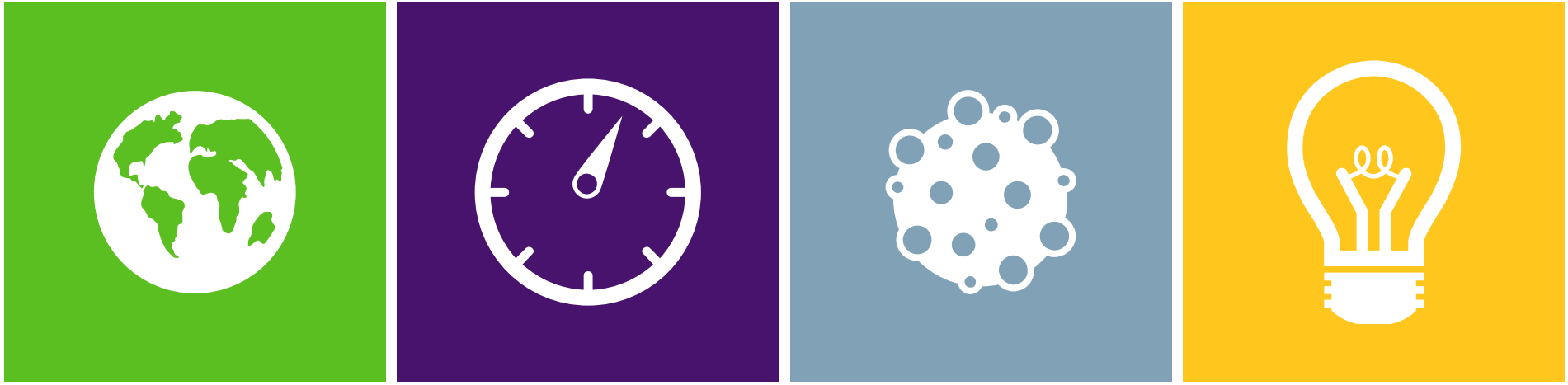

Personalized Medicine: Statistical & Programming challenges and standards

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Biostatistics and Programming
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PPD®

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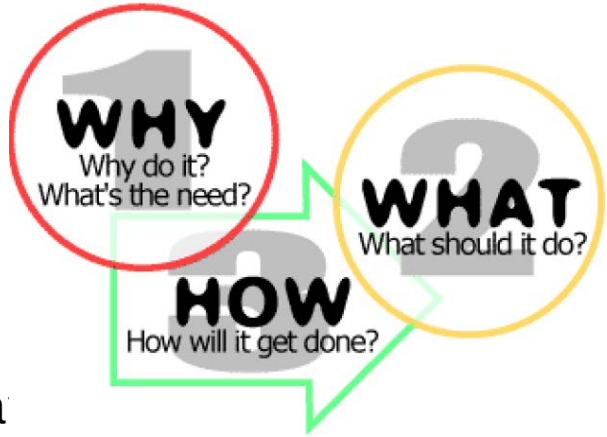
Personalized Medicine:



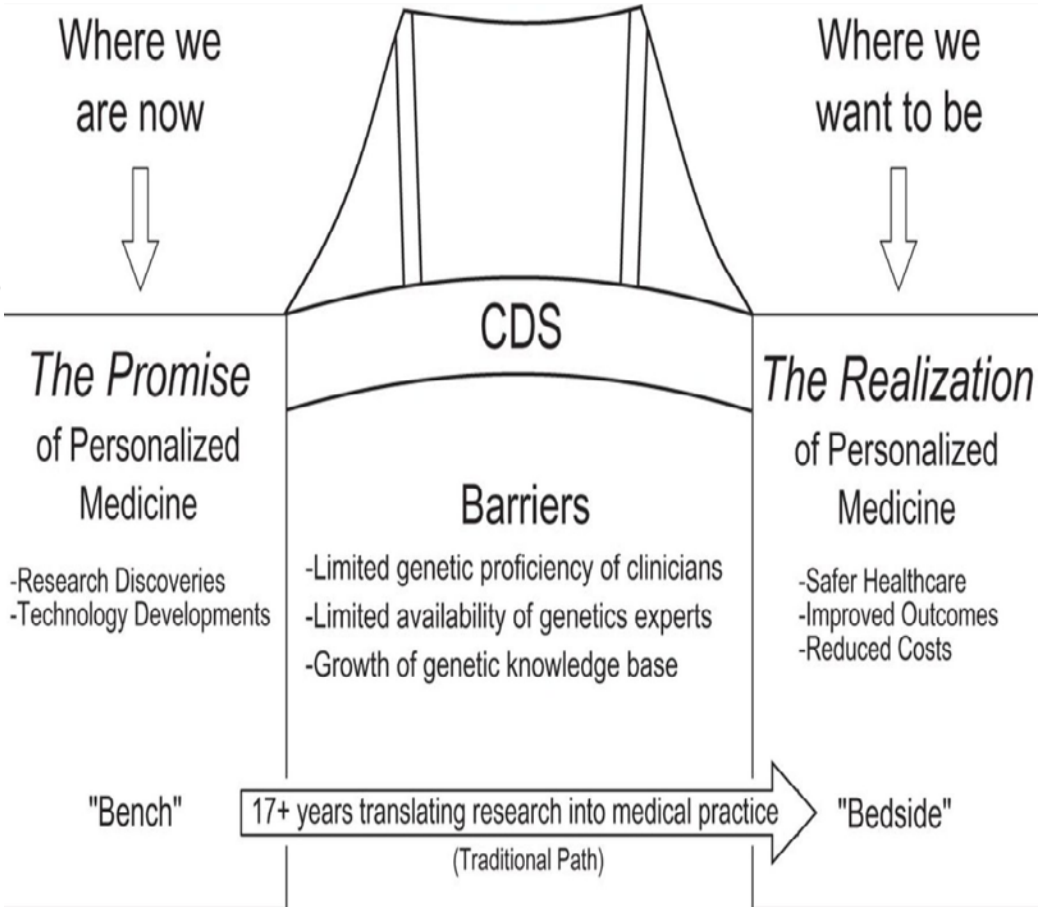
- ✓ Termed as an Individualized medicine
- ✓ Broad to narrow approach
- ✓ Develop treatments which will pay a wa for each of the patients and not the patient population on the whole
- ✓ Patients are treated based on their genetic information obtained
- ✓ Requires genetic profiling with a pattern based approach and analysis. This constitutes to the integration of genomics, proteomics data along with the clinical data in health care
- ✓ Personalized medicine does not mean creating medicines or medical devices unique to a patient, but rather the consideration of patient characteristics to optimize pharmaceutical treatment and/or overall care

Goals of Personalized Medicine Initiative:

- ✓ Develop quantitative estimates of risk for a range of diseases by integrating environmental exposures, genetic factors, and gene-environment interactions
- ✓ Identifying the determinants of safety and efficacy for commonly used therapeutics
- ✓ Discover biomarkers that identify individuals with an increased risk of developing common diseases
- ✓ Using home and mobile health (mhealth) technologies to correlate body measurements and environmental exposures with health outcomes
- ✓ Determining the clinical impact of loss of function mutations
- ✓ Developing new disease classifications and relationships
- ✓ Empowering participants with data to improve health
- ✓ Enrolling PMI cohort participants in clinical trials of targeted therapies

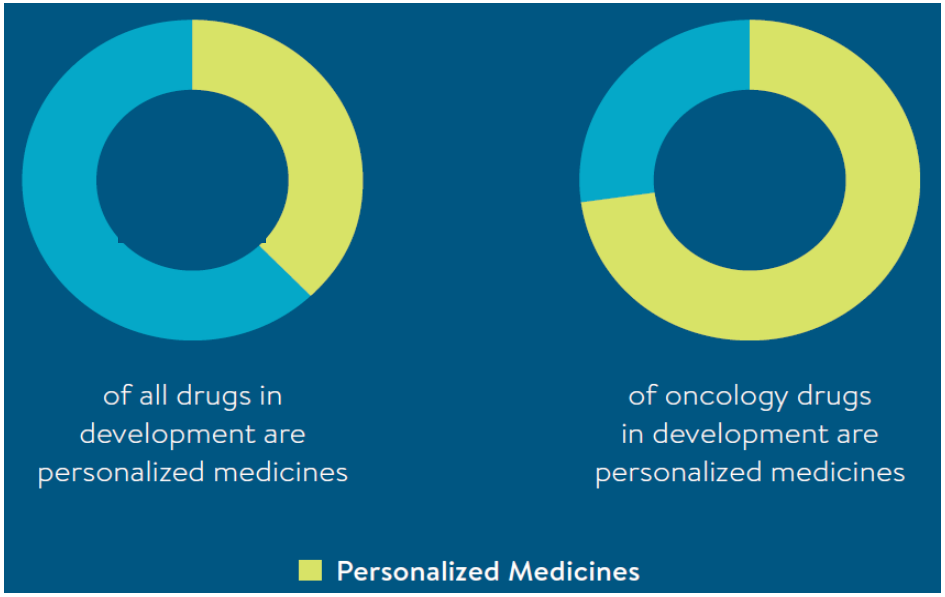
Clinical Decision Support (CDS) for GPM

- Directing targeted therapy and reducing trial and error prescribing
- Revealing additional targeted uses for medicines and drug candidates
- Increasing patient adherence to treatment
- Reducing high-risk invasive testing procedures and adverse drug reactions
- Helping to control the overall cost of health care



From: Clinical decision support for genetically guided personalized medicine: a systematic review
J Am Med Inform Assoc. 2012;20(2):388-400. doi:10.1136/amiajnl-2012-000892

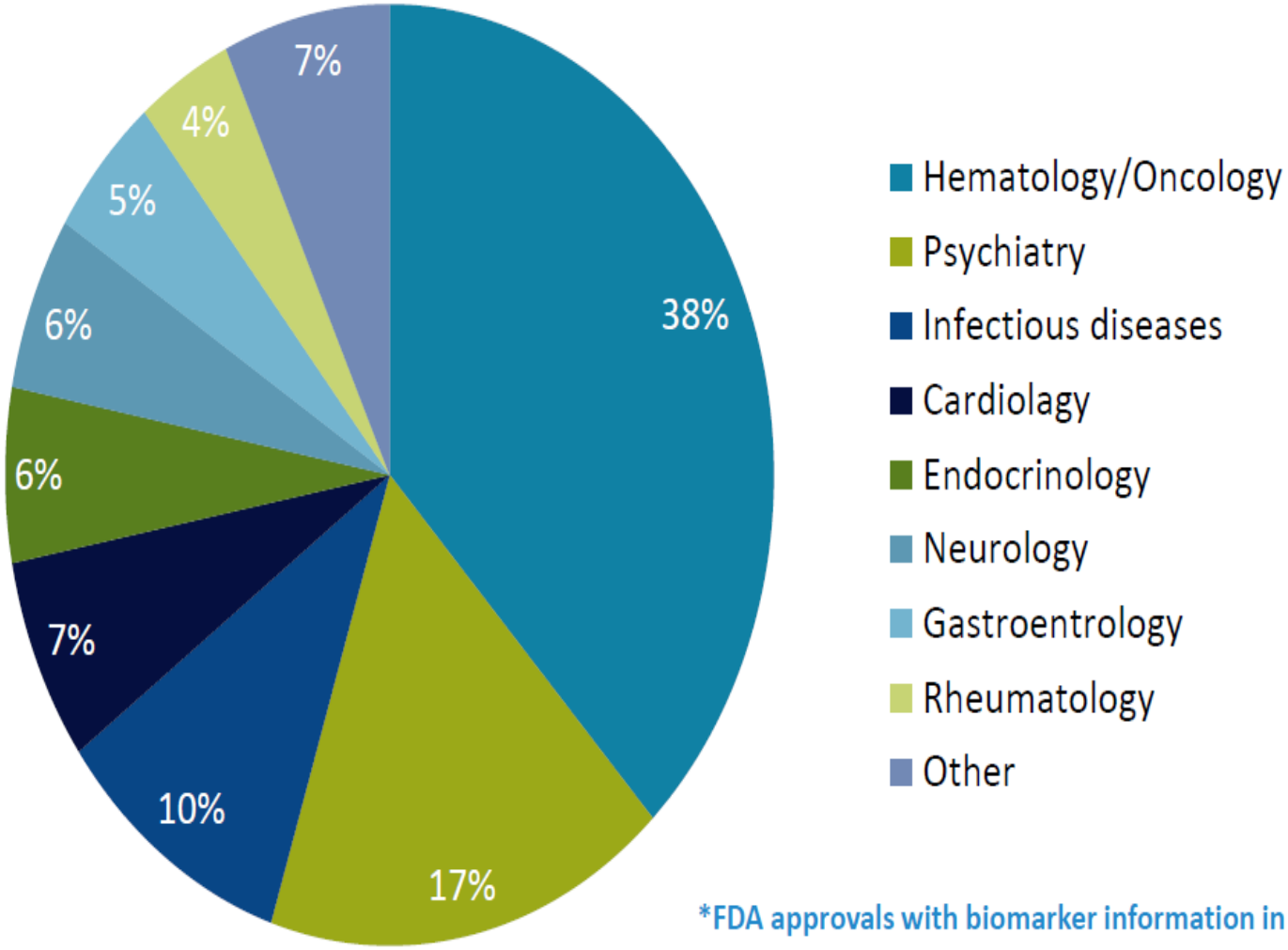
Biopharmaceutical Companies are committed



- ✓ > 40% of all compounds and > 70% of oncology compounds in the pipeline have the potential to be personalized medicines
- ✓ Biopharmaceutical companies nearly doubled their R&D investment in personalized medicines over the past five years, and expect to increase their investment by an additional > 30 percent in the next five years
- ✓ Biopharmaceutical researchers also predict a > 70% increase in the number of personalized medicines in development over the next five years

