# MEDICAL GENETICS

Marrow SS Medicine

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//ME801SS-SAP

# Contents

## Clinical Genetics

# PRECISION MEDICINE

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**Case scenario :**

- 2.7 Kg male baby, full term, normal vaginal delivery, exclusively breastfed.
- Born of non consanguineous marriage.
- Presented on day 4 with excessive lethargy, RBS : 40 mg/dL.
- Day 6 : Seizures, hypoglycemia without Ketonuria.

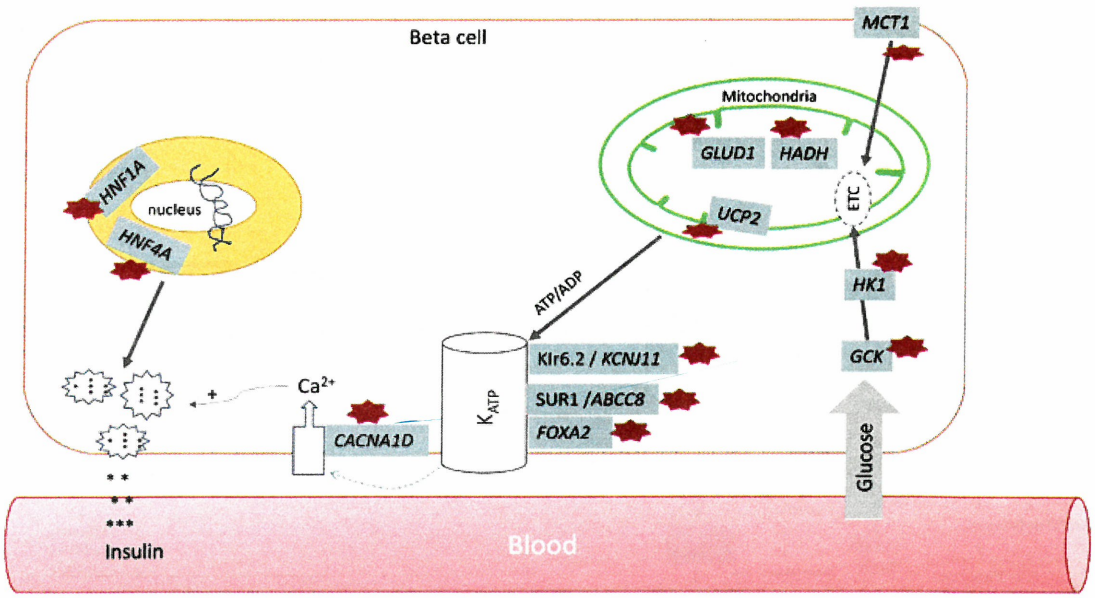
Critical sample :

- C-peptide : 2.72 ng/mL.
- RBS : 22 mg/dL.
- Serum insulin : 13.3 mU/mL.
- Thyroid, cortisol, GH : Normal

Diagnosis : Congenital hyperinsulinemia (Hyperinsulinemic Hyperglycemia/HIH).

Management :

- Diazoxide started : No response.
- Genetic analysis done : Heterozygous for ABCC8 mutation causing diffuse and focal lesions in pancreas.
- ABCC8 mutation is unresponsive to pharmacological treatment and requires pancreatectomy.



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## Precision medicine

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### Definition :

- Tailoring of medical treatment to the individual characteristics of each patient.
- To classify individuals into sub-populations.
- Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.
- Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics.

Personalized medicine vs Precision medicine :

Personalized medicine :

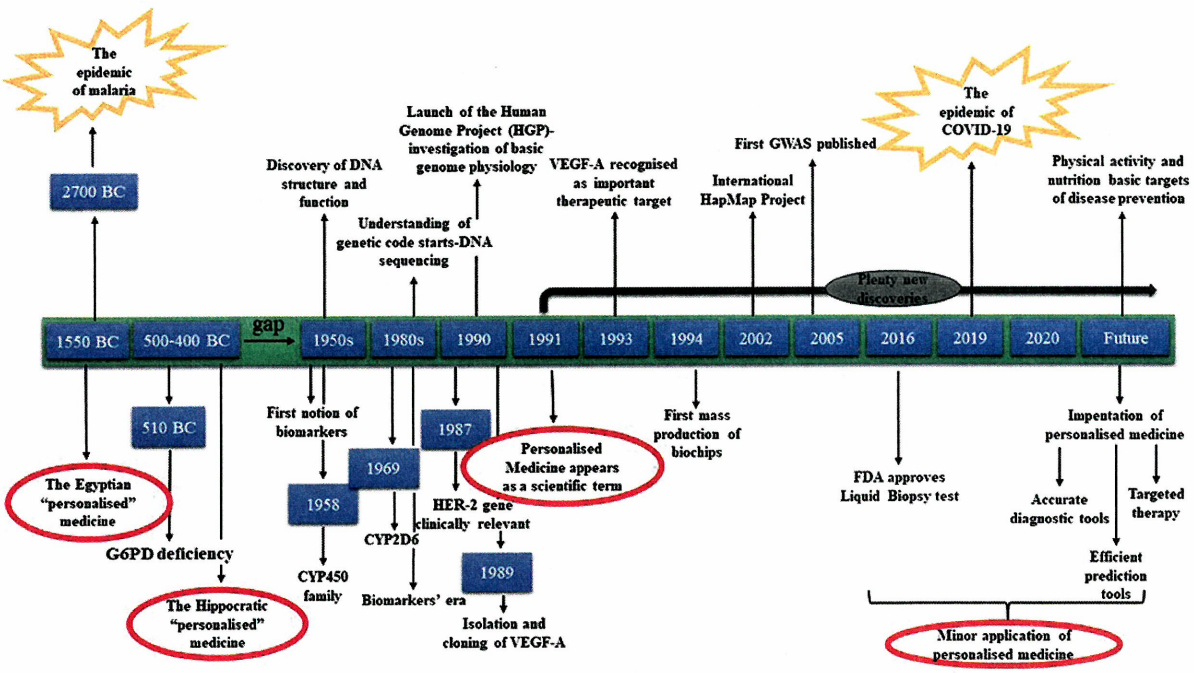
- Approach to patients that considers their genetic make-up but with attention to their preferences, beliefs, attitudes, knowledge and social context.

