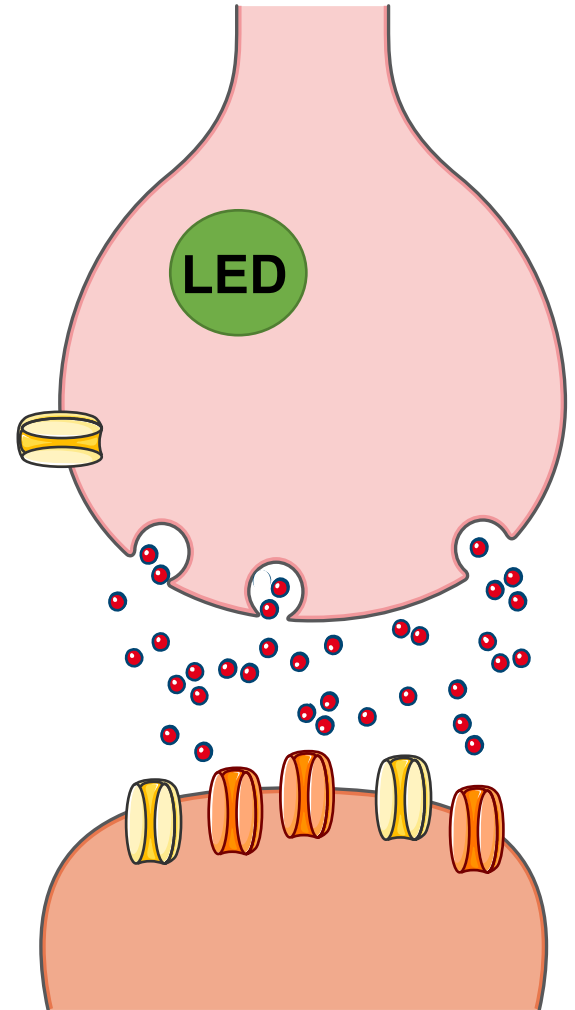


2.1. TARGET INDICATIONS



2.1. TARGET INDICATIONS: L-DOPA-INDUCED DYSKINESIA

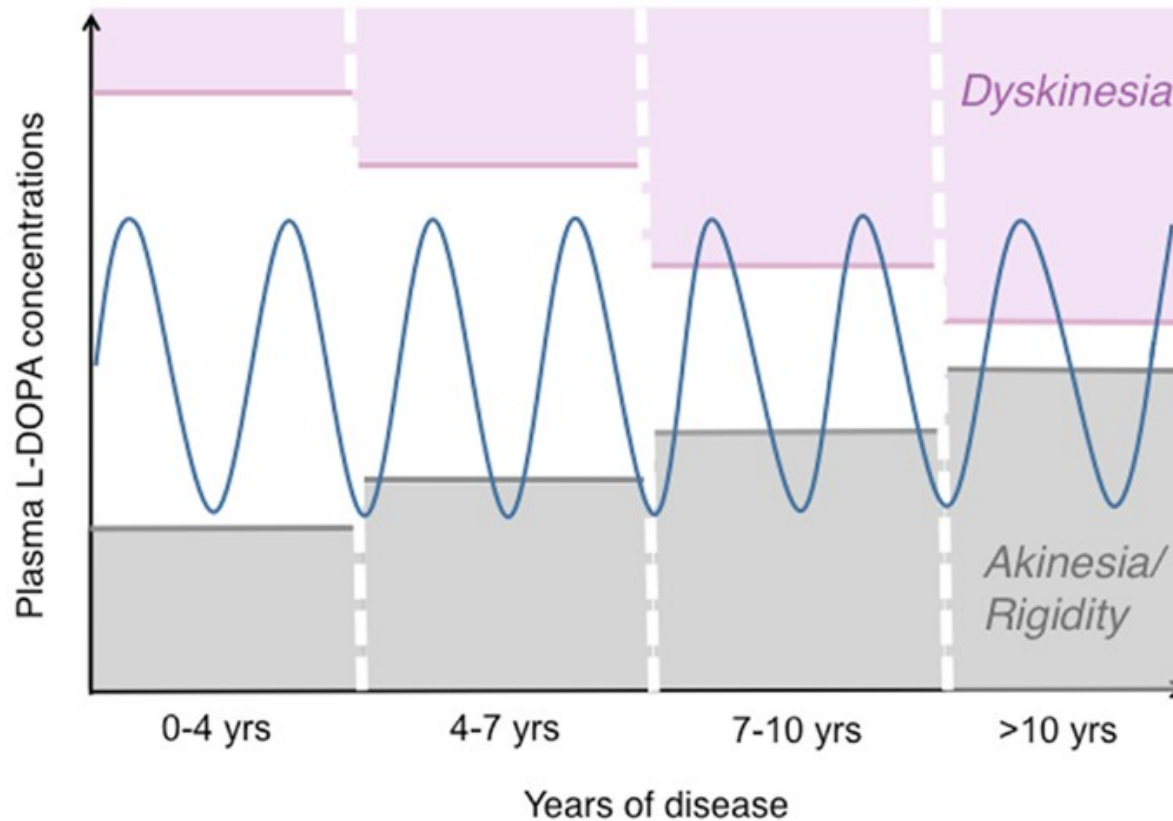
Nigral neurodegeneration
Early Stage



DYSKINESIA

