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Personalised Medicine(PM): Clinical Trial Design Considerations and Statistical Aspects

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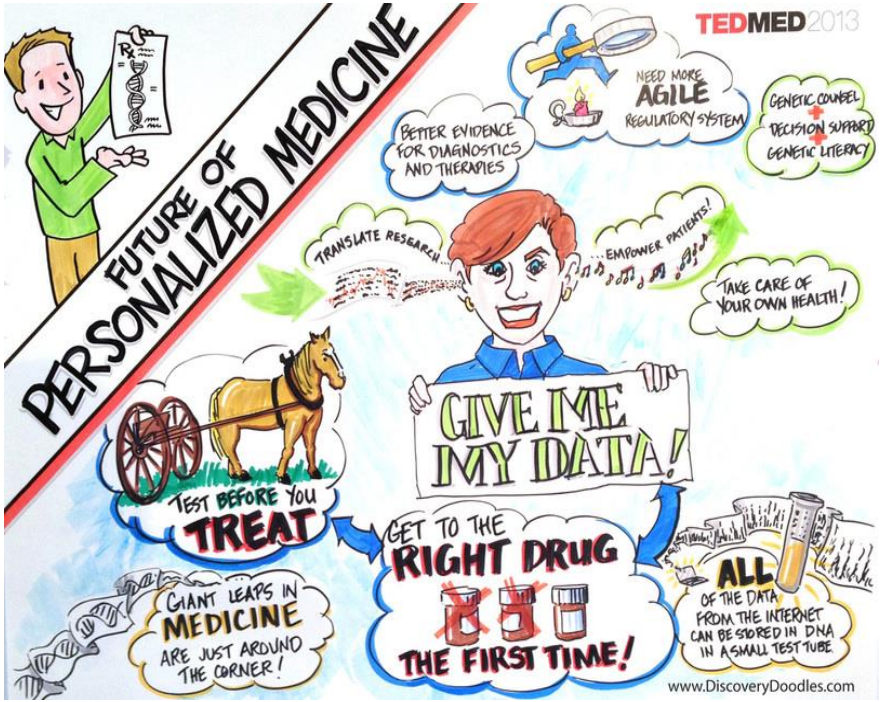
Agenda

- Introduction, Definition and Need
- Clinical Trial Design Considerations
- Statistical Aspects and Challenges
- Advantages
- Q&A

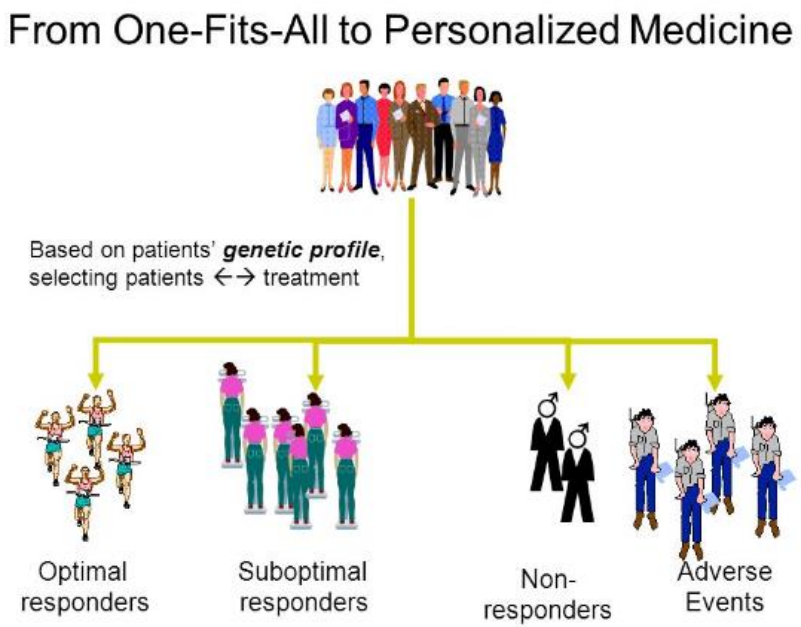
Introduction

- Concept dates back to many hundreds of years
- Underlying causes of diseases
- Sequencing of human genome set in motion the transformation of personalised medicine from an idea to a practice



Definition

- Right patient with the right drug
  at the right dose at the right time
- Tailoring of medical treatment to the individual characteristics, needs and preferences
- Science of individualised prevention and therapy



