Personalized Medicine: Promises and Challenges

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“It’s far more important to know what person the disease has than what disease the person has.”

~Hippocrates

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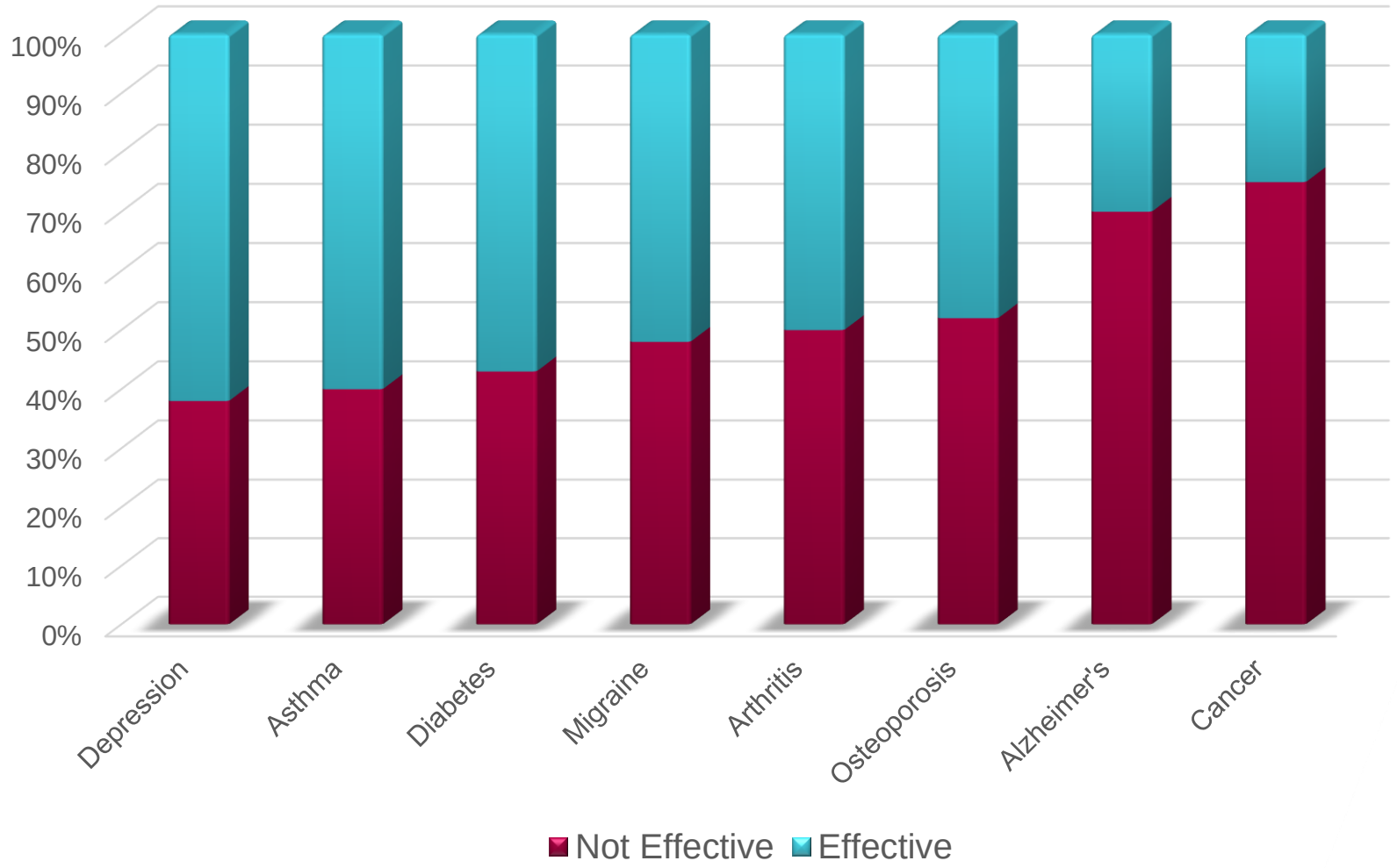
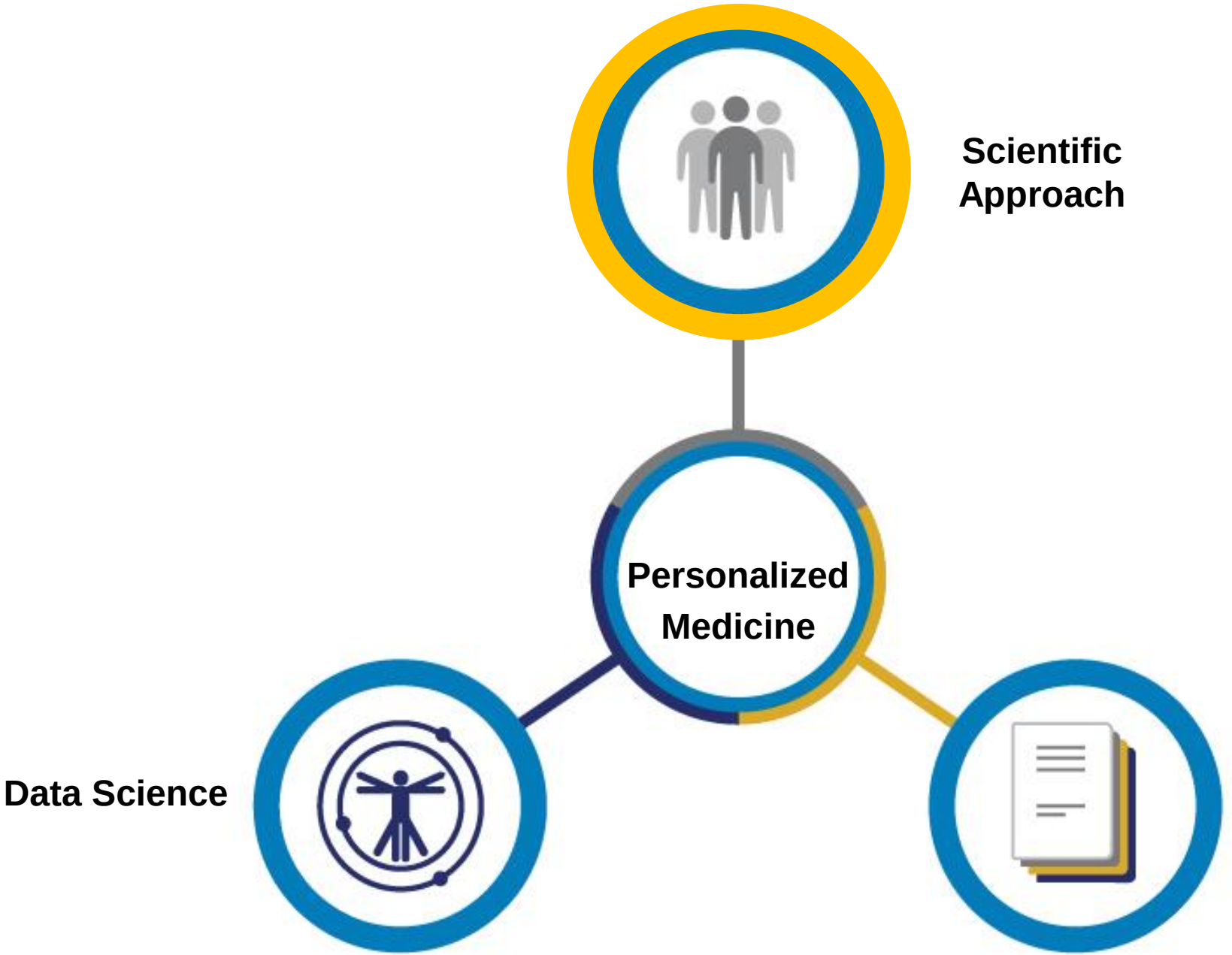
Conventional Medication Doesn’t Work for All Patients