Precision medicine :

- Model for health care delivery that relies heavily on genomic data, analytics, and information.

Both terms being used interchangeably.

### Evolution :



## Process of precision medicine

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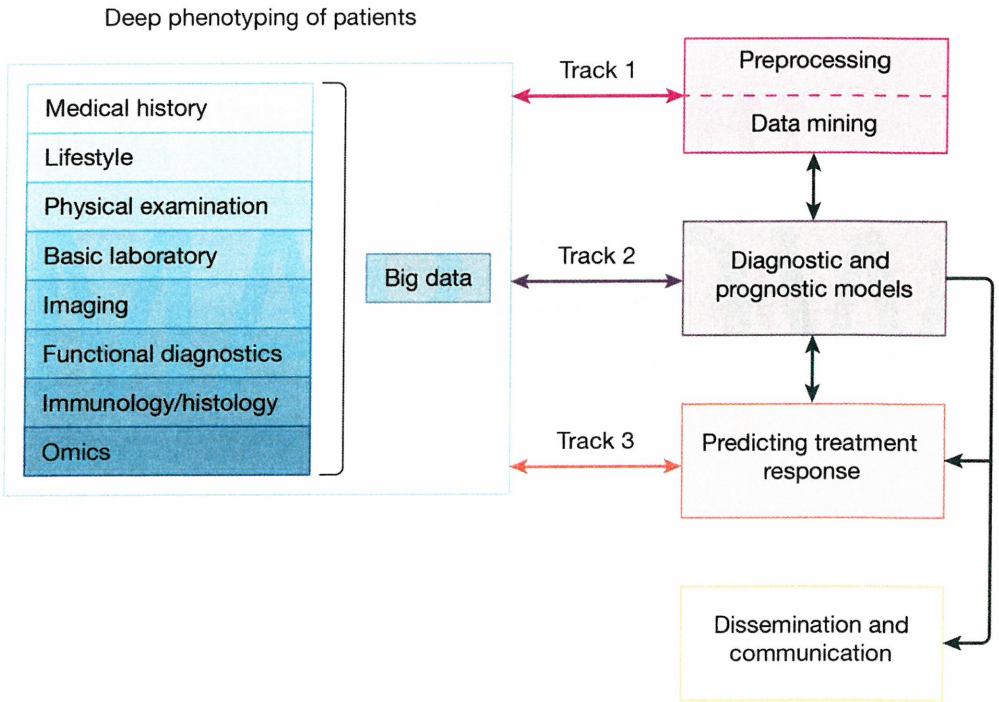


Asthma :

Polymorphisms dictate effect of inhalational corticosteroids.

### Applying precision medicine to asthma

| | Reference | Disease | Variable | Diagnostic and/or prognostic model |
|---|---|---|---|---|
| **Medical history and physical examination** | [9] | Asthma | Age and onset of disease | Within-subject response to montelukast is superior to fluticasone in childhood asthma in younger children and children with a shorter disease duration |
| **Lifestyle** | [10] | Atopic eczema | Cat exposure and genetics | Filaggrin loss-of-function main mutations (501x and 2282del4) and cat ownership at birth interact in their effects on the development of early-life eczema |
| **Basic laboratory tests** | [11-14] | Severe asthma | Eosinophil counts | Eosinophil counts in peripheral blood and/or bronchial lavage are predictors for treatment response to anti-IL-5 |
| **Imaging** | NA | NA | NA | No data available |
| **Functional diagnostics** | [9] | Asthma | Lung function and exhaled NO | Children with asthma respond in a different way to ICS and LTRA using $FEV_1$ as a clinical end-point. High NO levels and decreased lung function are predictors of a better treatment response to ICS |
| **Immunology/histology** | [15] | Asthma | Cytokine levels | Patients with asthma and high pretreatment levels of serum periostin (surrogate marker of Th2 inflammation) had greater improvement in lung function with the monoclonal anti-IL-13 antibody lebrikizumab than did patients with low periostin levels |
| **Omics** | [16] | Asthma | ADRB2 | Substitution at position 16 (rs1042713) in ADRB2 is associated with enhanced downregulation and uncoupling of β2-receptors. The use of a LABA as an "add-on controller" is associated with increased risk of asthma exacerbation in children carrying one or two A alleles at rs1042713 |

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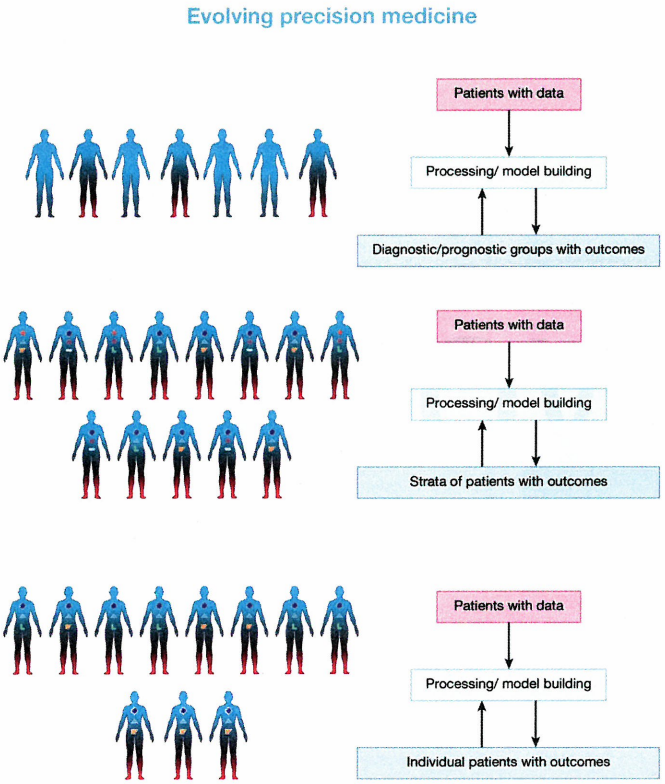
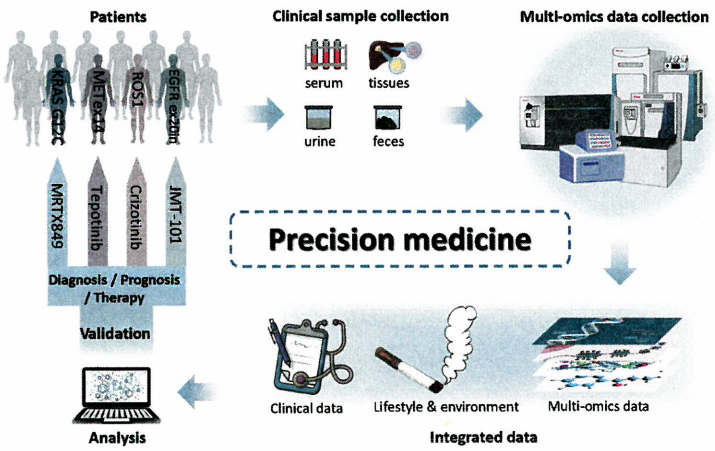