2.1. TARGET INDICATIONS: L-DOPA-INDUCED DYSKINESIA

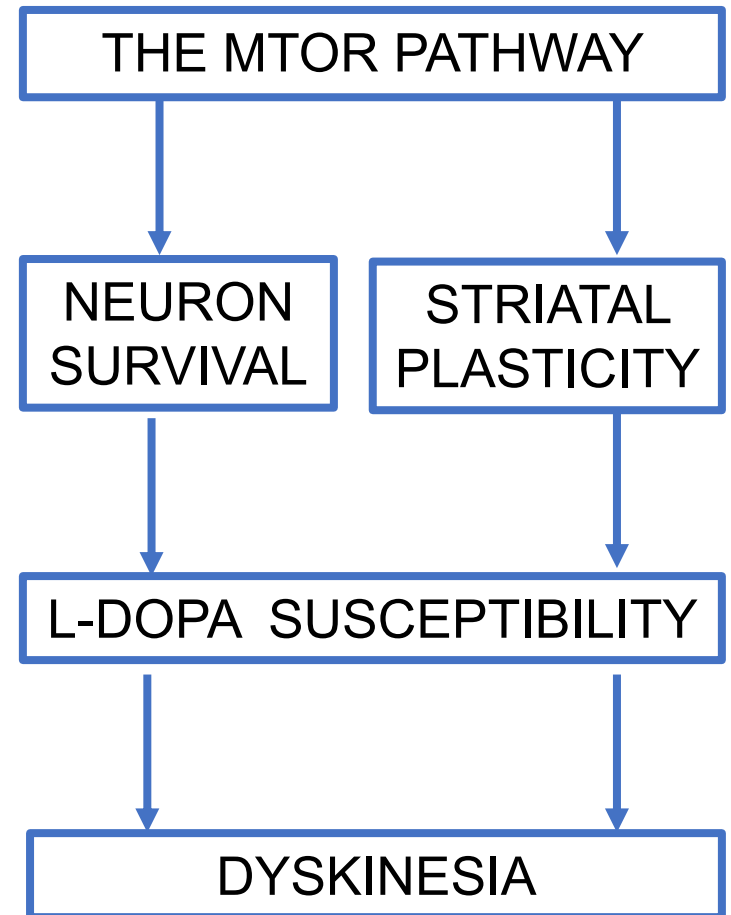
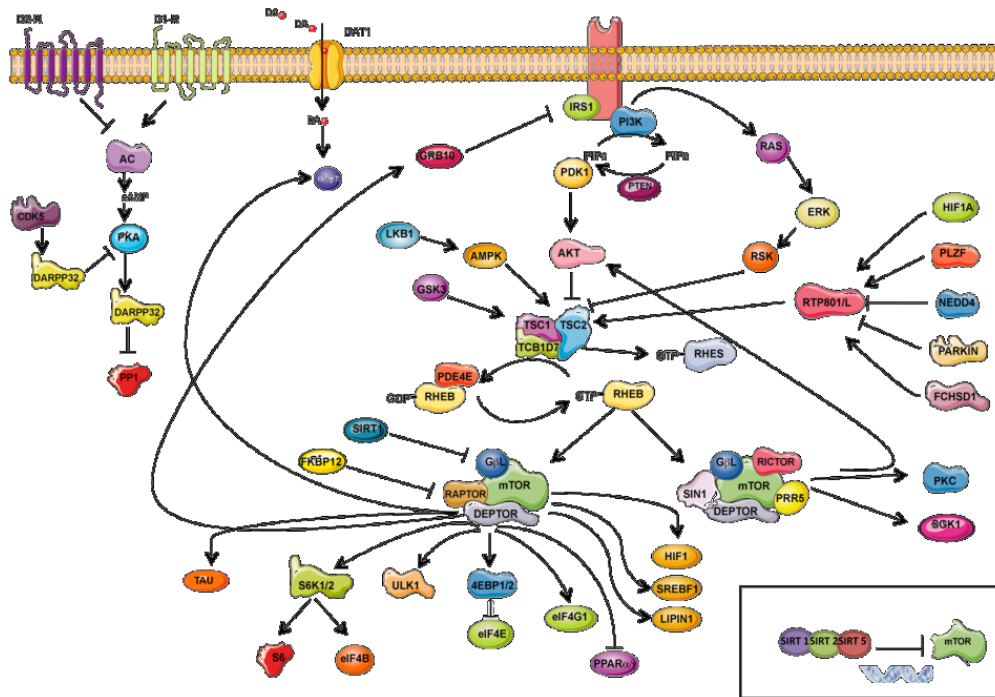
- Present in 50-80% of PD patients
- After 5-10 years of L-DOPA treatment