Source : Personalized Medicine Coalition


Scientific Approach
Personalized Medicine
Data Science
Regulatory Guidance

History of Personalized Medicine

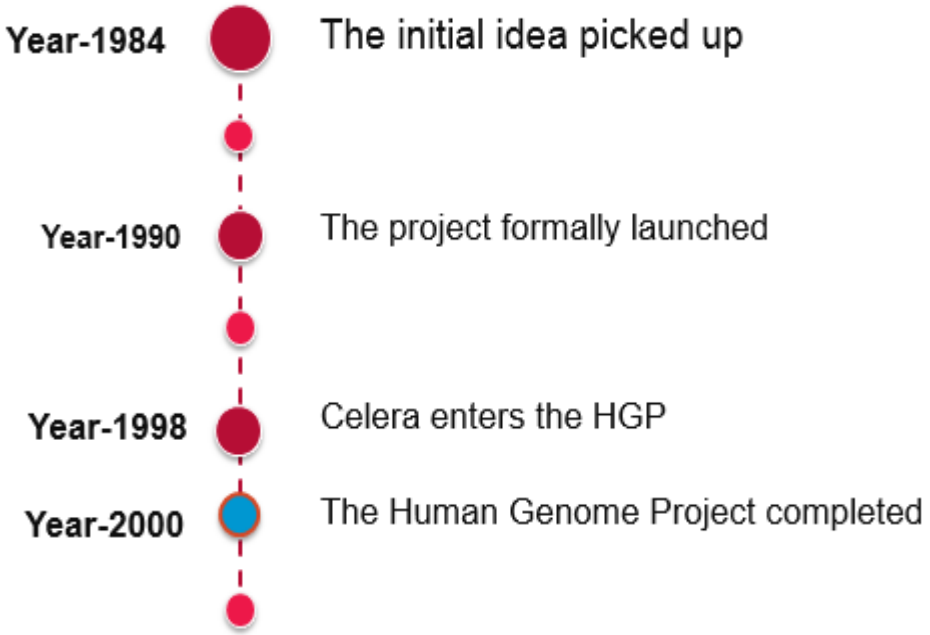
- The term personalized medicine first appeared in published works in 1999. However, some of the field's core concepts have been in existence since the early 1960s