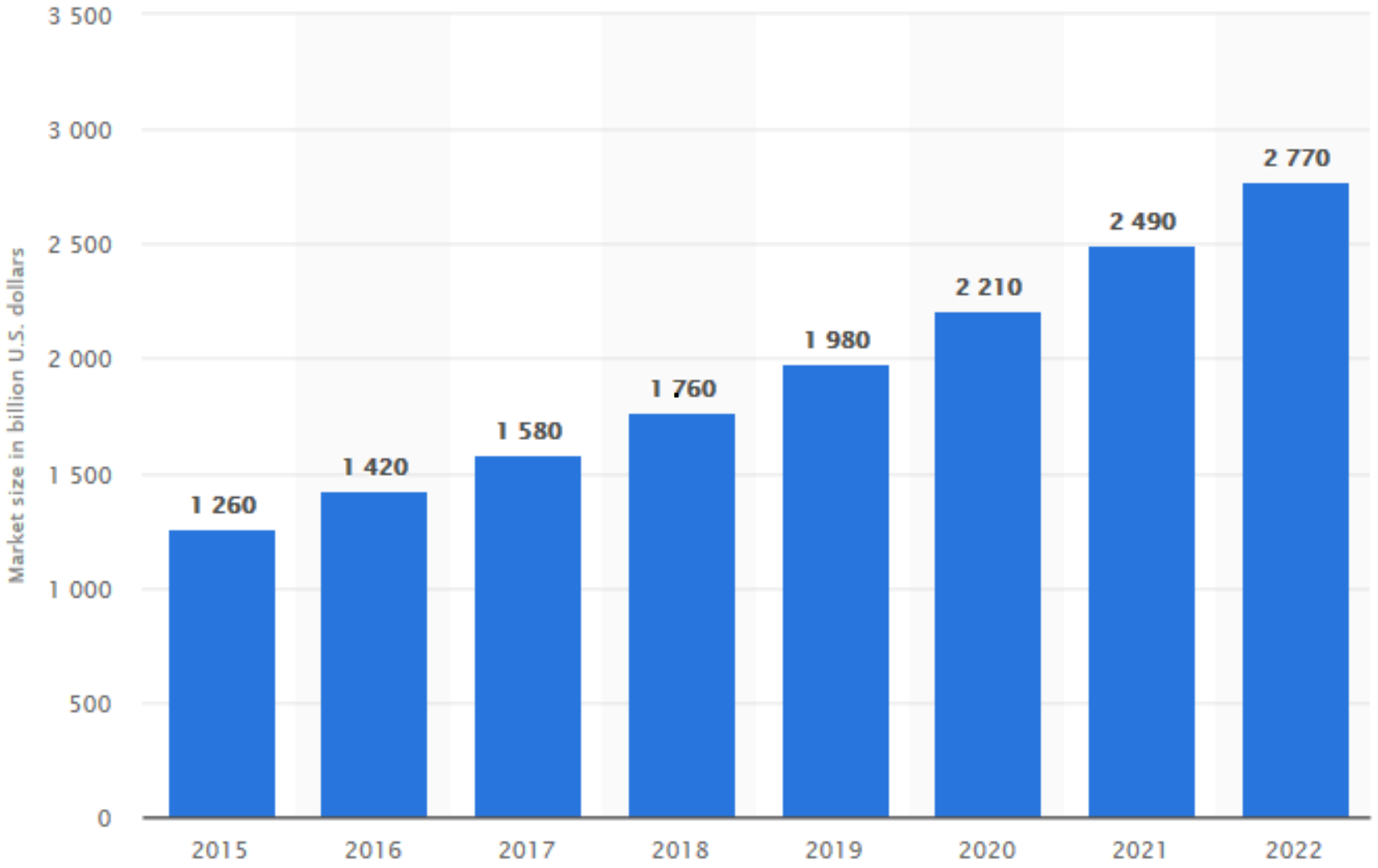
PERSONALIZED MEDICINES ARE BENEFITTING PATIENTS ACROSS MANY DIFFERENT DISEASES

Across a variety of therapeutic areas, an increasing number of treatments are personalized.*

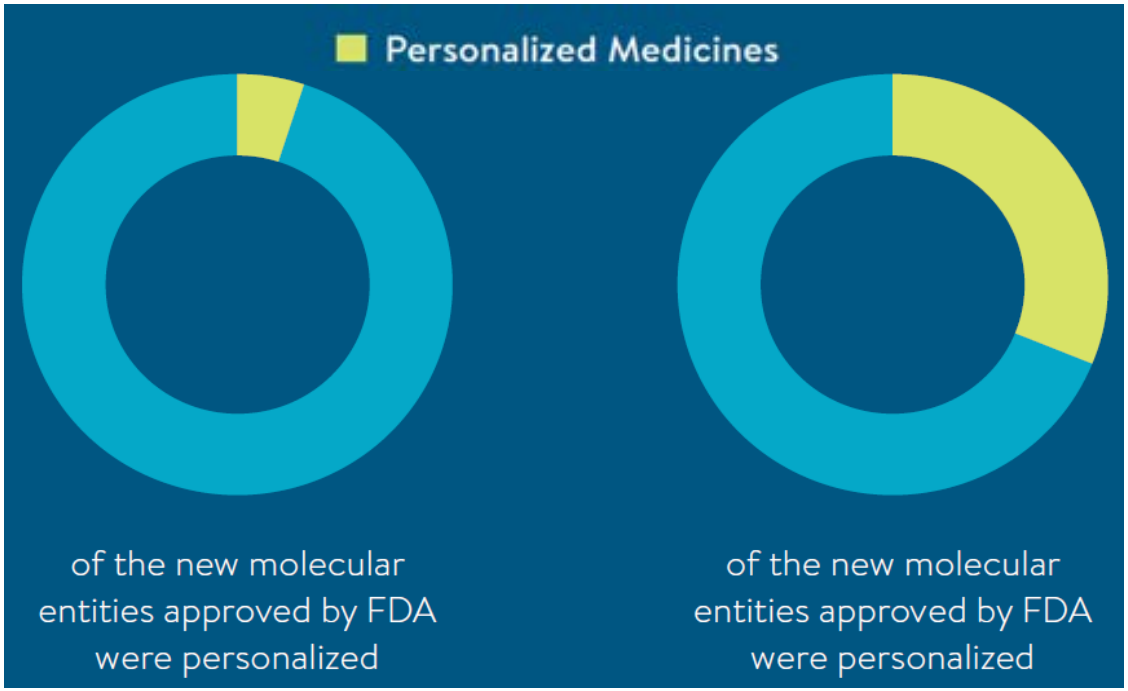


*FDA approvals with biomarker information in the approved labeling

Total global market for personalized medicine from 2015 to 2022



Personalized Medicine: FDA - Then and Now



- ✓ Personalized medicines accounted for just 5 percent of the new molecular entities FDA approved in the past
- ✓ After 2015, FDA accounted for more than 25 percent