Domains :




## Applications 00:09:44

### Paediatric epilepsies :

more than half of all epilepsies have genetic bases and single gene defects in ion channels or neurotransmitter receptors have been associated with several inherited forms of epilepsy.

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Goals :

- Seizure control.
- Better neurodevelopmental outcome.

Case 1 :

- 3 year old boy, 3rd born of non consanguineous marriage.
- Chief complaints of seizures from past 2.5 years
- Developmental delay
- No family history
- Examination findings : No dysmorphism, no focal deficit, hypotonia.

Semiology :

- First seizure at 6 month following vaccination, hemiclonic.
- Later, seizures were afebrile and myoclonic.

Investigations :

- EEG : Generalized spike wave.
- MRI : No structural abnormality.

Diagnosis : Dravet syndrome (SCNIA).

Dravet syndrome :

SCNIA :

- Loss-of-function of the protein → Reduced activity of inhibitory interneurons → Increase of cortical excitability.
- Truncation mutations and missense variants in the voltage sensor or pore region are more likely to cause a severe phenotype.

Treatment :

Sodium channel blockers :

- Carbamazepine, oxcarbamazepine, phenytoin.
- Some cases of Dravet have paradoxically increased seizure frequency to the sodium channel blockers.
- Higher expression in inhibitory bipolar as compared to excitatory pyramidal neurons, effect of sodium channel blockers on inhibitory interneurons outweighs the effect on excitatory neurons → Decrease in inhibition → Increase of seizures.

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Stiripentol :

- GABAergic effect of stiripentol compensates for the decreased activity of inhibitory interneurons.

Fenfluramine :

- Serotonergic effects but the exact anti-convulsive mechanism has not been elucidated yet.

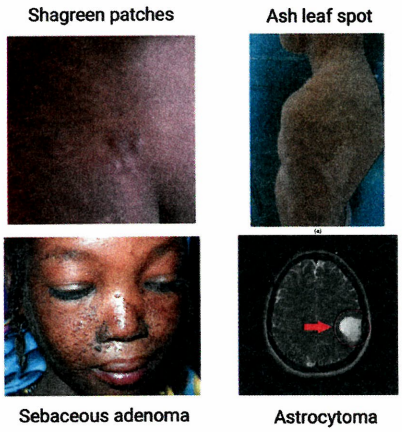
Case 2 :

History :

- 6 year old boy 1st born to non-consanguineous marriage.
- Chief complaint of infantile spasms since 1 month of life.
- Development delay.
- No seizures in family.

On examination :

- Ash leaf macule, CNS normal.
- Mother has ash leaf macules.




Semiology : Initially infantile spasms, later complex partial seizures, not responding to anti-epileptic drugs.
EEG : Hypsarrythmia.
MRI : Cortical tubers, subependymal nodules.

Diagnosis : Tuberous sclerosis (TSC1, TSC2).

Tuberous sclerosis :

mTOR :

- Mutations in TSC1 and TSC2 → mTOR overactivity → Occurrence of tumors.
- Patients with TSC2 mutations are more likely to develop epilepsy.
- Treatment : mTOR inhibitor Everolimus effectively reduces subependymal giant-cell astrocytoma volume and seizure frequency.