2.1. TARGET INDICATIONS: L-DOPA-INDUCED DYSKINESIA

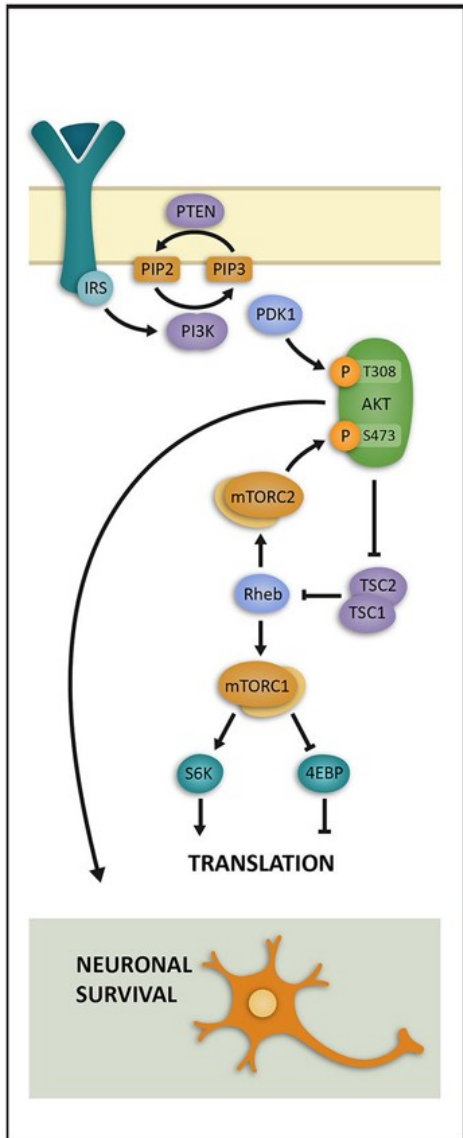


2.2 INNOVATIVE MECHANISM OF ACTION: THE MTOR PATHWAY



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Physiological conditions



MTOR/AKT INACTIVATION in PD