- Two key discoveries have allowed for significant progress within the field of personalized medicine
  - — single nucleotide polymorphism (SNP) genotyping
  - — HGP (microarray/NGS)

- The ability to identify these polymorphisms is crucial, as SNPs have been linked to patient susceptibility to various disease processes and drug therapy responsiveness

The Human Genome Project

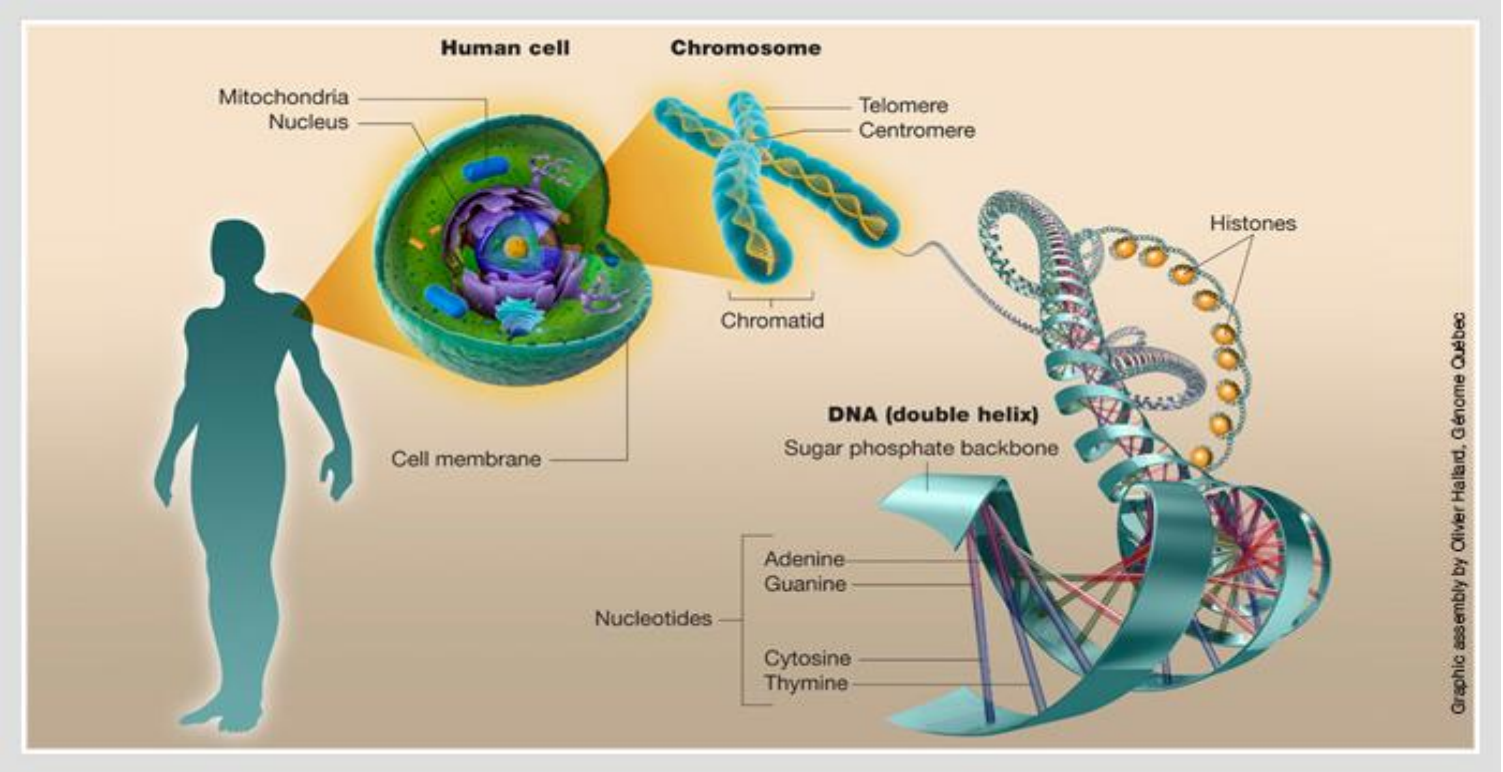
- The Human Genome Project (HGP) was an international scientific research project with the goal of determining the sequence of nucleotide base pairs that make up human DNA, and of identifying and mapping all of the genes of the human genome from both physical and functional standpoint



What is Genomics?