TRADITIONAL CLINICAL TRIAL DATA FLOW

Patient Records at site

CRA

Case Report Form

Data Manager

DM Database

Programming & Tech Ops

TLFs

Medical Writer

Clinical Study Report

Biostatistics & Programming

Analysis Database

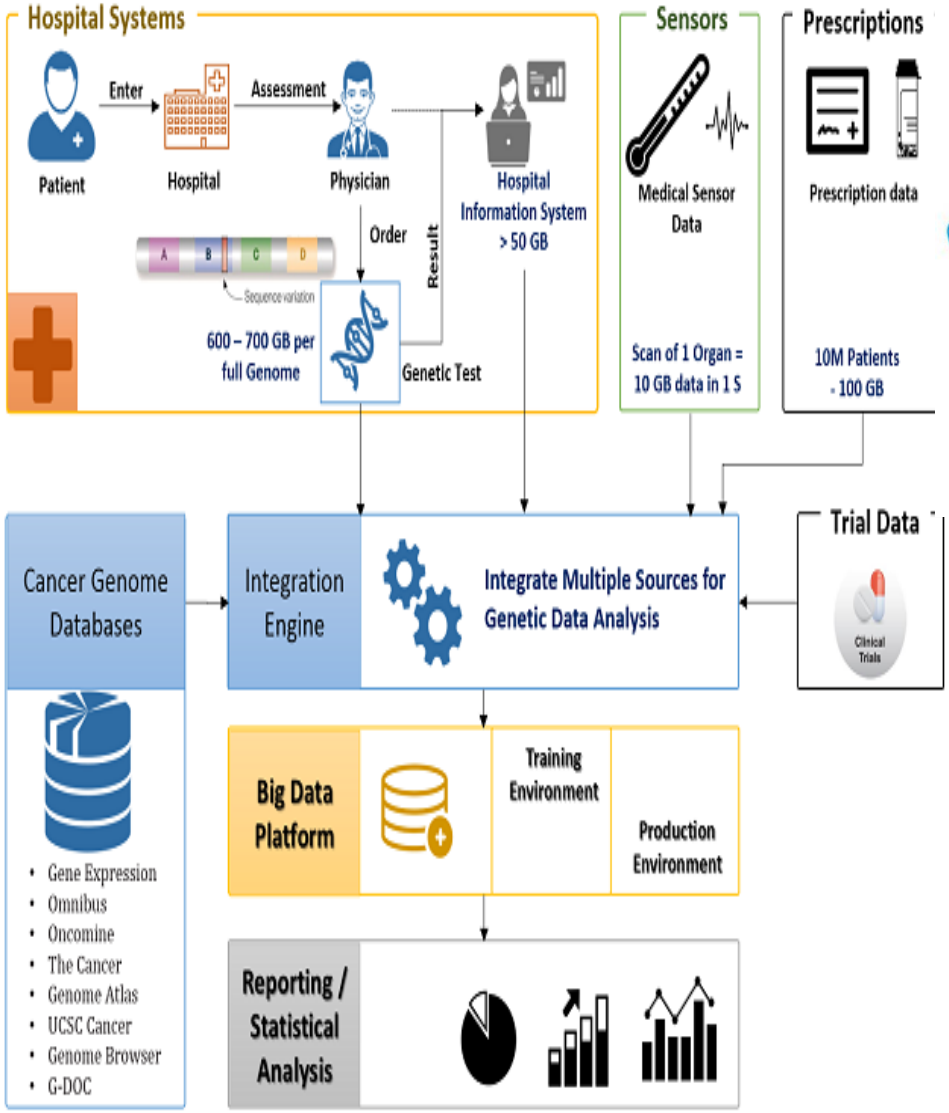
Regulatory Affairs

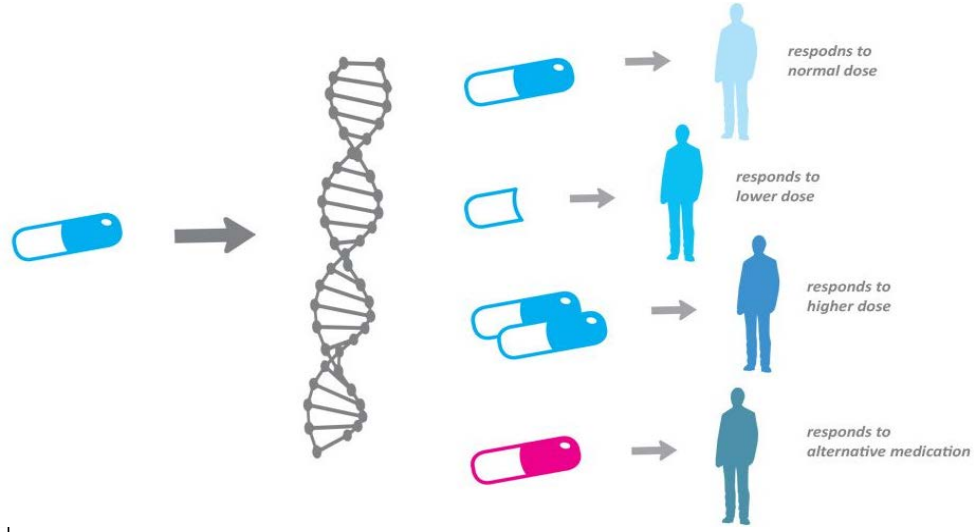
Submission Package

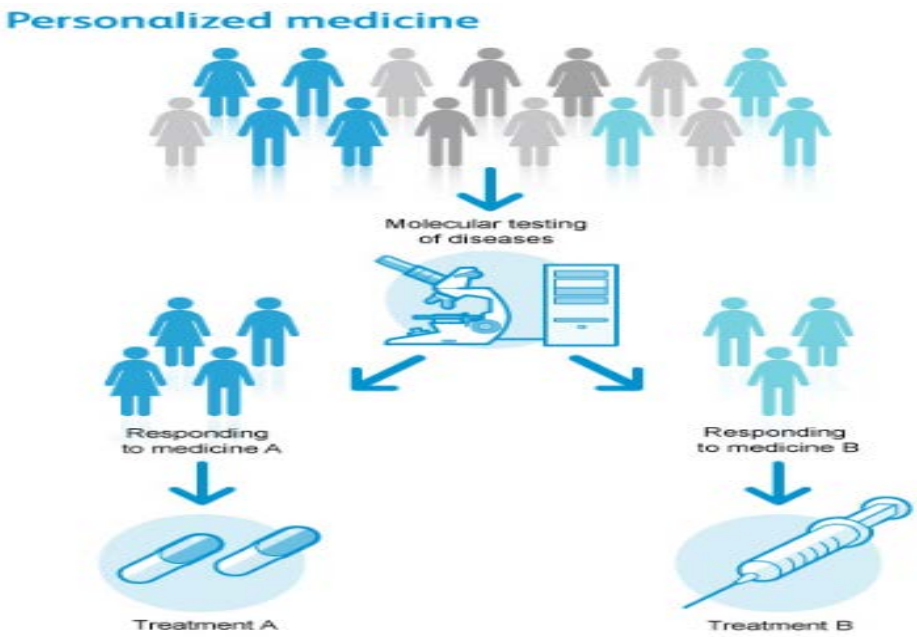
Regulatory Agency

Review & Approval

Personalized Medicine – A New ERA







Biomarkers (Biological Markers):