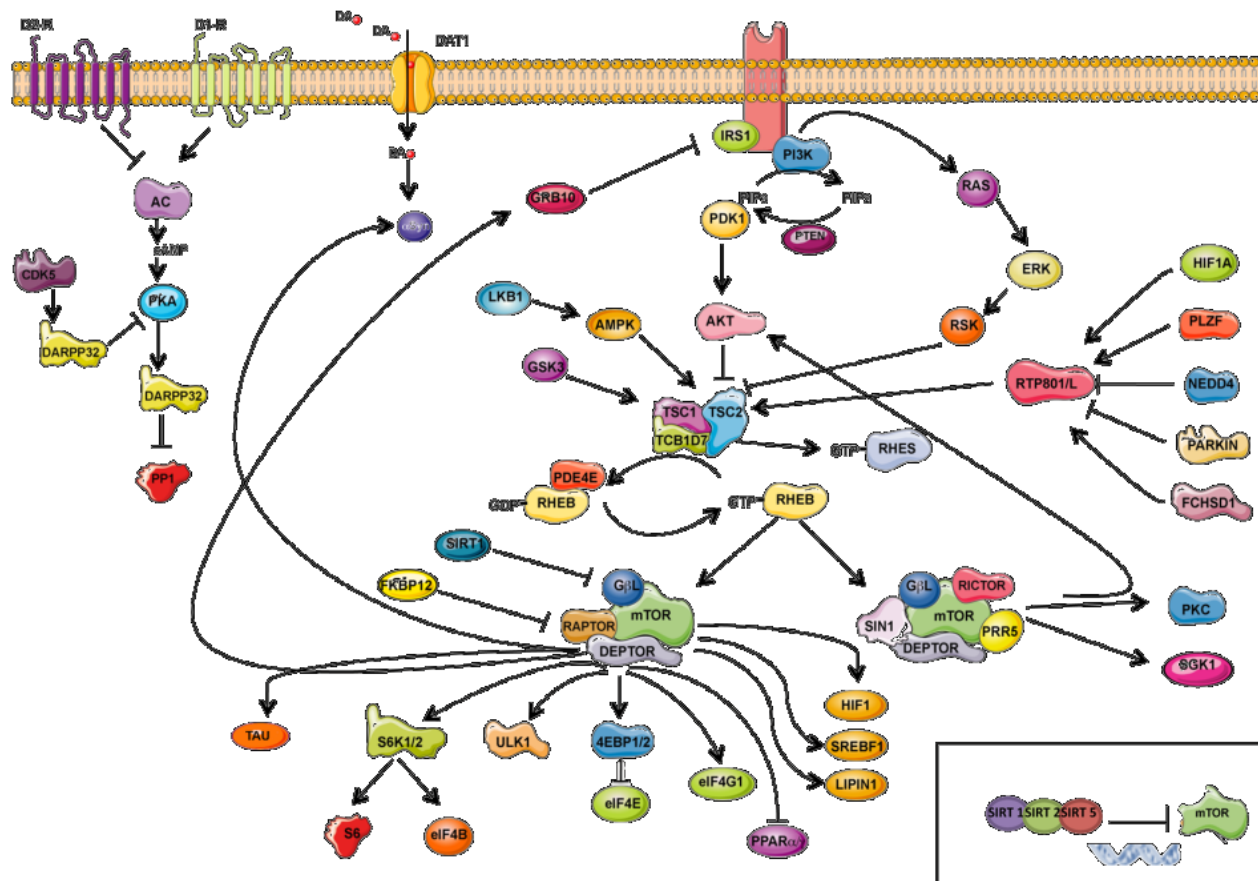
Malagelada C et al., 2006, 2008,
2010

MTOR INHIBITION IN STRIATUM PREVENTS LID IN L-DOPA-TREATED MICE AND RAT

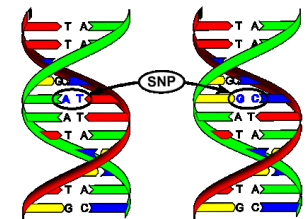
Decressac M et al., 2013
Subramaniam S et al., 2012
Santini E et al., 2009