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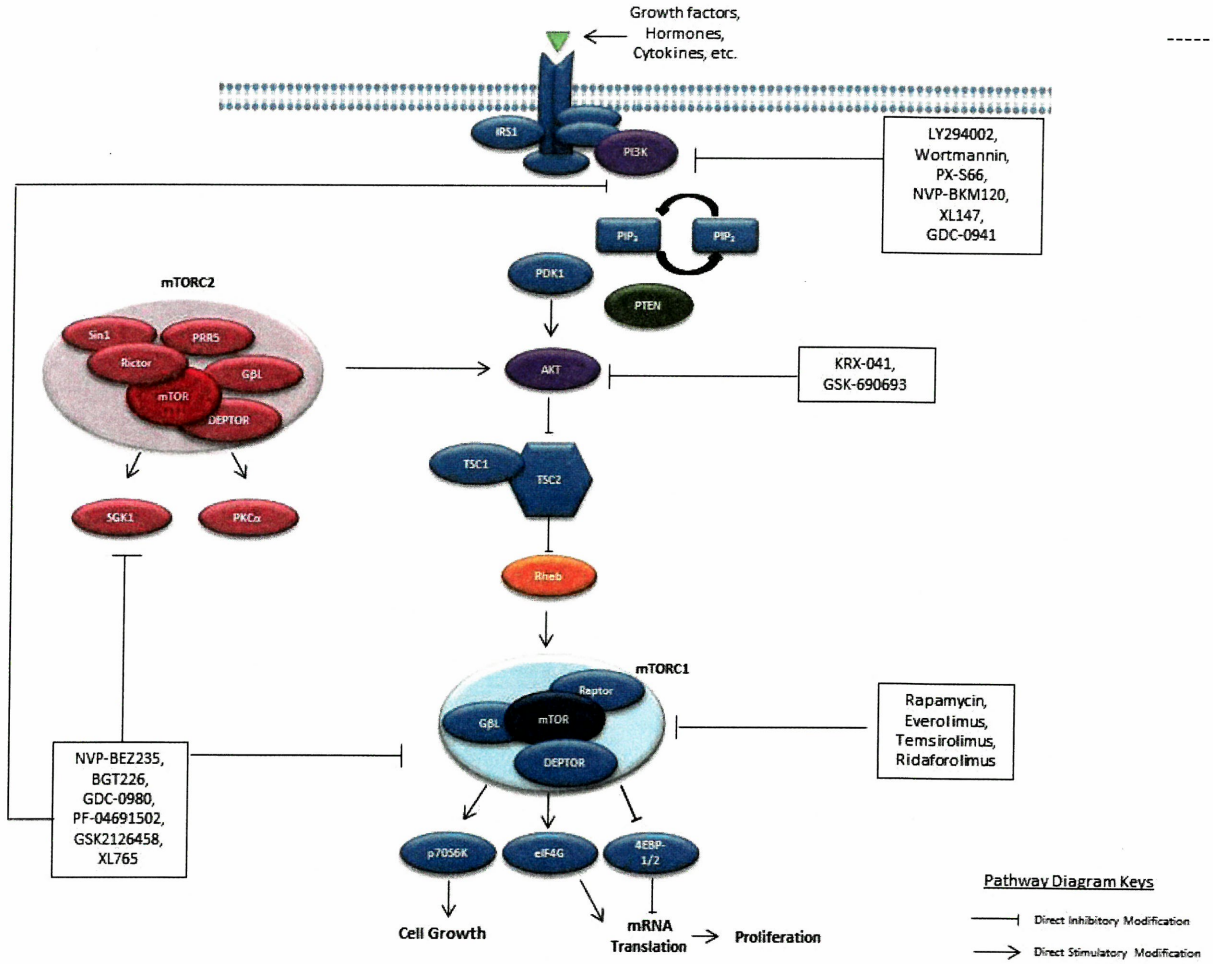
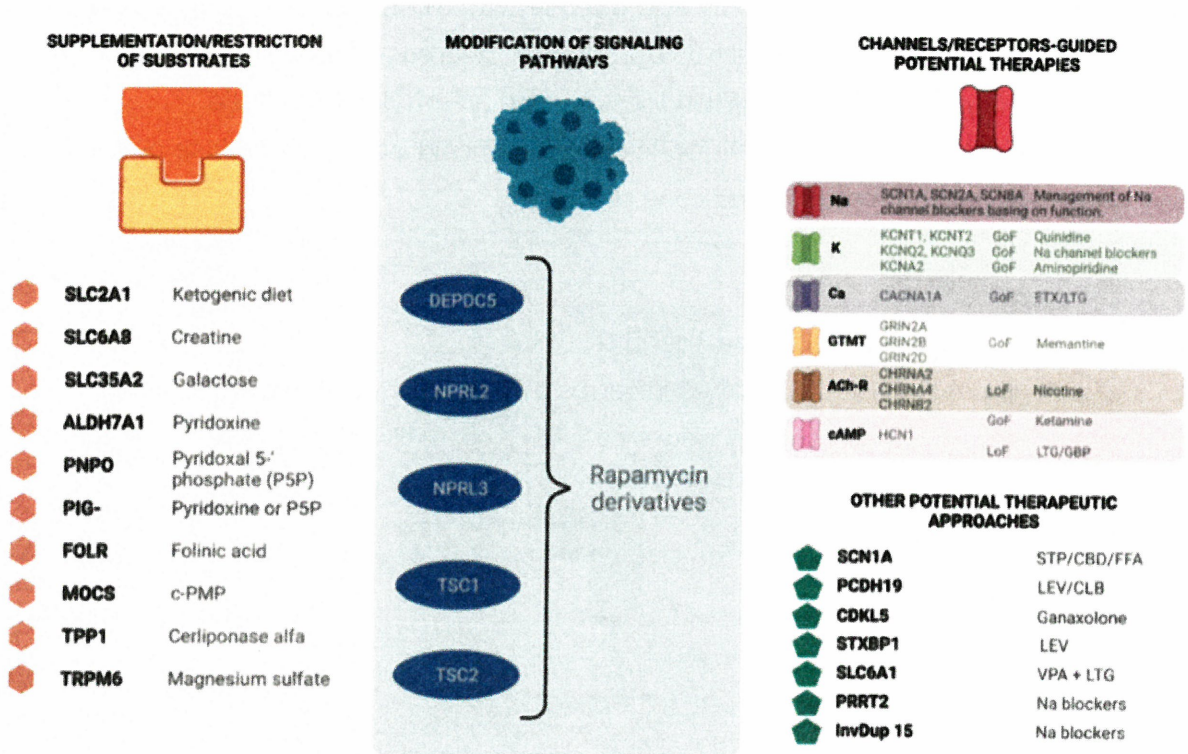