Study of the genome of an organism

The genome, a combination of the words “gene” and “chromosome”, is the complete set of hereditary instructions in each cell of every living thing that are needed by the organism for its development and functioning.

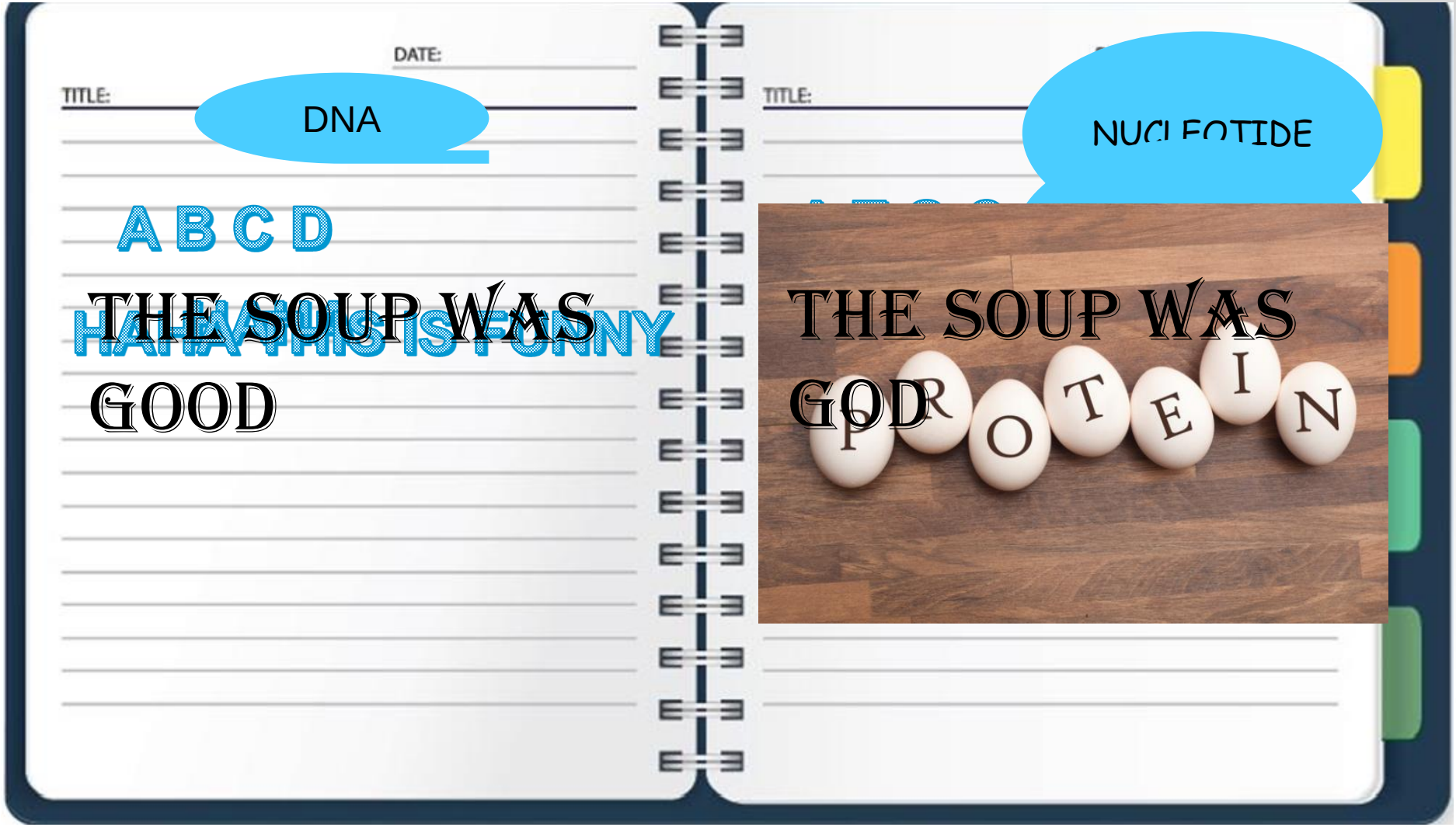


My Notebook --- A Programmer's Way of Understanding Genes

GENOME

DNA

NUCLEOTIDE



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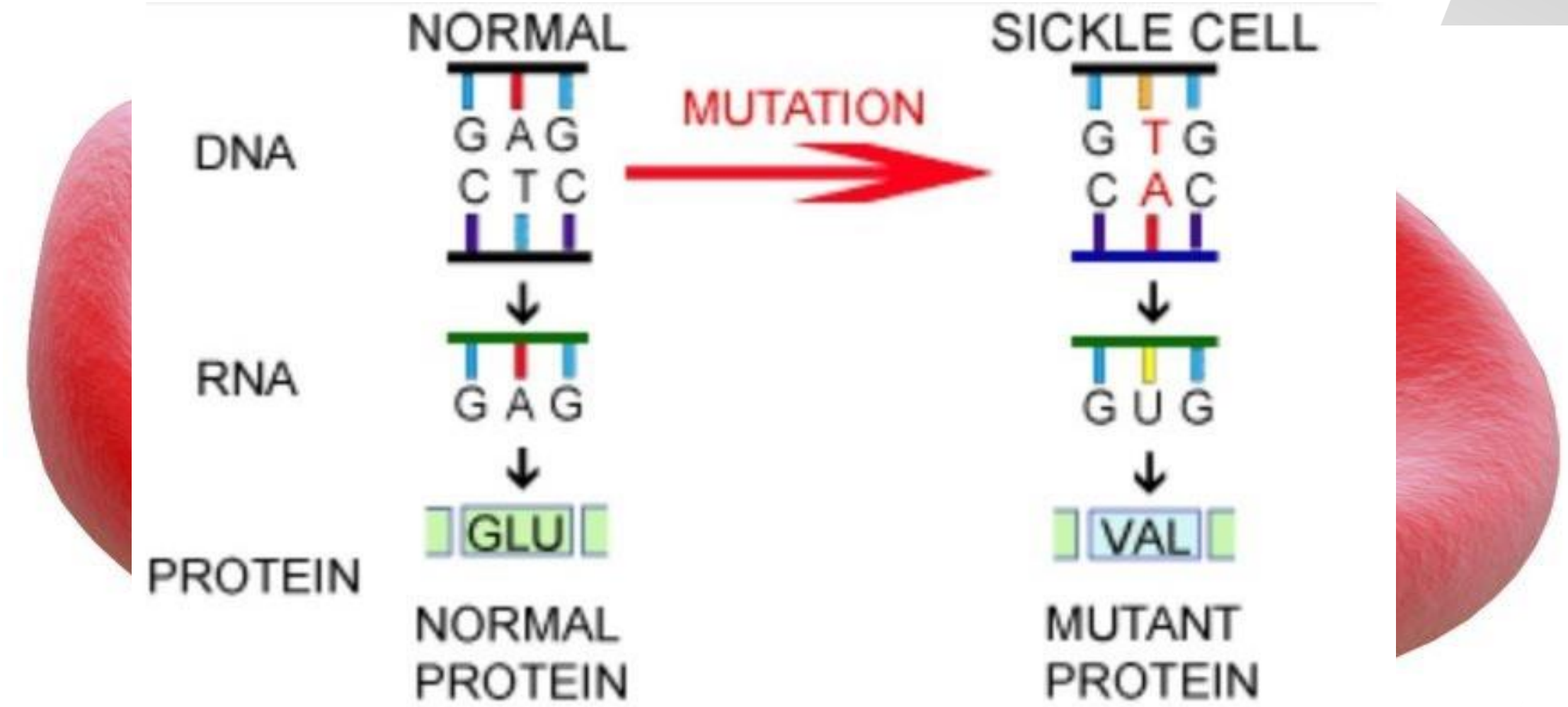
Sickle Cell Anemia