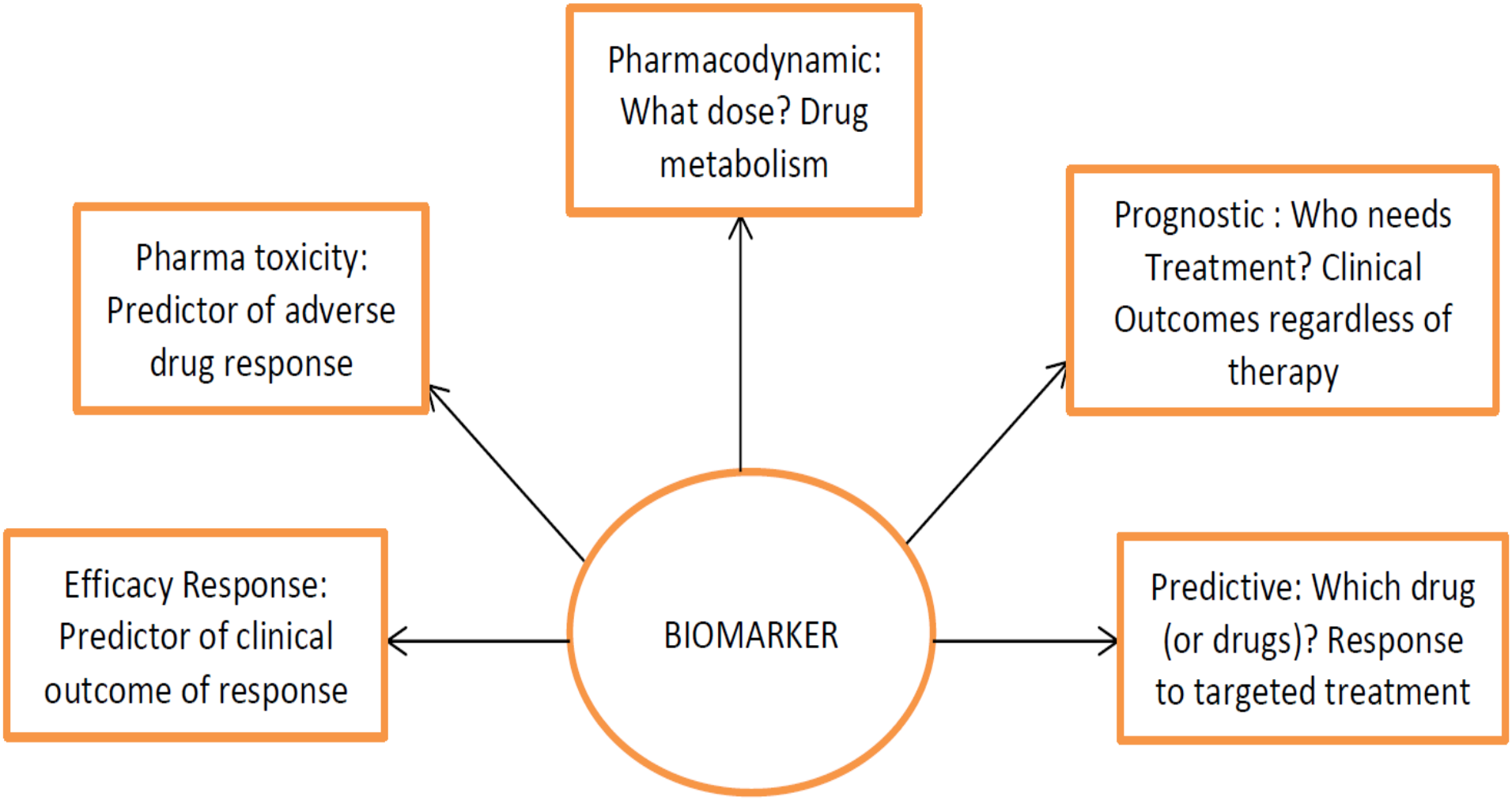
"**Biomarker**" - Measurable indicator of some biological state or condition.

- ✓ Biomarkers indicate when and to what extent a physiological or biological process has taken place in the body of a person.
- ✓ Normally happening in the body or during a development of a disease. (or) Response to drug in a patient undergoing treatment.
- ✓ Can be used for both in diagnosis and for monitoring a success of a therapy.

Significance: Drug development - Early and Late phase clinical trials.

- ✓ In early phase clinical trials is to support proof of concept, dose selection and as **go/no-go** decision-making tool.
- ✓ In late phase clinical trials, disease biomarkers or pharmacogenomics biomarkers help provide better understanding of inter-patient variability in response.

Application of Biomarkers in Clinical Trials:

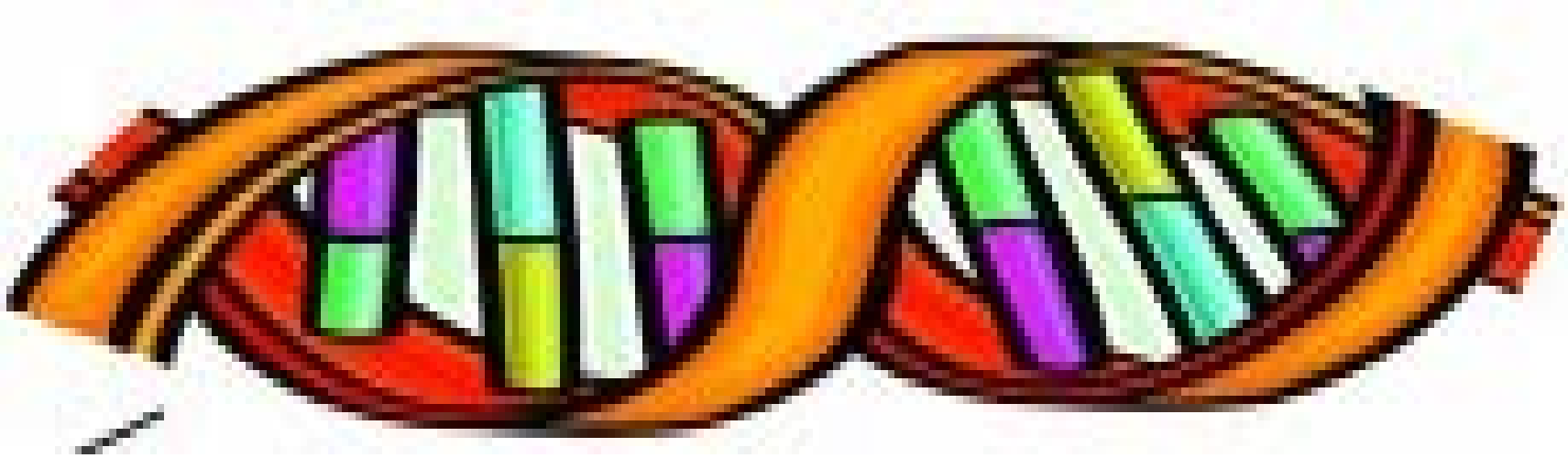


ICH Definitions:

- A **genomic biomarker** is a measurable **DNA and/or RNA characteristic** that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.