2.2 INNOVATIVE MECHANISM OF ACTION: SNPs IN THE MTOR PATHWAY

RATIONALE: SNPs IN THE MTOR PATHWAY TO IDENTIFY HIGHLY SUSCEPTIBLE PD PATIENTS TO L-DOPA

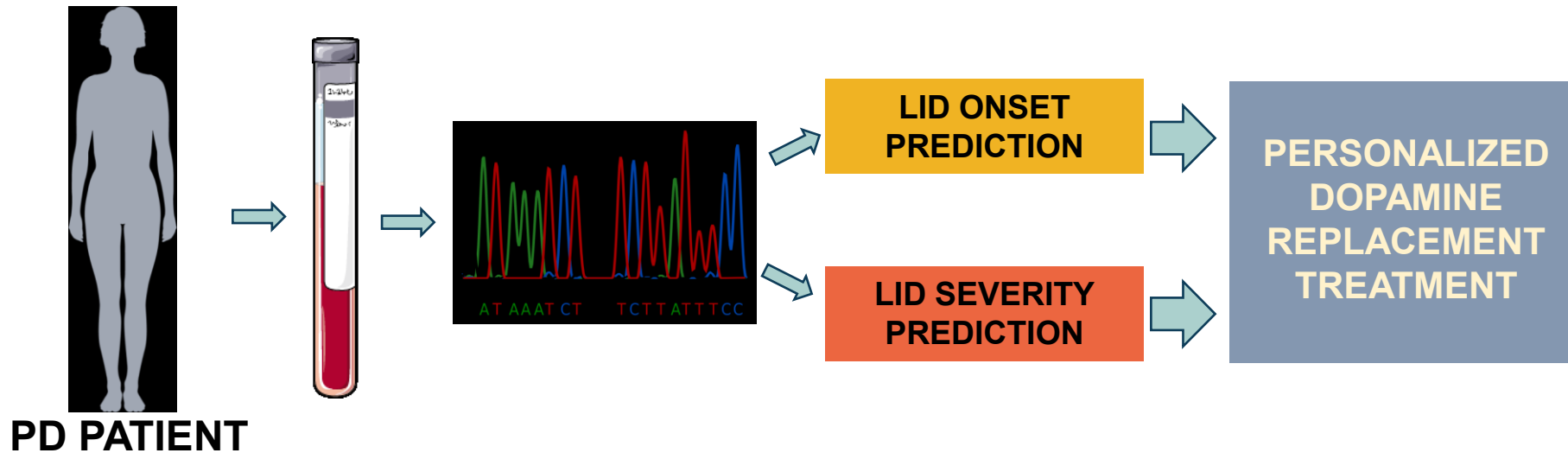


64 GENES
64 SNPs



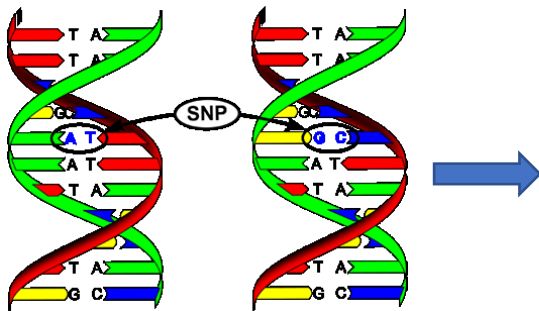
2.2. L-DOPA-INDUCED DYSKINESIA PREDICTOR

- A PREDICTOR FOR LID EARLY ONSET AND SEVERITY IN SUBJECTS DIAGNOSED OF PD BASED ON SNPs COMBINATIONS



2.2. PHARMACOGENETIC LID PREDICTOR

PROOF OF CONCEPT: population of 401 PD patients with recorded DA replacement therapy



SNPS: particular markers in specific genes

LID ONSET PREDICTION

rs1043098 *EIF4EBP2*, rs2043112 *RICTOR*,
rs4790904 *PRKCA*

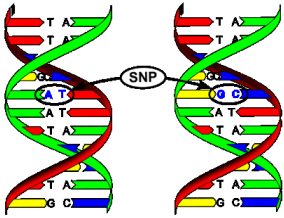
LID SEVERITY PREDICTION

rs1292034 *RPS6KB1*, rs12628 *HRAS*,
rs6456121 *RPS6KA2* and rs456998 *FCHSD1*

Personalized
dopamine
replacement
treatment

SPECIMENS TYPE	DNA (from blood or saliva samples)
INSTRUMENTATION REQUIRED	Thermocycler/PCR machine
TIME REQUIRED	2 hours
ESTIMATED PRICE	Less than 100 Euros