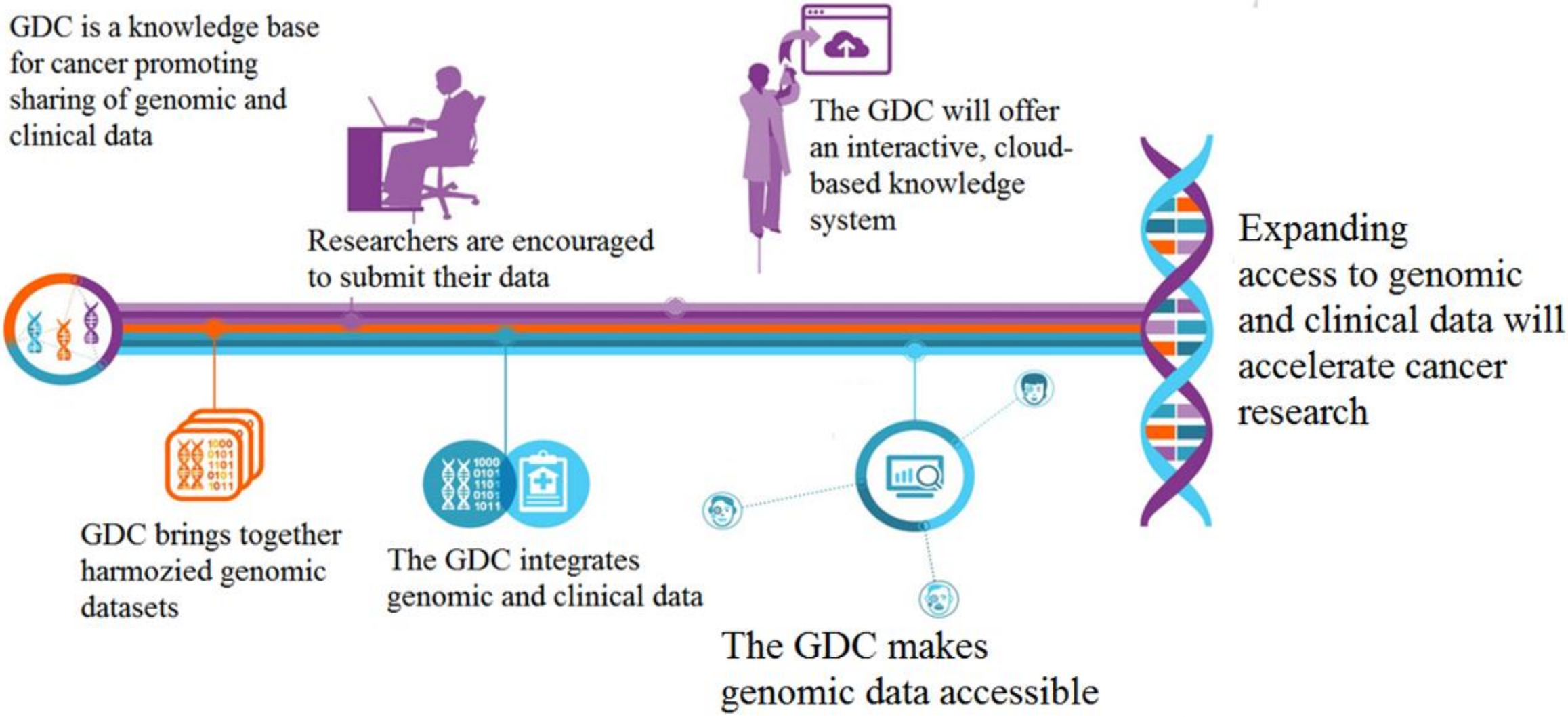


New Possibilities PM presented

- Understanding ABACAVIR

- Abacavir, a nucleotide reverse transcriptase inhibitor used to treat patients with HIV
- It is known to cause a hypersensitivity reaction in some patients within six weeks of the onset of therapy
- In 2002, two independent studies demonstrated a possible genetic link between the hypersensitivity reaction and the major histocompatibility complex class I allele HLA-B*57:01 (Mallal 2002; Hetherington 2002)
- This landmark study demonstrated that a patient's genome can predict response to a specific drug therapy
- Moreover, this study was so persuasive that the Food and Drug Administration and the European Medicines Agency altered the abacavir label to advise testing for the HLA-B*57:01 allele prior to initiating abacavir therapy (Novelli 2010)

Genomic Data Commons



Genomic Data Commons

Clinical Trial Sequencing Project

- A collaborative project between NCI's CCG and DCTD
- Launched out of a joint aspiration to promote the use of genomics in NCI-sponsored clinical trials of the National Clinical Trial Network (NCTN)
- CTSP's goal is to elucidate the molecular basis of response and resistance to therapies studied
- The cancer types currently under study are breast cancer, renal cell carcinoma, and diffuse large B-cell lymphoma
- The genomic and anonymized clinical data from CTSP will be made publically available in the Genomic Data Commons (GDC) to benefit the cancer research community

