INTERINDIVIDUAL VARIABILITY IN DRUG RESPONSE
Variation in Drug Response

Gender
Disease
Body Mass
Interactions
Variation in Drug Response
Agents
Genetic Factors

Reported to account for 20-95% of these variability


Awareness of influence of genes on drug action → PHARMACOGENETICS

Deals with causal relation between the genotypic differences among individuals and variation in their drug response in terms of efficacy, toxicity → selection, personalization, dose adjustments …

When totality of an individual’s genetic make-up was mapped → GENOME

20,000-25,000 → 20,000 protein-coding genes
3 billion DNA base pairs → 4 letter language
Nucleotide sequence → 99% alike & differ by 1%
90% (>10 million) → SNPs

Their % in population & in different ethnicity

Reported to account for 20-95% of these variability

PHARMACOGENOMICS

Deals with the impact of diverse, multiple genes within an individual’s genome, on his variability in response to a specific drug, in the context of the genomic variation in the whole population

IMPACT OF GENOMICS
On CV THERAPY

Choosing right drug, in right dose to the right person

Genomic Information
Obtained from Patient’s Genomic Makeup
to predict outcomes to refine therapeutic selection
Retrieved from Populations to drive drug research, design → enabling drug companies to launch NEW drugs that “BEST FIT” to patient’s genomic variations

A rare variants in PCSK9 → associated with low LDL in African-Americans → so lead to development of PCSK9-Inhibitors.
Is significant in response to clopidogrel, warfarin, statins & some β-blockers / antiarrhythmics
Is on lesser scale with, hydralazine, ACE Is , ARBS, isosorbide dinitrate, aspirin, prasugrel, ticagrelor, dabigatran

INTERPATIENT VARIABILITY
Polymorphisms exits in
- Transporters
- Enzymes
- Linkers
- Receptors
- Signaling Molecules

Patients → No benefits / Develop intolerable or serious ADRs

PREDICT HAZARDS TO BE AVOIDED FOR BETTER SAFETY

GUIDE THE THERAPEUTIC SELECTION FOR BETTER EFFICACY

STATI → OATP1B1 Hepatic Transporter → entry of statins in liver
SLOC1B1 gene
(rs2900478) SNPs (rs4363657) / (rs4149056) ⇒ CC, CT & TT variants
CC variant ⇒ ↓ Statin hepatic transporter function
↑ Circulating blood levels
↑ risk of muscle toxicity than TT

SEARCH Trial a GWAS done to correlate development of MYOPATHY
- Simvastatin 40mg ⇒ 221% higher in CC vs TT
- Atorvastatin 20mg ⇒ 144% higher in CC vs TT
- Rosuvastatin 40mg ⇒ 117% higher in CC vs TT

Was associated with a smaller LDL-C reduction in response to statin therapy

Was associated with

Guide the Therapeutic Selection for better Efficacy
**PREDICT HAZARDS TO BE AVOIDED FOR BETTER SAFETY**

**GUIDE THE THERAPEUTIC SELECTION FOR BETTER EFFICACY**

**WARFARIN (DYNAMIC)**
Inhibits VK epoxide reductase (VKORC1)

**VKAS (KINETIC)**

Is metabolized by CYP2C9 → Inactive

Two variants CYP2C9*2, CYP2C9*3

<table>
<thead>
<tr>
<th></th>
<th>Asians</th>
<th>Caucasians</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2: Arg144Cys</td>
<td>4%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>*3: Ile359Leu</td>
<td>8%</td>
<td>16%</td>
<td>6%</td>
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</table>

**WARFARIN RESISTANCE**

Dose requirements → approximately 20% lower with CYP2C9*2

35% lower with the CYP2C9*3 compared with the CYP2C9*1

**REGULATIONS SET:**

Recommended warfarin starting dose in mg/day according to VKORC1 and CYP2C9 genotypes per the FDA-approved warfarin labeling