2.2. PHARMACOGENETIC LID SEVERITY PREDICTOR



LID SEVERITY PREDICTION

rs1292034 *RPS6KB1*, rs12628 *HRAS*,
rs6456121 *RPS6KA2* and rs456998 *FCHSD1*

Sensitivity	83,0%
Specificity	85,7%
Precision	86,1%
NPV	83,5%
Accuracy	84,2%

2.3. DIFFERENTIAL FEATURES FACING THE MARKET



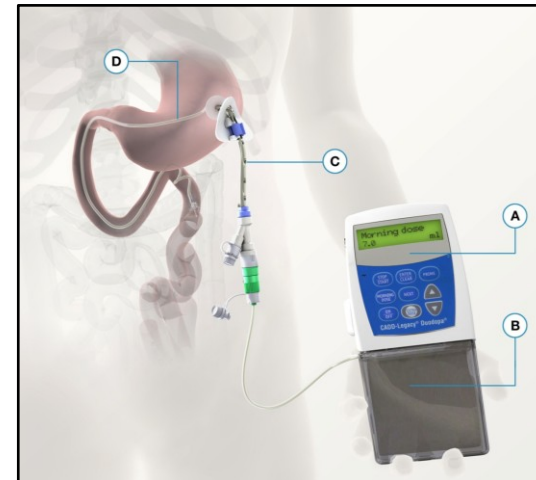
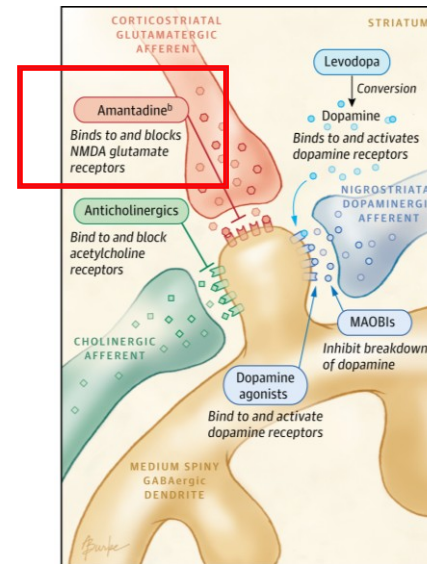
**NO CURRENT PHARMACOGENETIC TEST IN THE MARKET TO
PREDICT DYSKINESIA ONSET/SEVERITY**

2.3. LID TREATMENTS SO FAR

PHARMACOLOGICAL THERAPY

► Medication treatment:

- **Amantadine** is an NMDA receptor antagonist with a promising anti-dyskinetic effect. However, its sustained effect over time is still controversial.