## Precision medicine in pediatric epilepsies :



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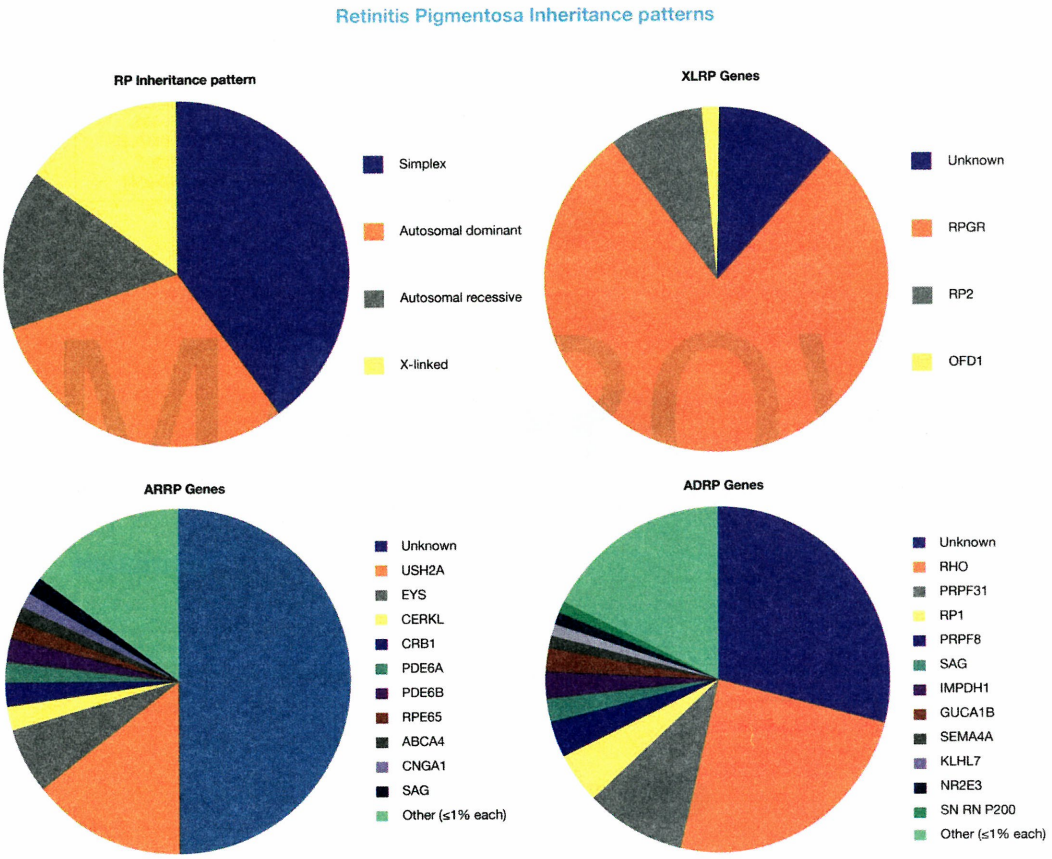
## Retinitis pigmentosa :




## Leber's Congenital Amaurosis (LCA) :

- Heterogeneous group of eye disease with mostly autosomal recessive.
- Clinical features : Nystagmus, severely decreased visual acuity in early infancy and complete blindness by the 3rd–4th decade of life
- RPE65 associated LCA : Deficiency of retinoid isomerohydrolase of the retinal epithelium result in rod cone dystrophy.

Treatment :

- US FDA approved gene therapy Luxturna.
- Improved visual outcomes in terms of improved visual acuity and light sensitivity threshold 2 years post infusion, with static course beyond.
- Subretinal injection after vitrectomy in each eye.

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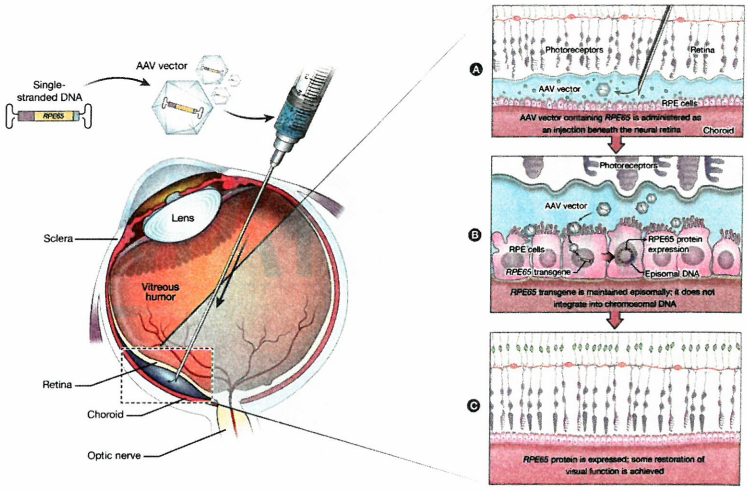
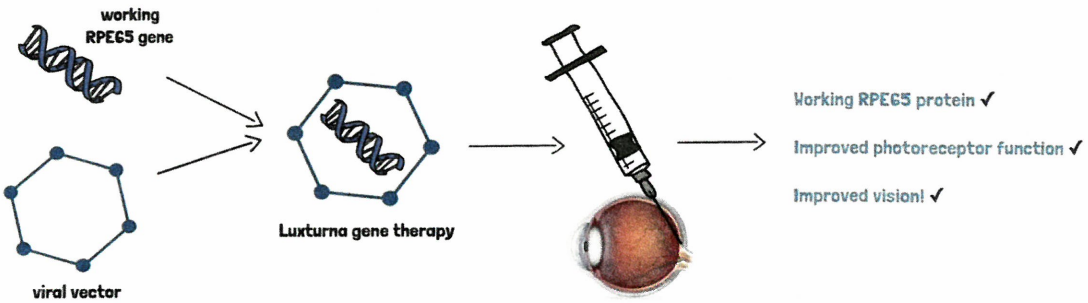
## Human gene therapy for RPE65-associated Leber's congenital amaurosis




Subretinal injection after vitrectomy




Luxturna

### Marfan syndrome :

- AD, connective tissue disorder.
- Pathogenic variants in FBN1 gene
- Aortic root dilation : Losartan v/s Atenolol.
- PHN study : No difference in the rate of aortic dilation.

Atenolol :

- ADRB1 variants
- ADRB1-rs1801253 CC > CG/GG types.
- Better response to atenolol.

Losartan : CYP2C9 variants.

No difference in response.

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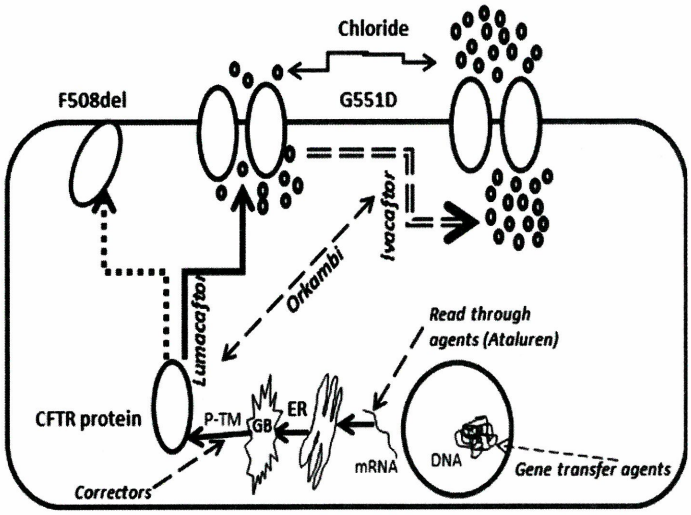
## Cystic fibrosis :

AR. variants in CFTR gene.

| Subcategory | Functional effect | Example variant |
|---|---|---|
| I | No functional protein | G542x |
| II | Trafficking defect | F508del |
| III | Defective regulation | G551D |
| IV | Decreased conductance | R117H |
| V | Reduced synthesis | 3120+1G >A |
| VI | Reduced stability | Q1412x |

Targeted therapy :




Impact of CFTR modulator use on outcomes in people with severe cystic fibrosis lung disease :

- FEV1 % predicted : >10% absolute increase.
- 55% reduction in exacerbations.
- Increase in weight and quality of life.
- >10% (absolute) over placebo in forced expiratory volume in 1 s (FEV1) % predicted and a 55% reduction in the frequency of pulmonary exacerbations.
- IVA treatment also resulted in an increase in weight and respiratory-related quality of life.