Single Nucleotide Polymorphism

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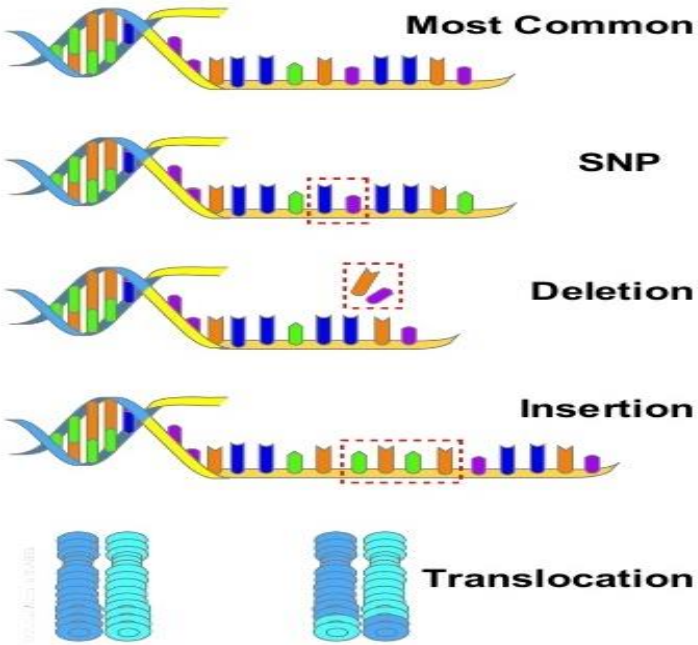
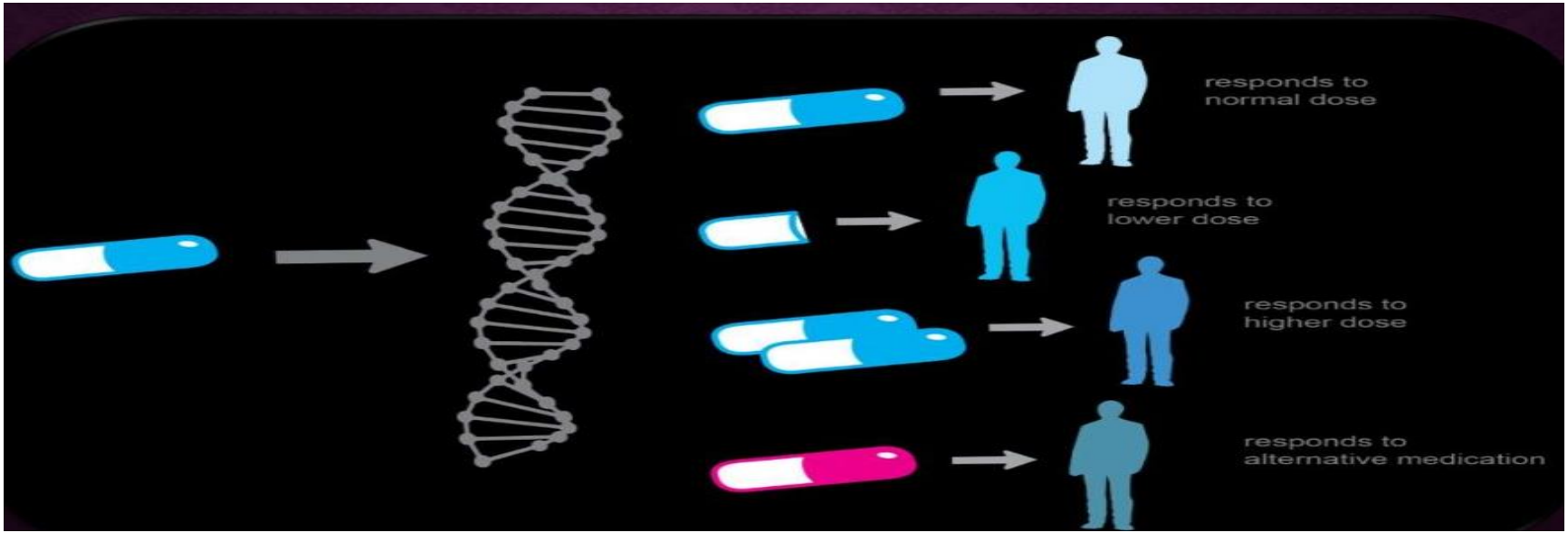
Single Nucleotide Polymorphism(SNP):
Major source of variation:

- Single base change- AAGCCTA to AAGCTTA
- Mistake during normal DNA replication
- Copy number variations



Diversity in Responses

- Due to variation in gene



What to Consider ?