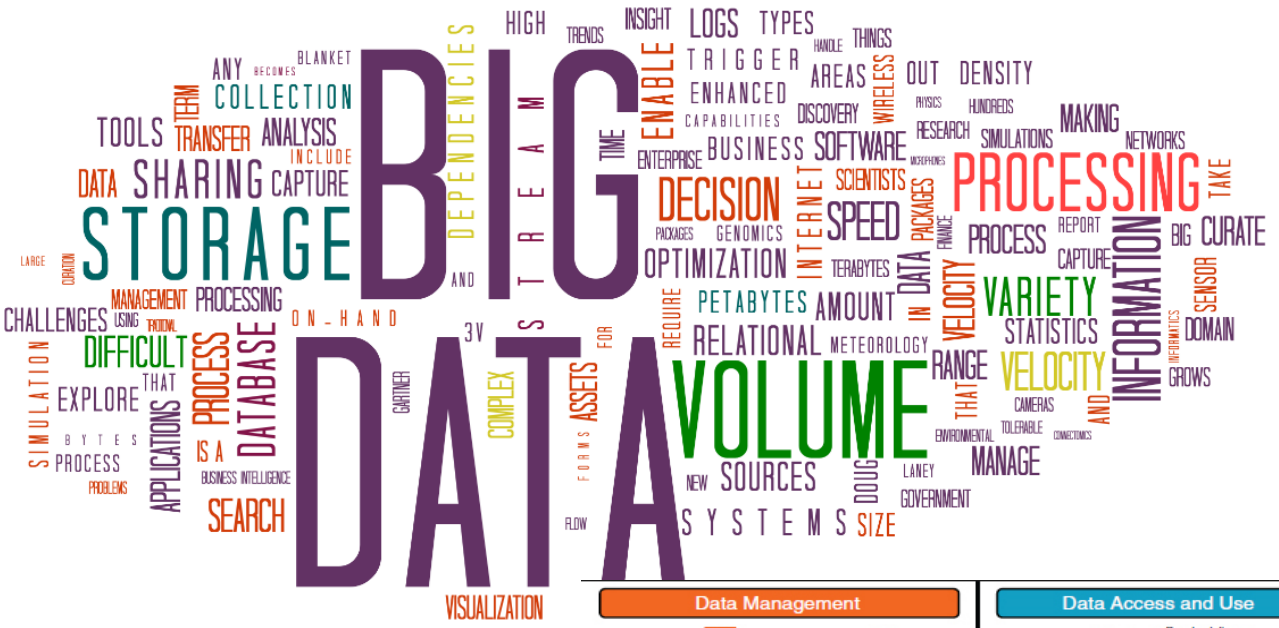
- ✓ **Pharmacogenomics (PGx)** is the study of variations of **DNA and RNA characteristics** as related to drug response.

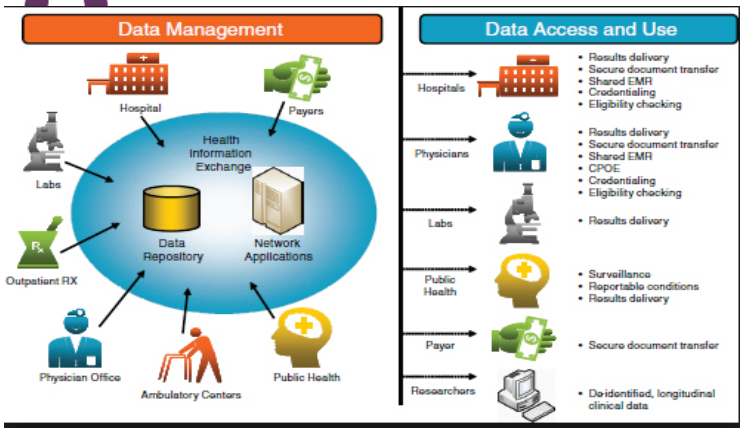
- ✓ **Pharmacogenetics (PGt)** is a subset of PGx, which is the study of variations in **DNA sequence** as related to drug response.



Data to Information Challenges:

- ✓ Data integration and Interactive machine learning
- ✓ Data structure and standardization
- ✓ Storage Capacity
- ✓ Processing Speed
- ✓ Diversity in Data
- ✓ Worth in Data
- ✓ Associated Data
- ✓ Volatility
- ✓ Real time analytics
- ✓ Accuracy/Reliability/Genuineness
- ✓ Visualization and Decision Making
- ✓ Data privacy, security, ethics, evaluation