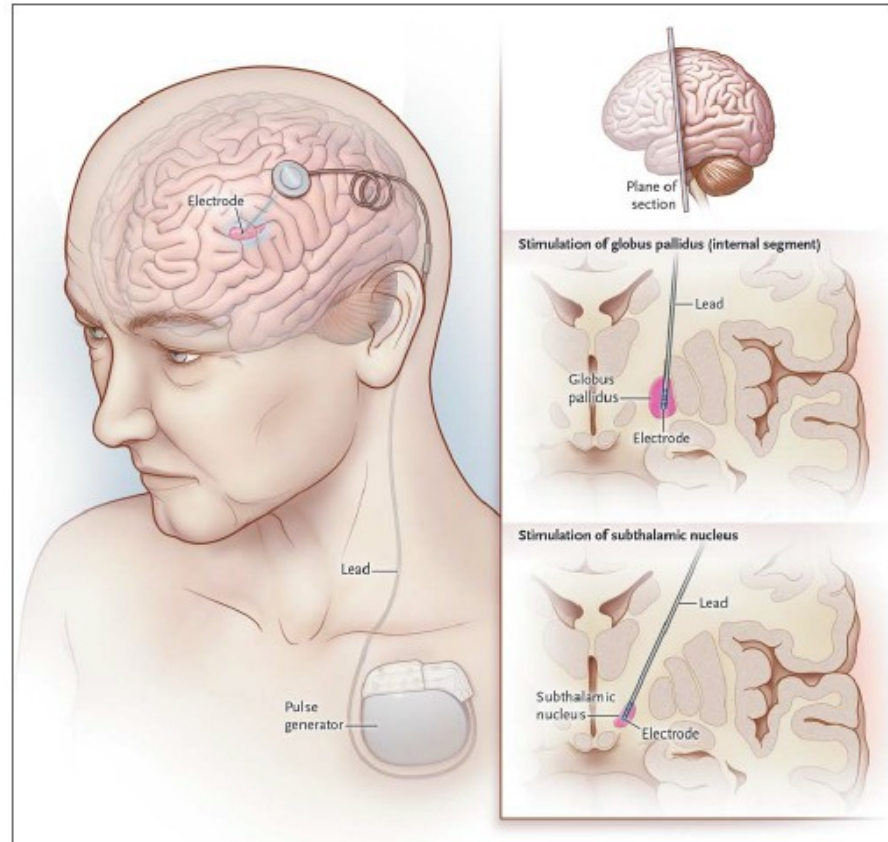


2.3. LID TREATMENTS SO FAR

SURGERY

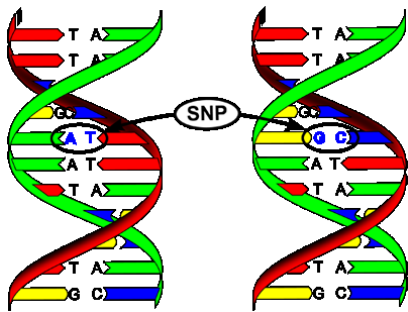
► Surgical techniques:

DBS of GPi or STN are effective treatments but PD patients have to have specific criteria for the surgery. Side effects: infection, hematomas, executive alterations...



2.3. PHARMACOGENETIC LID PREDICTOR

THE ULTIMATE GOAL IS TO AVOID, OR AT LEAST, DELAY THE APPEARANCE AND THE SEVERITY OF LID IN NEWLY DIAGNOSED PATIENTS WITH PD.



SNPS: particular markers
in specific genes



LID ONSET PREDICTION

rs1043098 *EIF4EBP2*, rs2043112 *RICTOR*,
rs4790904 *PRKCA*

LID SEVERITY PREDICTION

rs1292034 *RPS6KB1*, rs12628 *HRAS*,
rs6456121 *RPS6KA2* and rs456998 *FCHSD1*



**Personalized?
dopamine?
replacement?
treatment**

2.4. CURRENT STATUS OF DEVELOPMENT

Market Assessment



Interviews to 3 first-class neurologists expert in PD

1. Head of the Department of Neurology at Virgen de las Nieves University Hospital (Spain):

“The test could be very useful in Clinical Trials of anti-dyskinetic drugs to stratify patients regarding LID risk.”

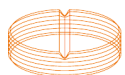
2. Medical Director at Muhammad Ali Parkinson Center at Dignity Health St. Joseph’s Hospital (USA)

“If the risk of developing LID is higher, then we are going to be more conscious in using L-DOPA, and more aggressive in using agonists instead of L-DOPA, and amantadine, and we are going to pay more attention to the patient to prevent them from really get out of hand”

“If it costs 100\$ most people would pay for it (out of the pocket) to know if they are going to develop dyskinesia or not”

3. Consultant neurologist at NHS Greater Glasgow and Clyde (UK)

“The test could be useful to moderate the dose in those patients who request more medication”