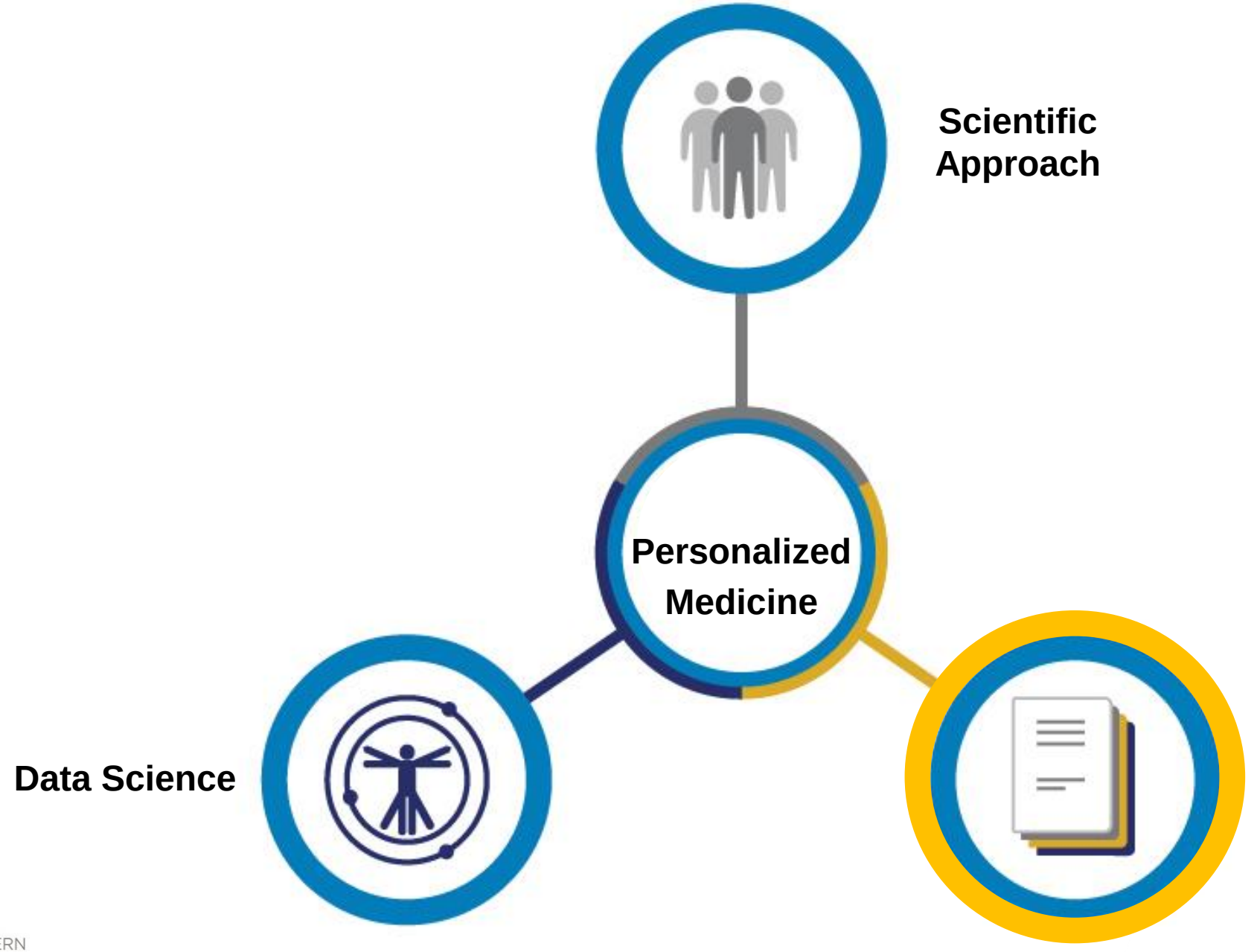
Breast Cancer and TAILORx

- Trial Assigning Individualized Options for Treatment (TAILORx) is an NCI-sponsored clinical trial
- Investigating whether some breast cancer patients may be treated effectively without undergoing chemotherapy, and if a gene expression test can help choose the best individualized treatment
- The trial enrolled over 10,000 women with estrogen receptor (ER-positive), human epidermal growth (Her2-negative) breast cancer that had not spread to the lymph nodes
- The trial grouped patients based on the score obtained from the gene expression test, into low, middle, and high chance of recurrence
- Initial results indicate that low-risk women fare well when spared chemotherapy and that the gene expression test is a clinically helpful tool for determining the best treatment for individual patients

The TAILORx Breast Cancer Trial was originally published by the National Cancer Institute.