- Identify high-risk group who can benefit more
- Investigators need to clarify the purpose and scale of the trial
- FDA strongly encourages randomised trials that include both biomarker-positive and biomarker-negative patients
- Assess causality at the level of individuals
- Determine the trial type based on the specific clinical problem, the related biomarker and the realistic constraints.

Clinical Trial Designs for PM

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Designs of predictive biomarker related trials: advantages and disadvantages.			
Designs	**Properties**	**Advantages**	**Disadvantages**
Enrichment design	Only enroll biomarker positive patients	Good for biomarker with clear evidence and/or low prevalence	Cannot gather treatment information for all population; cannot test for the companion diagnostic tool validity
All-comers design	Enroll both biomarker-positive and -negative patients	Complete treatment information for overall population	Large sample size with high cost; biomarker effect might be diluted
Biomarker strategy design	Patients are randomized to biomarker strategy group and control group	Complete information gathered; able to test companion diagnostic tools	Scale and cost might be large

Clinical Trial Designs for PM

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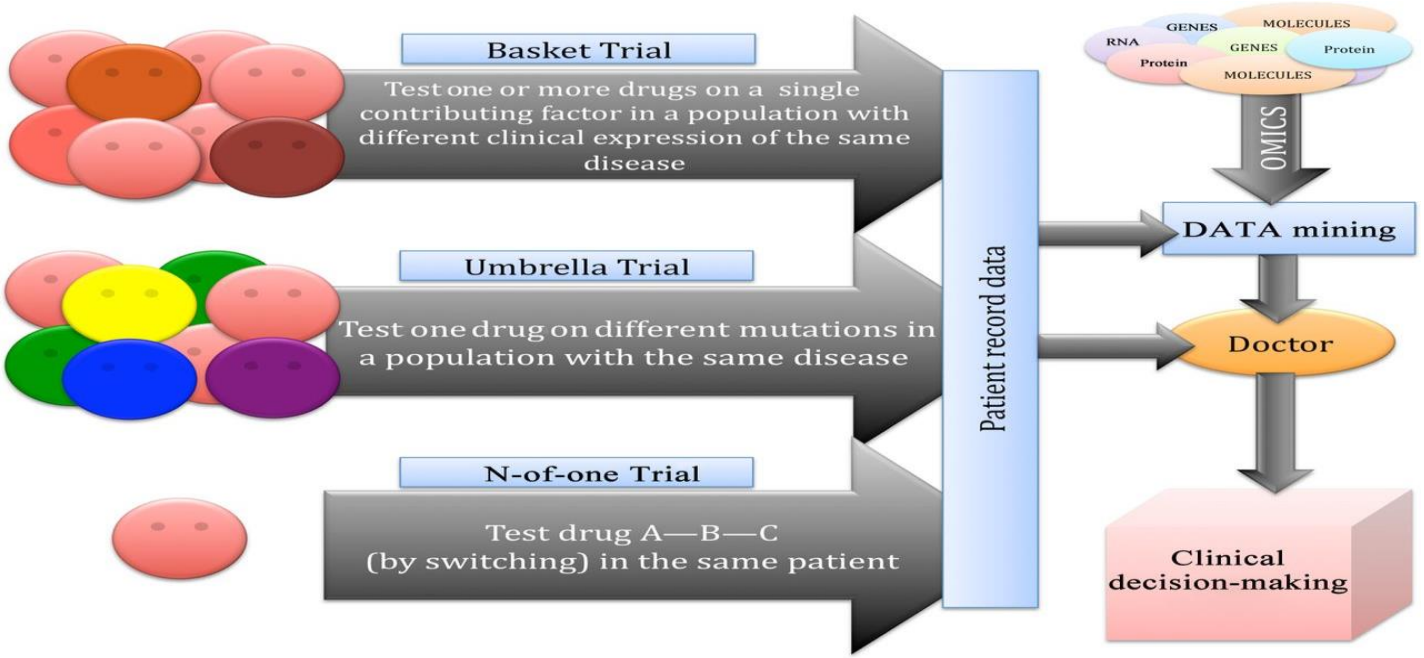
Designs of predictive biomarker related trials: advantages and disadvantages.			
Adaptive enrichment design	Two-stage design with subpopulation selection at the second stage	Flexible design with smaller expected sample size than all-comers but still contain information for biomarker-negative group	Logistically complicated; need complex simulation studies to determine sample size; multiple prerequisite needed to proceed
Group sequential design	Designs with several interims to make go/no-go decisions	Smaller expected sample size; decisions can be made during interims to save cost; proven effective treatment can be accessible to all patients early	Logistically challenging; extra complexity involved in the biomarker-related trials
Seamless design	A design in combination of two phases	Smaller expected sample size; shortened duration of the drug development process	Logistically challenging; complexity in sample size calculation