## Oncology :

Introduction of tyrosine kinase inhibitor imiatinib in chronic myeloic leukemia, as monotherapy can lead to long lasting molecular remission.

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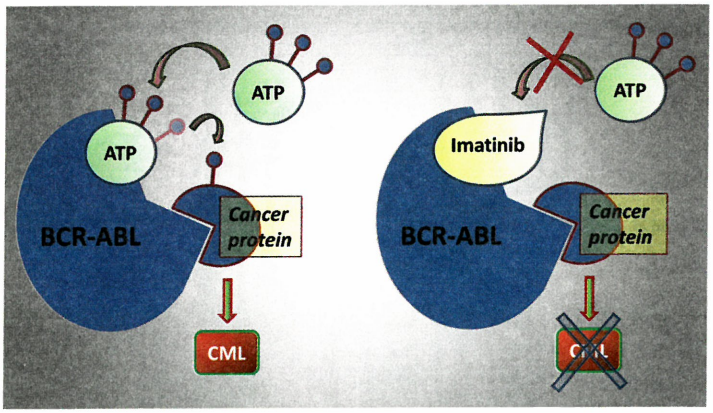


| Inhibitor target | Example molecular biomarkers | Example therapeutics | Example paediatric tumors |
|---|---|---|---|
| ALK | ALK mutation/fusion<br>NTRK1/2/3 fusion<br>ROS1 fusion | Crizotinib | Neuroblastoma<br>Embryonal sarcomas |
| SMO | PTCH1 mutation<br>SUFU mutations<br>GLI1 amplification | Vismodegib | Medulloblastoma |
| PARP1 | BRCA1/2 mutation<br>EWSR1-FLI1 fusion<br>ATM mutation | Olaparib<br>Rucaparib | Ewing Sarcoma |
| Multikinase inhibitors | FLT3 mutation or internal tandem | Sorafenib | AML |

## Fabry's disease :

Case :

- 7 years boy, born to non-consanguineous couple.
- Symptomatic from 6 years of age with skin lesions, acroparesthesias, hypo-hidrosis.
- Normal vision and hearing, without seizures/neurological deficits.
- Similar findings in the elder brother.

Diagnosis : Fabry Disease .

### Pharmacological chaperones :

- Missense variants may cause protein misfolding, which might lead to premature degradation.
- Pharmacological chaperones may interact with the mutant enzyme and prevent or delay its degradation.
- Eg : Migalastat used in Fabry disease.

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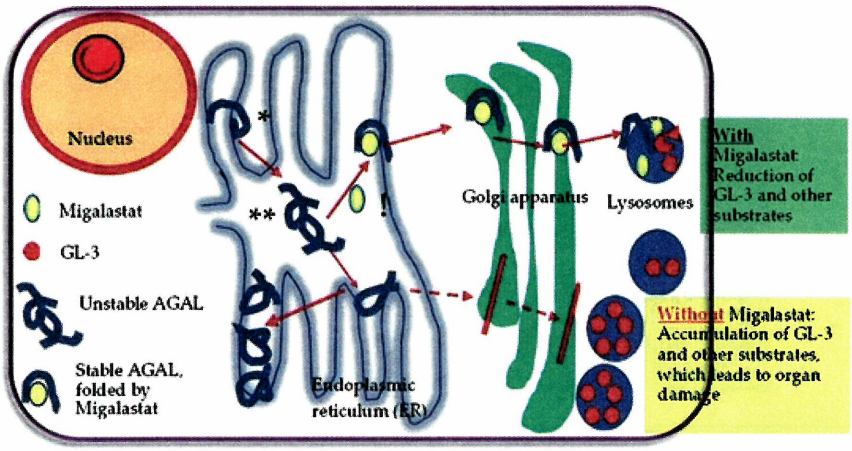


## Amenable GLA variants based on the in vitro assay

| DNA Change (Long) | DNA Change (Short) | Protein Change (1-letter Code) | Protein Change (3-letter Code) |
|---|---|---|---|
| c.43G>A | c.G43A | p.(A15T) | p.(Ala15Thr) |
| c.44C>G | c.C44G | p.(A15G) | p.(Ala15Gly) |
| c.53T>G | c.T53G | p.(F18C) | p.(Phe18Cys) |
| c.58G>C | c.G58C | p.(A20P) | p.(Ala20Pro) |
| c.59C>A | c.C59A | p.(A20D) | p.(Ala20Asp) |
| c.65T>G | c.T65G | p.(V22G) | p.(Val22Gly) |
| c.70T>C or c.70T>A | c.T70C or c. T70A | p.(W24R) | p.(Trp24Arg) |
| c.70T>G | c.T70G | p.(W24G) | p.(Trp24Gly) |
| c.72G>C or c.72G>T | c.G72C or c.G72T | p.(W24C) | p.(Trp24Cys) |
| c.95T>C | c.T95C | p.(L32P) | p.(Leu32Pro) |
| c.97G>T | c.G97T | p.(D33Y) | p.(Asp33Tyr) |
| c.98A>G | c.A98G | p.(D33G) | p.(Asp33Gly) |

### Duchene muscular dystrophy (DMD) :

Mutations in DMD gene :

- Largest human gene : 79 exons (2.2 Mb).
- High mutation rate.
- 1/3rd cases : De novo mutation.
- Large variation of mutations.
- Majority of patients : Deletion (68%) or duplication (11%), small mutations (20%).
- If no mutations are found : Intronic location <0.5%/under-represented.