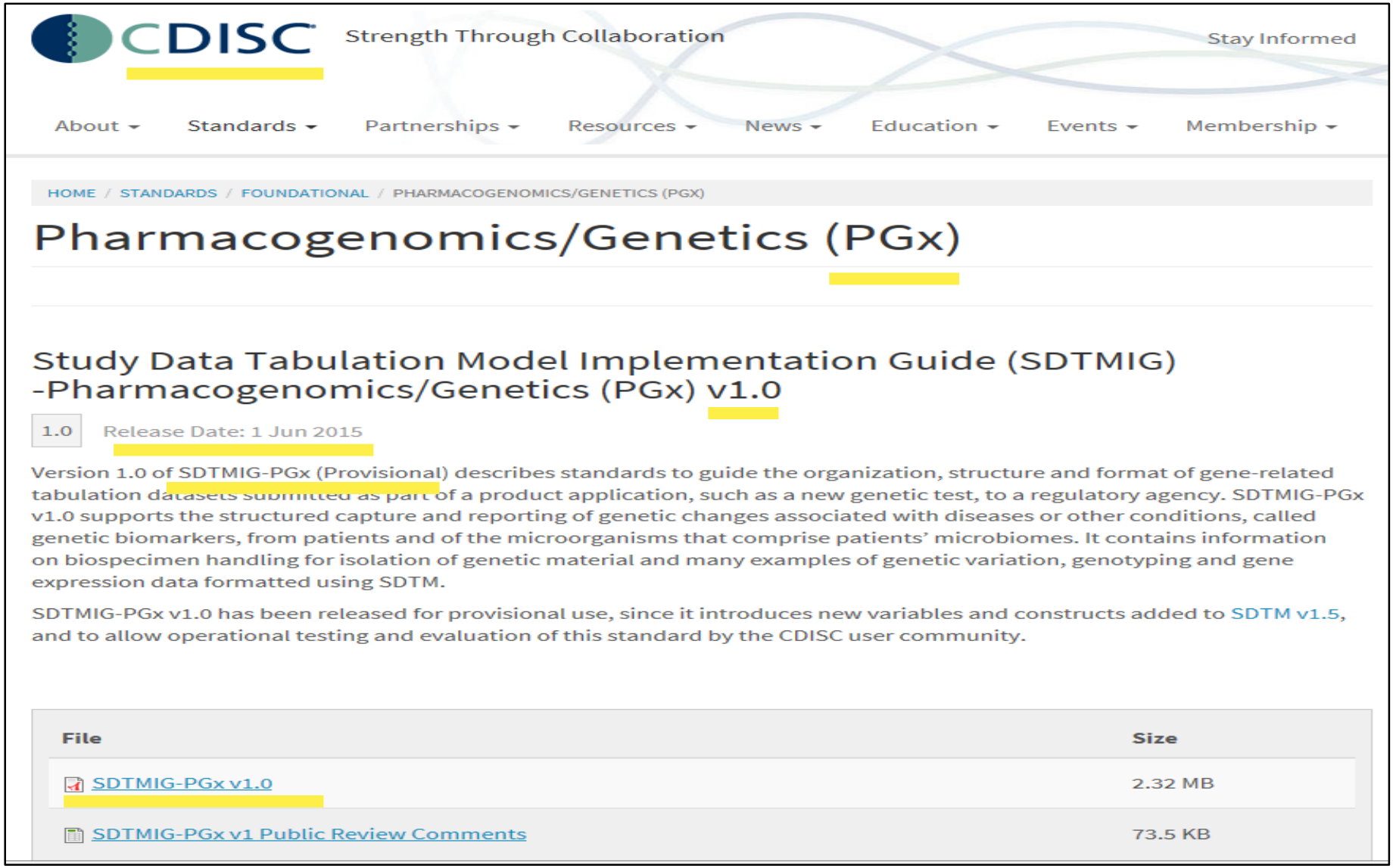




PGx Findings Domain: SAS Programmer's challenge

- ✓ A genetic variation data - Random character strings (A T G (U) C) Holds some hidden meaning that need to be decoded again by some complex algorithm which a programmer has to implement.
- ✓ PGx domain needs very specific programming to derive certain variables from the captured raw data in order to make them data structure complaint.
- ✓ Developing macros to automate standardized algorithms across the domains and major operations effective to handle complex strings such as using regular expressions and string functions.
- ✓ Mapping codes - NCBI (National Center for Biotechnology Information) and GenBank along with medical dictionaries like MeddRA and WHODRUG.
- ✓ P-Value, fold-change, ratio, genetic change, amino-acid change, etc.
- ✓ Significantly different from the current available findings module Lab data, Vital Signs, Pharmacokinetic data, etc.;

Standards:



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Pharmacogenomics/Genetics (PGx)

Study Data Tabulation Model Implementation Guide (SDTMIG) -Pharmacogenomics/Genetics (PGx) v1.0

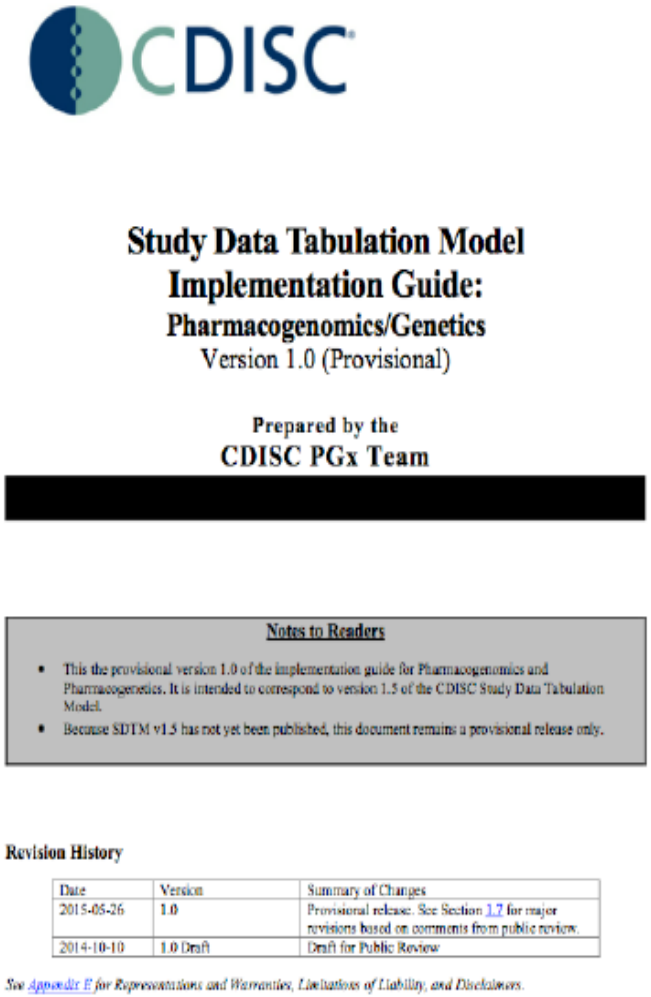
1.0 Release Date: 1 Jun 2015

Version 1.0 of SDTMIG-PGx (Provisional) describes standards to guide the organization, structure and format of gene-related tabulation datasets submitted as part of a product application, such as a new genetic test, to a regulatory agency. SDTMIG-PGx v1.0 supports the structured capture and reporting of genetic changes associated with diseases or other conditions, called genetic biomarkers, from patients and of the microorganisms that comprise patients' microbiomes. It contains information on biospecimen handling for isolation of genetic material and many examples of genetic variation, genotyping and gene expression data formatted using SDTM.

SDTMIG-PGx v1.0 has been released for provisional use, since it introduces new variables and constructs added to SDTM v1.5, and to allow operational testing and evaluation of this standard by the CDISC user community.

File	Size
SDTMIG-PGx v1.0	2.32 MB
SDTMIG-PGx v1 Public Review Comments	73.5 KB

Study Data Tabulation Model Implementation Guide: Pharmacogenomics/Genetics Version 1.0 (Provisional)



Study Data Tabulation Model Implementation Guide:
Pharmacogenomics/Genetics
Version 1.0 (Provisional)

Prepared by the
CDISC PGx Team

[redacted]

Notes to Readers

- This the provisional version 1.0 of the implementation guide for Pharmacogenomics and Pharmacogenetics. It is intended to correspond to version 1.5 of the CDISC Study Data Tabulation Model.
- Because SDTM v1.5 has not yet been published, this document remains a provisional release only.