New Approaches of Clinical trial



Statistical Aspects & Challenges

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New and general statistical methods are needed to analyse clinical data for personalised medicine.

Specifically, it is important to address the following questions:

– Are the most classical statistical methods (such as statistical methods based on maximum likelihood estimators or moment estimators) still valid?
– Can one use some nonparametric methods, such as re-randomisation tests?
– How does one perform subgroup statistical analysis?

Statistical Aspects & Challenges

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Personalised medicine raises new challenges for the design of clinical trials, such as:

- More covariates (biomarkers) have to be considered
- Particular attention needs to be paid to the interaction between treatment and covariates (biomarkers).
- Missing data
- Population heterogeneity
- Delayed responses

Other Challenges

- Patient data are messy, incomplete and diverse.
- Visualising and analysing medical big data.
- Requires sufficient understanding of the underlying biological concepts and analysis algorithms to carry out data integration and interpretation.
- Programming errors and studies outlining wrongly mapped Single Nucleotide Polymorphism (SNP) in commercial SNP chips have been reported.
- Chance of encountering deviations increases with the number of different measurements in a fixed sample.

Harmonising Data

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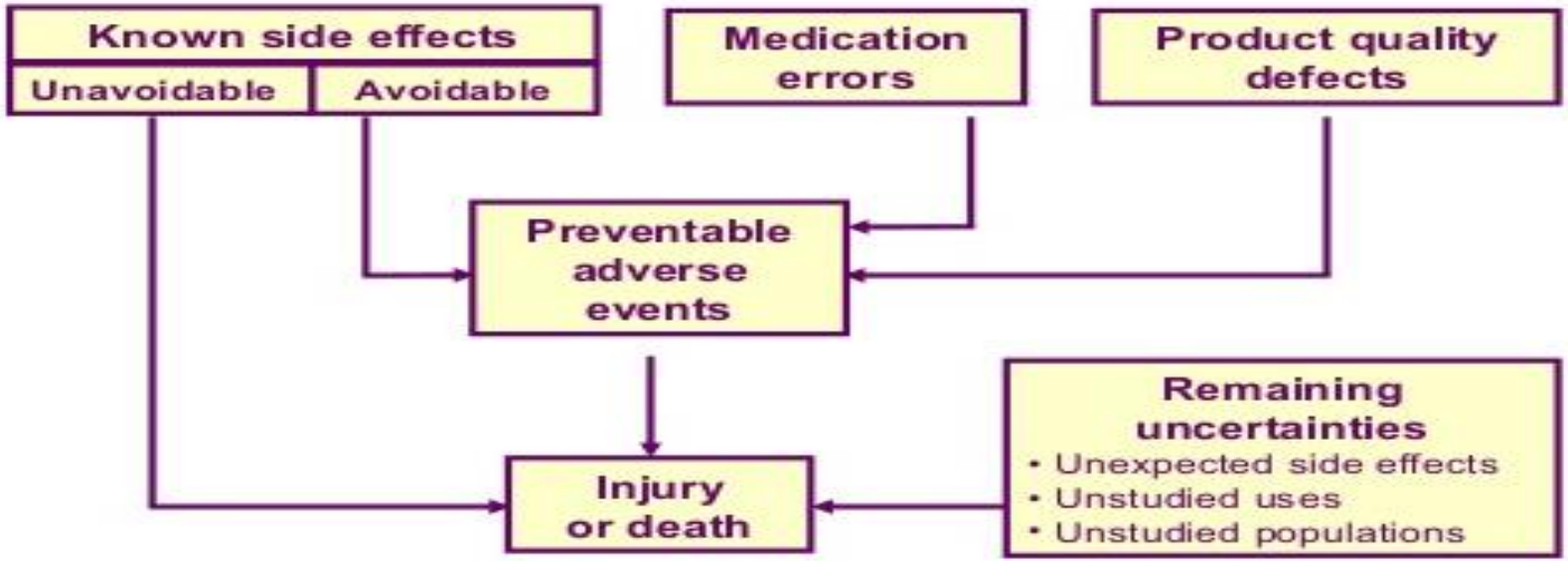
- Promoting sophisticated flexible SAS programs that may be updated regularly.
- Integrating multiple data types into one single data set that holds maximum information.
- Metadata (data about data) helps to harmonise studies and enable proper reproducibility of research results.