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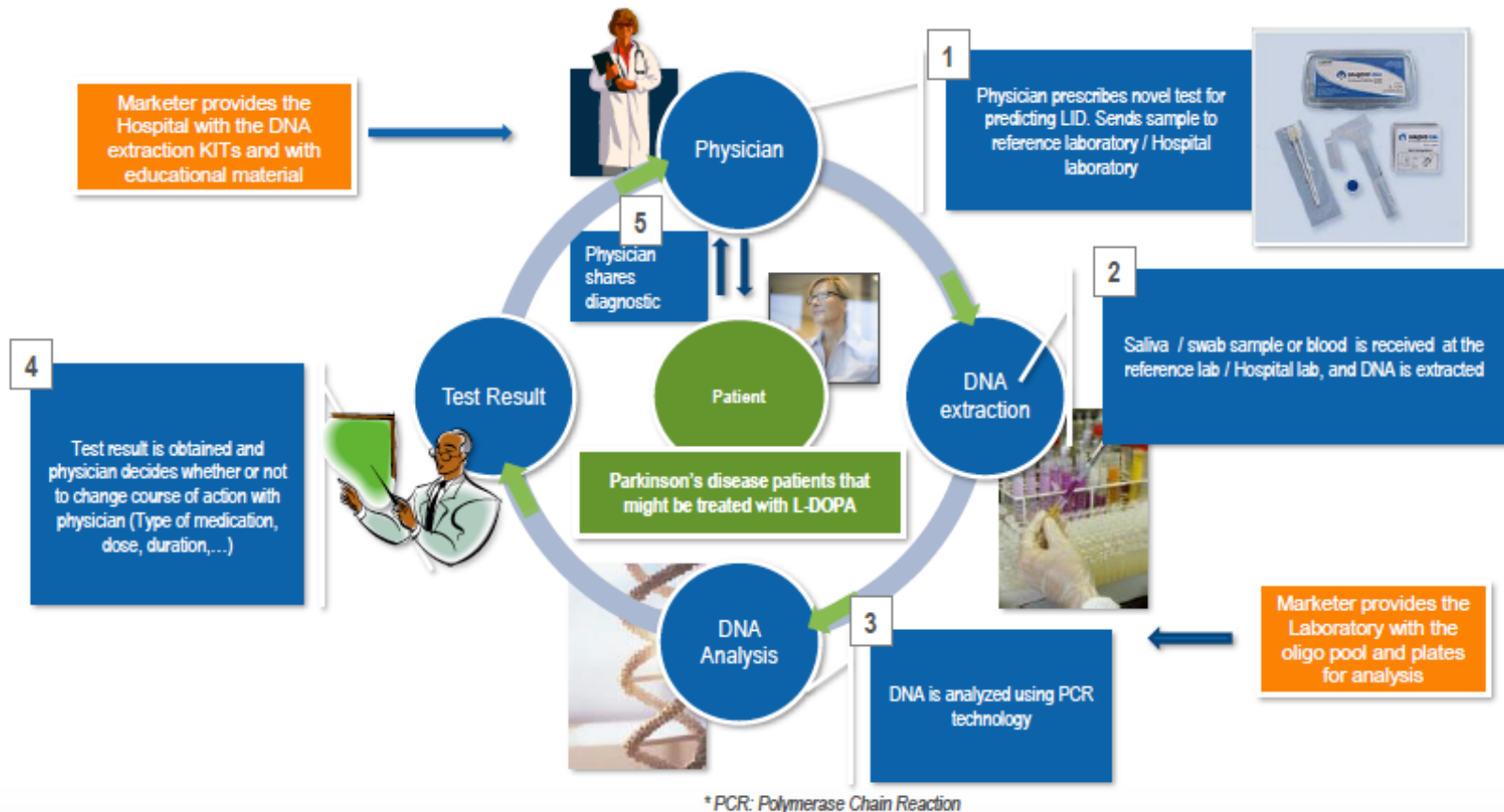


2.4. LID PREDICTOR IMPLEMENTATION

Sent to Experts



Illustration of how the novel test for predicting LID might be used by the prescribers



2.4. CURRENT STATUS OF DEVELOPMENT

PHARMACOGENETIC TEST IMPLEMENTATION: CONVERSATIONS WITH THE CLINICAL BIOCHEMISTRY SERVICE IN THE HOSPITAL CLÍNICA TO RUN THE TESTS (FEASIBILITY, PRICE, DIAGNOSTICS)



2.4. IPR PROTECTION

European Patent Application Filed in EPO – 04/05/2017

1. Title:

- ☐ Method for predicting early onset and severity of Levodopa Induced Dyskinesia (LID) in subjects diagnosed of Parkinson Disease (PD)

2. Applicants:

- ☐ Universitat de Barcelona (UB)
- ☐ Institut d'Investigacions Biomèdiques August Pi i Sunyer
- ☐ Hospital Clínic de Barcelona

3. Subject matter of protection

- ☐ The *in vitro* method based on specific SNP's identification
- ☐ Its applications on selecting PD patients to receive a treatment different from levodopa or on better deciding levodopa dosage

2.4. PITFALLS AND RISKS

1. SNPS VALIDATION IS DIFFICULT IN POPULATIONS WITH VERY DIFFERENT GENETIC BACKGROUND
2. BUDGET MANAGERS IN HOSPITALS/INSURANCE COMPANIES NOT WILLING TO SPEND MONEY FOR THE TEST
3. THE TEST IS NOT A CURE BUT IS A METHOD TO PREVENT WORSENING CONDITIONS
4. NEUROLOGISTS COULD BE HESITANT TO CHANGE THE DOSAGE REGIME/OTHER DA AGONISTS BASED ON THE TEST RESULTS

3. PARTNERING OPPORTUNITIES

3. PARTNERING OPPORTUNITIES

- LICENSE AGREEMENT



- COLLABORATION TO
VALIDATE TECHNOLOGY IN
A SECOND POPULATION OF
PD PATIENTS



ANY
QUESTIONS
?