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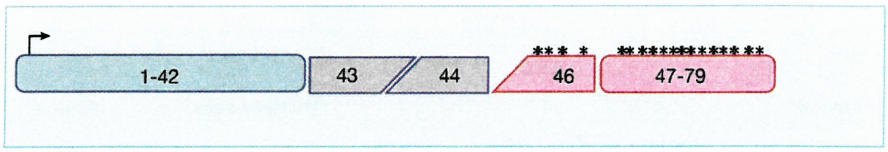
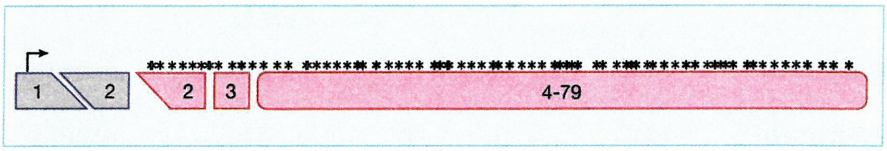
## Mutations in DMD gene

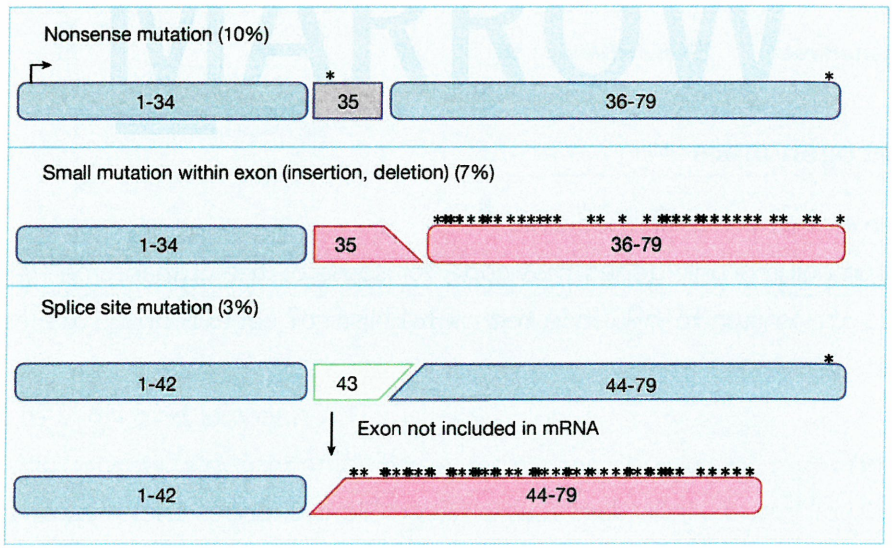
**A** Deletion of one or more exons (68%)

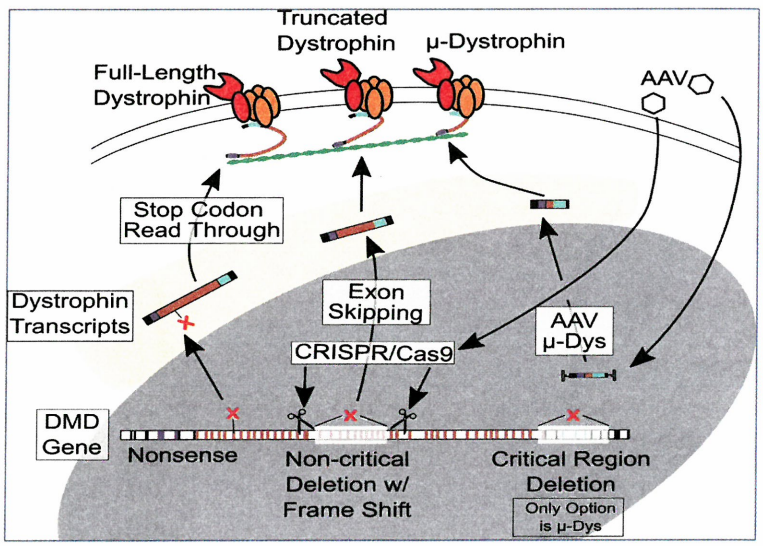



**B** Duplication of one or more exons (11%)




**C** Small mutations (20% )



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Targeted therapy :

- Despite FDA approval evidence for clinically meaningful response is lacking.
- Cost exorbitent .

| Name | ASO | | | Target exon | Phase |
|---|---|---|---|---|---|
| | Nucleic acid | Size | Route | | |
| **Eteplirsen** | PMO | 25 | IV | 51 | Approved |
| **Golodirsen** | PMO | 25 | IV | 53 | Approved |
| **Viltolarsen** | PMO | 21 | IV | 53 | Approved |
| **Casimersen** | PMO | 25 | IV | 45 | Approval stage |
| **Renadirsen** | ENA/2'RNA | 18 | SC | 45 | I/II |

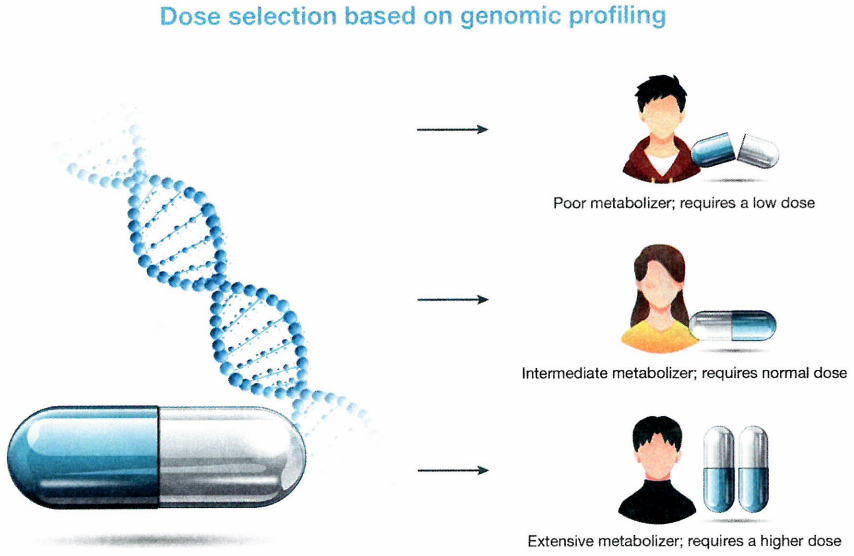
## Pharmacogenomics

00:29:14

Core element of precision medicine.
Variants in polymorphic genes that code for some of the cytochrome P450 (CYP) enzymes are known to influence the metabolism of certain drugs are called pharmacogenes.