Sources of Risk



Advantages

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Risk Assessment:
Genetic testing to reveal predisposition to disease

Diagnosis:
Accurate disease diagnosis enabling individualized treatment strategy

Prevention:
Behavior/Lifestyle/ Treatment intervention to prevent disease

Treatment:
Improved outcomes through targeted treatments and reduced side effects

Detection:
Early detection of disease at the molecular level

Management:
Active monitoring of treatment response and disease progression

Promise of Personalised Medicine

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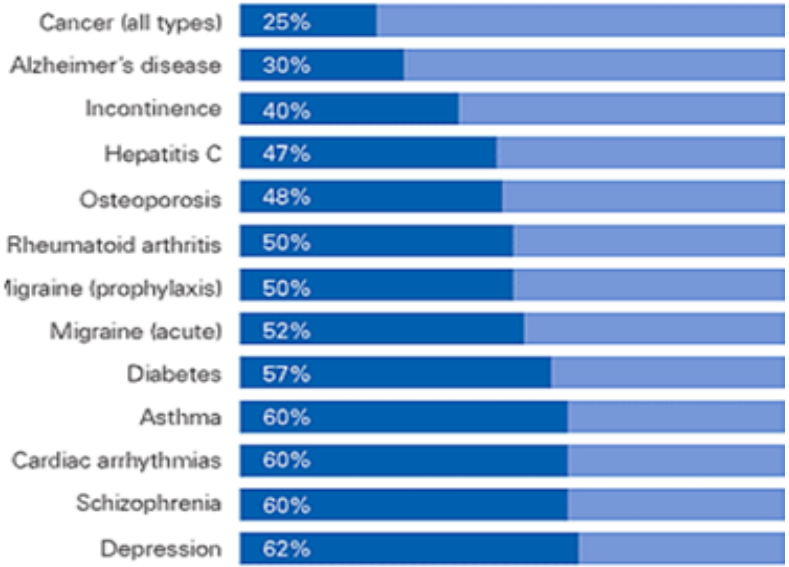
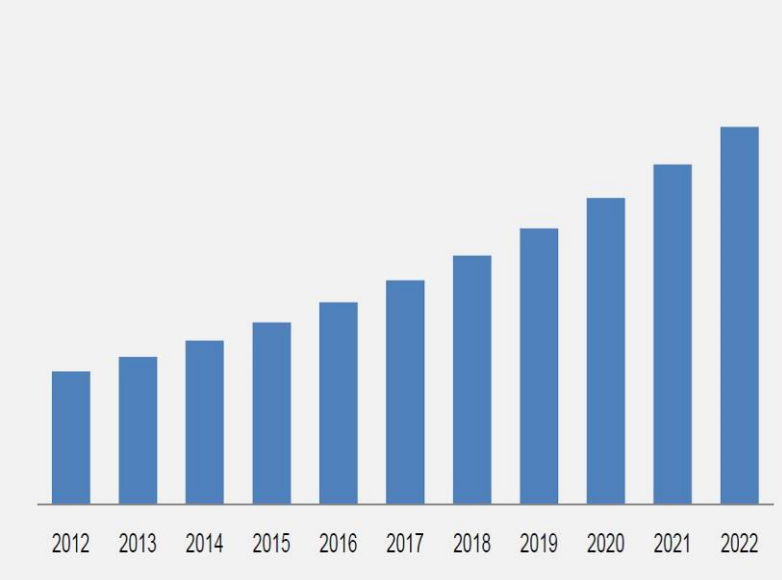
Rate of efficacy achieved with standard drug treatment indicates need for improvement



Steady growth of the PM market is observed in last few years & predicted to grow further



Personalised Medicine: Building a bridge to the future

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