<table>
<thead>
<tr>
<th>VKORC1 -1639</th>
<th>CYP2C9</th>
<th></th>
<th></th>
<th></th>
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<tr>
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<td>*1/*2</td>
<td>*1/*3</td>
<td>*2/*2</td>
<td>*2/*3</td>
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<td>5–7</td>
<td>3–4</td>
<td>3–4</td>
<td>0.5–2</td>
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<tr>
<td>AG</td>
<td>5–7</td>
<td>3–4</td>
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<td>0.5–2</td>
<td>0.5–2</td>
</tr>
<tr>
<td>AA</td>
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<td>3–4</td>
<td>0.5–2</td>
<td>0.5–2</td>
<td></td>
</tr>
</tbody>
</table>

- **FDA 2010:** dosing table based on CYP2C9 & VKORC1 genotypes
- **Prescribing instructions** for necessity to conduct pretreatment testing
- **Routinely genotype** all patients newly starting warfarin during hospitalization for CYP2C9 and VKORC1 variants

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GUIDE THE THERAPEUTIC SELECTION FOR BETTER EFFICACY

CLOPIDOGREL

PY12 receptor antagonist
[C34T & G52T]

\[ \uparrow \text{platelet reactivity} \]

Lack of efficacy

(\textit{DYNAMIC})

(IS a PRODRUG $\rightarrow$ ACTIVATED BY CYP2C19 ENZYME)

Three variants CYP2C19*2, CYP2C19*3, CYP2C19*17

\[ \downarrow \text{681G}$\rightarrow$A Splicing defect in Caucasians:15%, Asians: 40%, Africans:25%, Native Americans:20%} \]

 Leads to loss of enzy. function

So drug exhibits lack of efficacy

FDA; In 2010 issued a boxed warning indicating potential reduced efficacy (increased thrombotic outcomes) based on CYP2C19 genotype

CPIC; Necessitates the need for alternative therapy in post-ACS patients or in those undergoing PCI.

AHA & ACC issued a clinical alert to provide physicians with guidance on the necessity of genotyping for CYP2C19 in clopidogrel-treated patients

**Clinical implementation of** CYP2C19 genotyping in patients started on the drug to assist with antiplatelet selection after PCI.

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$\beta$-

Many genes were found to induce survival differences with $\beta$-blockers were given in hypertension & HF

**ADRB1** $\leftarrow$ ADRB1, ADRA2C, GRK5, and GRK4

\[ \downarrow \text{Associated with hypertension + } \uparrow \text{risk of HF outcomes & death} \]

Bucindolol proved superiority benefits $\rightarrow$greatest $\downarrow$BP & HF outcomes

**GENOTYPE TARGETED CLINICAL TRIALS**, (enrolling bucindolol vs SR metoprolol only those patients with ADRB1 Arg389Arg genotype $\rightarrow$ for FDA approval

**CYP2D6** Deletion & duplication polymorphisms $\rightarrow$ Loss of function $\rightarrow$ Poor Metabolizers $\rightarrow$ Lead to side effects. $??????$

**No clinical implications** $\rightarrow$ because it undergoes dose titration $\rightarrow$ beats/min $\rightarrow$minimizing impact of pharmacokinetic differences

**ACE**

ACE ENZYMES I/D polymorphism $\rightarrow$ 287 base-pair difference

DD; $\uparrow$ ACE activity

DD is in $>30\%$ population

Strong susceptibility to: LVH, IHD, restenosis cardiomyopathy / IR & Diabetes, Nephropathy

These patients WILL NOT BENEFIT from ACE Is
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**Barriers**
- Information
- Technical standardization
- Costs
- Industrial; >blockbuster drugs

**Challenges**
- Regulatory
- Ethical
- Legal

**CLINICAL IMPLEMENTATION**

Admit that the extraordinary progress in genomic science, coupled with the declining cost of sequencing technologies, has turned Genomic impact on **OPTIMIZING THERAPY** into a reachable reality.

Yet it seems that the unresolved constrains did delay the time-line of arrival to final destination: Personalized CV Therapy.
THANK YOU
Prof. Omnia Nayel