**Definition :**

The study of how an individual's genomic profile influences their response to medications is called pharmacogenomics (PGx), which is a core element of precision medicine.



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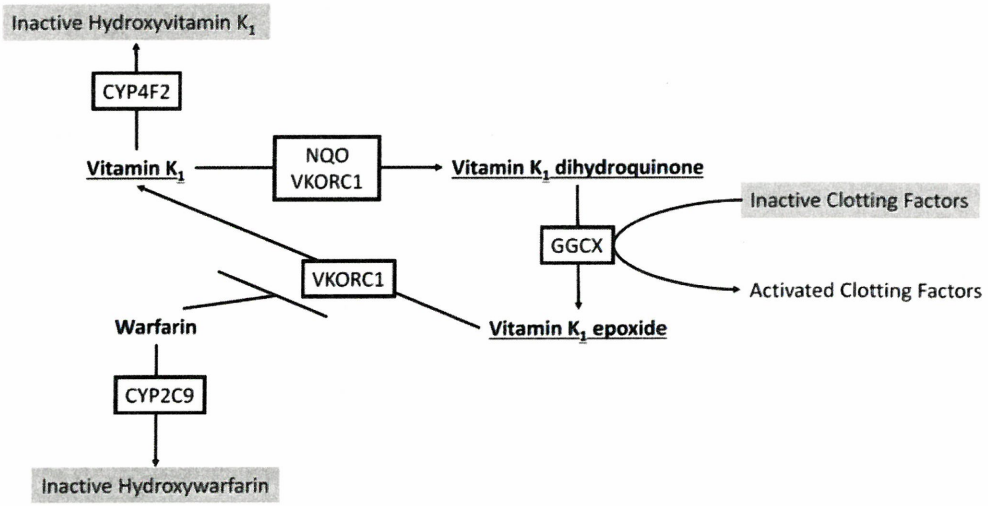
## Warfarin :

VKORC1 variant : Lower activity of drug target.
Longer time of drug action.

CYP2C9 variant : Intermediate or poor metabolism.
Long plasma retention of drug.

CYP4F2 variant : Decreased vitamin K metabolism.
Higher warfarin dose.




**Three Ranges of Expected Maintenance COUMADIN Daliy Doses Based on CYP2C9 and VKORC1 Genotypes†**

| VKORC1 | CYP2C9 | | | | | |
|---|---|---|---|---|---|---|
| | *1/*1 | *1/*2 | *1/*3 | *2/*2 | *2/*3 | *3/*3 |
| GG | 5-7 mg | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | 0.5-2 mg |
| AG | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg |
| AA | 3-4 mg | 3-4 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg | 0.5-2 mg |

†Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

Dosage and administration :
Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.

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Indian data :

The GSA Analysis has revealed that CYP4F2 V433M (MAF: 39.425%), VKORC1 1639 G > A (MAF : 20.5%), CYP2C9*3 (MAF : 9.925%, and CYP2C9*2 (MAF : 4.575%) are common in Indian population.

## Gaucher disease :

Eliglustat therapy and CYP2D6 genotype.

| CYP2D6 metabolizer status | Eliglustat dosage |
|---|---|
| Ultrarapid metabolizer | May not achieve adequate concentrations |
| Normal metabolizer | 84 mg twice daily |
| Intermediate metabolizer | 84 mg twice daily |
| Poor metabolizer | 84 mg once daily |
| Indeterminate metabolizer | Specific dosage cannot be recommended |

| Class | Drug | Gene | Actionable Result | Guideline Availability | | Therapeutic Recommendations [1] |
|---|---|---|---|---|---|---|
| | | | | DPWG | CPIC | |
| Lipid lowering agents | Atorvastatin | *SLCO1B1* | rs4145096 (521T > C) carriers | √ | - | AD |
| | Simvastatin | *SLCO1B1* | | √ | √ | LD, AD, M |
| Antidepressants | Citalopram | *CYP2C19* | PM, UM | √ | √ | LD (PM), AD (PM, UM) |
| | Sertraline | *CYP2C19* | PM, UM | √ | √ | LD (PM), AD (PM, UM) |
| | Amitriptyline | *CYP2C19*<br>*CYP2D6* | PM, RM, UM<br>IM, PM, UM | -<br>√ | √<br>√ | LD (PM), AD (PM, RM, UM)<br>LD (IM, PM), AD (PM, UM) |
| Analgesics | Codeine | *CYP2D6* | IM, PM, UM | √ | √ | AD (UM, PM), M (IM) |
| | Tramadol | *CYP2D6* | IM, PM, UM | √ | - | AD (IM, PM, UM),<br>ID (IM, PM), LD (UM) |
| Anti-platelet | Clopidogrel | *CYP2C19* | IM, PM | √ | √ | AD |
| Anticoagulant | Warfarin | *VKORC1*<br>*CYP2C9*<br>*CYP2C* region | *VKORC1 c.-1639G > A*<br>**2, *3, *5, *6, *8, *11*<br>rs12777823 | √<br>√ | √<br>√<br>√ | LD [2]<br>LD [2]<br>LD |
| Anticonvulsant | Carbamazepine | *HLA-B*<br>*HLA-A* | *HLA-B*15:02* detected<br>*HLA-A*31:01* detected | -<br>- | √<br>√ | AD, M<br>AD, M |
| Antibiotic | Flucloxacillin | *HLA-B* | *HLA-B*57:01* detected | √ | - | AD, M |

## Challenges :

- Evidence generation and building expertise.
- Patient involvement.
- Cost of new medicines.
- Legal and ethical issues.
- Health care provider expectations on earlier access of new medicines.