Revision History

Date	Version	Summary of Changes
2015-05-26	1.0	Provisional release. See Section 1.7 for major revisions based on comments from public review.
2014-10-10	1.0 Draft	Draft for Public Review

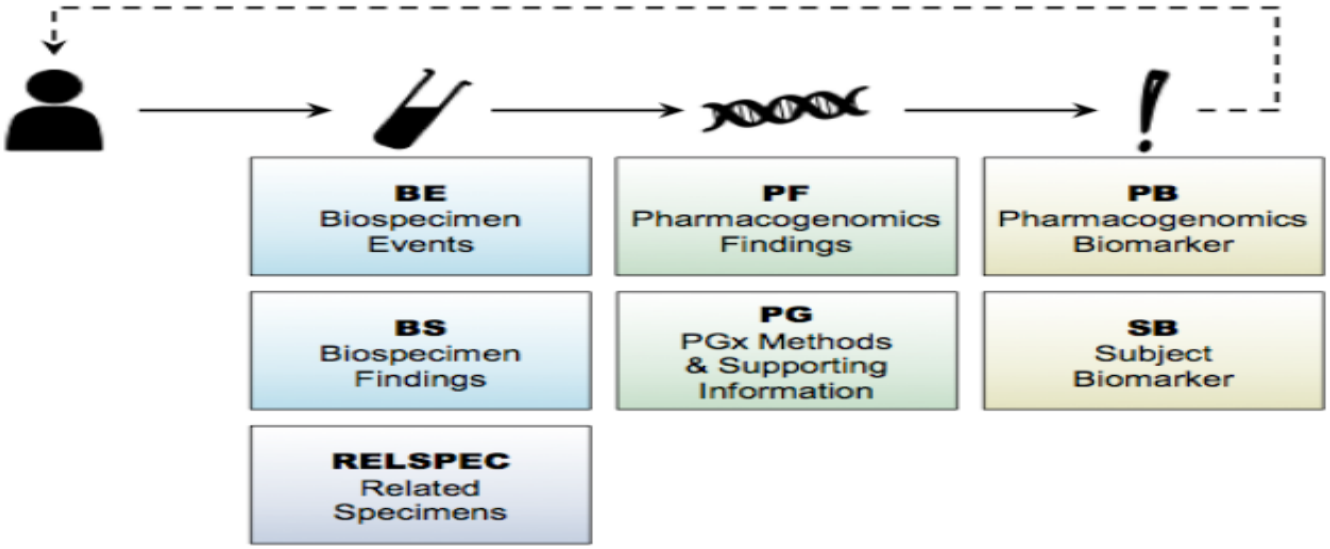
See Appendix F for Representations and Warranties, Limitations of Liability, and Disclaimers.

Strategy for Implementing SDTM Standards on PGx Datasets

- ✓ What data should be used to create SDTM PGx datasets?
- ✓ How to track the transformations of PGx data?
- ✓ How to create SDTM PGx datasets?
- ✓ When should the generation of SDTM PGx datasets occur during the clinical trial process?

- ➢ **CAN PGX DATA FIT INTO EDC?**

Classification of SDTMIG-PGx Domains



From Study Data Tabulation Model Implementation Guide: Pharmacogenomics/Genetics Version 1.0

Data category and domain class for PGx datasets

Class / Category	General Observation Class		Special-Purpose
	Event	Finding	
Data about biospecimens	BE	BS	RELSPEC
Data about genetic observations		PF, PG	
Data that define a genetic biomarker or assign it to a subject			PB, SB

Classification of SDTMIG-PGx Domains (Contd..)

☑ Biospecimen Events(BE)

The Biospecimen Events domain is used to capture information about actions taken that affect a specimen or alter its status.

☑ Biospecimen Findings(BS)

The Biospecimen Findings domain contains the details regarding the characteristics of biospecimens and extracted samples (e.g., RNA, DNA) such as specimen volume, quantity of extracted sample, specimen condition and the integrity of the DNA or RNA samples.

☑ RELSPEC Dataset(RELSPEC)

The Related Specimens dataset holds the hierarchy of specimen relationships.

Classification of SDTMIG-PGX Domains (Contd..)

☑ Pharmacogenomics/Genetics Findings(PF)

The Pharmacogenomics/Genetics Findings domain contains the results of genetic variation and gene expression tests. For genetic variation tests, the results may include portions of the genetic sequence and comparisons with reference gene sequences.

☑ Pharmacogenomics/Genetics Methods and Supporting Information(PG)

The Pharmacogenomics/Genetics Methods and Supporting Information domain contains additional data that may affect interpretation of PF data, such as setup processes, test or sequencing parameters, and QC observations.

☑ Pharmacogenomics/Genetics Biomarker (PB)

The Pharmacogenomics/Genetics Biomarker domain documents known associations between observed variations and medical conclusions (e.g., disease diagnosis, resistance of a virus to a particular drug).

☑ Subject Biomarker (SB)

The Subject Biomarker domain holds data about any genetic biomarkers (as defined in PB) that a subject may have.

Data Level Metadata of SDTMIG-PGx Domains

Dataset	Description	Class	Structure	Purpose	Keys*	Location
PB	Pharmacogenomics/ Genetics Biomarker	Special Purpose Domains	One record per biomarker used in the study	Tabulation	STUDYID, PBMRKRID, PBMRKR	pb.xpt
SB	Subject Biomarker	Special Purpose Domains	One record per subject per observed biomarker in the study	Tabulation	STUDYID, USUBJID, SBMRKRID	sb.xpt
BE	Biospecimen Events	Events	One record per instance per biospecimen event per biospecimen identifier per subject	Tabulation	STUDYID, USUBJID, BEREFID, BETERM, BESDTC	be.xpt
BS	Biospecimen Findings	Findings	One record per measurement per biospecimen identifier per subject	Tabulation	STUDYID, USUBJID, BSREFID, BSTESTCD	bs.xpt
PF	Pharmacogenomics/ Genetics Findings	Findings	One record per finding per observation per biospecimen per subject	Tabulation	STUDYID, USUBJID, PFREFID, PFTESTCD, PFGENRI, PFSTRESC	pf.xpt
PG	Pharmacogenomics/ Genetics Methods and Supporting Information	Findings	One record per observation per biospecimen per run per subject	Tabulation	STUDYID, USUBJID, PGREFID, PGTESTCD, PGGENRI, PGNSPCES, PGNSTRN, PGDTC	pg.xpt
RELSPEC	Related Specimens	Special-Purpose Datasets	One record per specimen identifier per subject	Tabulation	STUDYID, USUBJID, REFID	relspec.xpt

From Study Data Tabulation Model Implementation Guide: Pharmacogenomics/Genetics Version 1.0

REFERENCES

+ http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The-Personalized-Medicine-Report1.pdf
+ https://academic.oup.com/jamia/article/20/2/388/2909233#86475255
+ http://www.ijbh.org/ijbh2015-1.pdf#page=43
+ https://www.pharmasug.org/proceedings/2017/DS/PharmaSUG-2017-DS05.pdf
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+ https://www.cdisc.org/
+ https://www.fda.gov/

Personalized medicine: Building a bridge to the future

Thank You For Listening

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