Studies Planned Ahead

- **ECOG-ACRIN E2805 Trial of Renal Cell Carcinoma**
- CCG will receive tissue samples of renal cell carcinoma (RCC), the most common kidney cancer in adults
- CCG will analyze approximately 400 tissue samples from the ECOG-ACRIN E2805 trial of sunitinib and sorafenib to learn more about genomic drivers of RCC development, metastasis, and recurrence
- **Diffuse Large B Cell Lymphoma Trial**
- CCG will perform a comprehensive molecular analysis of tissue samples of Diffuse Large B Cell Lymphoma (DLBCL)
- The goal of CCG's in-depth analysis of the DNA, RNA, and protein of DLBCL samples from this trial is to bolster the findings with rich molecular data and to add key information, including multi-platform analysis of DLBCL subtypes and predictors of tumor resistance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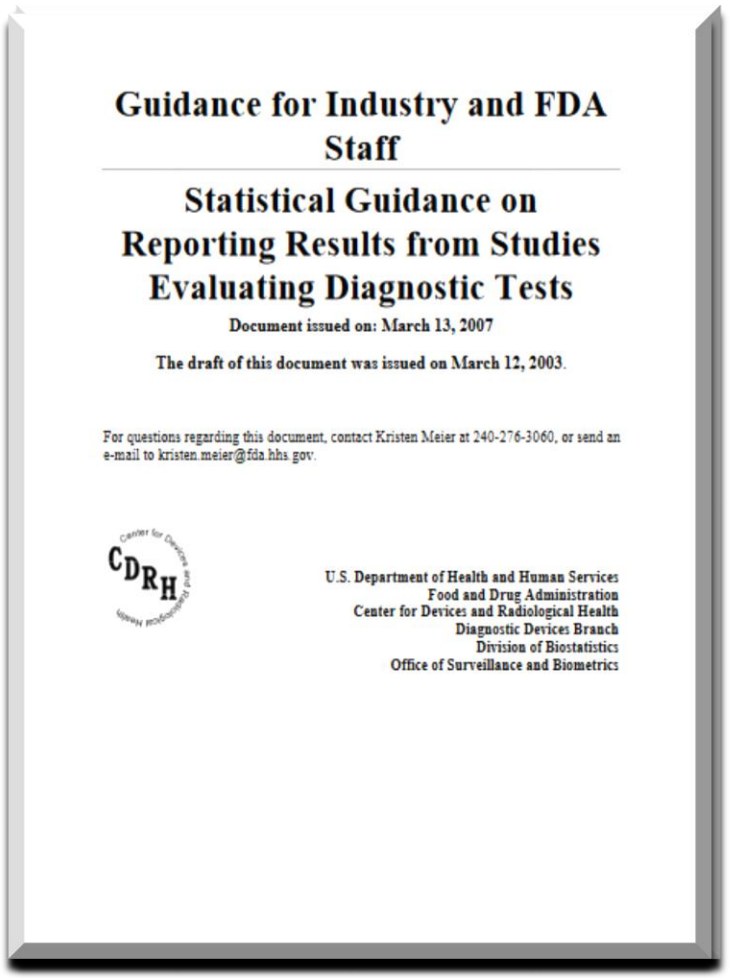
Challenges for Personalized Medicine

- Limited understanding of human body
- Common conditions
- Access to personalized therapeutics
- Lack of infrastructure
- Investment uncertainties
- Outdated disease classification system
- Clinical implementation of new diagnostics

Regulatory Pathways and Policies



Guidance for Industry and FDA Staff

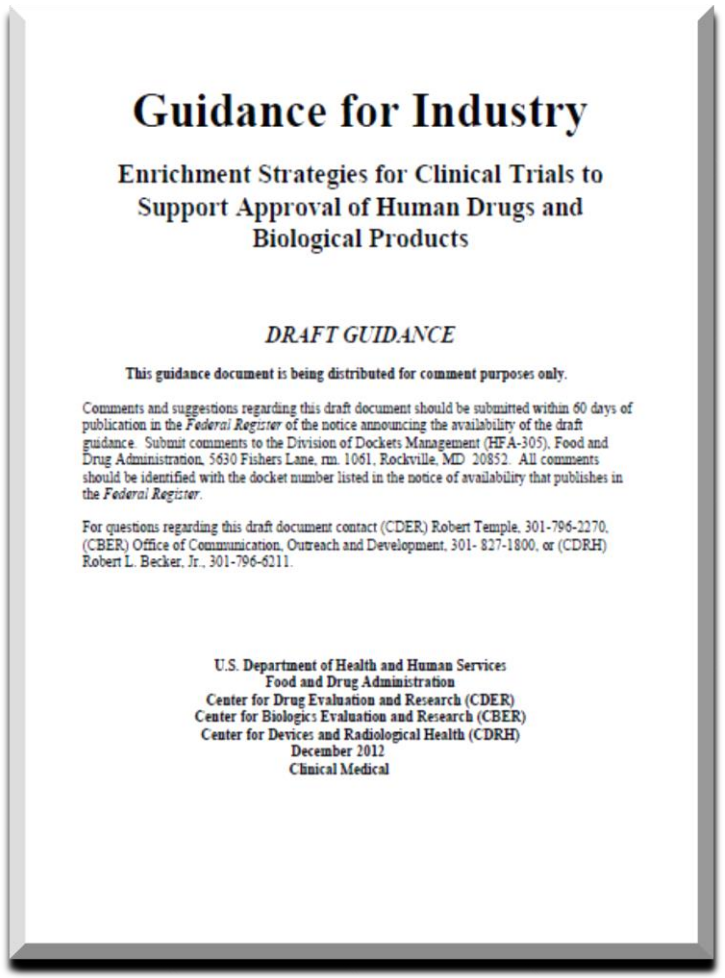
Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests

Document issued on: March 13, 2007

The draft of this document was issued on March 12, 2003.

For questions regarding this document, contact Kristen Meier at 240-276-3060, or send an e-mail to kristen.meier@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Diagnostic Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics



Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

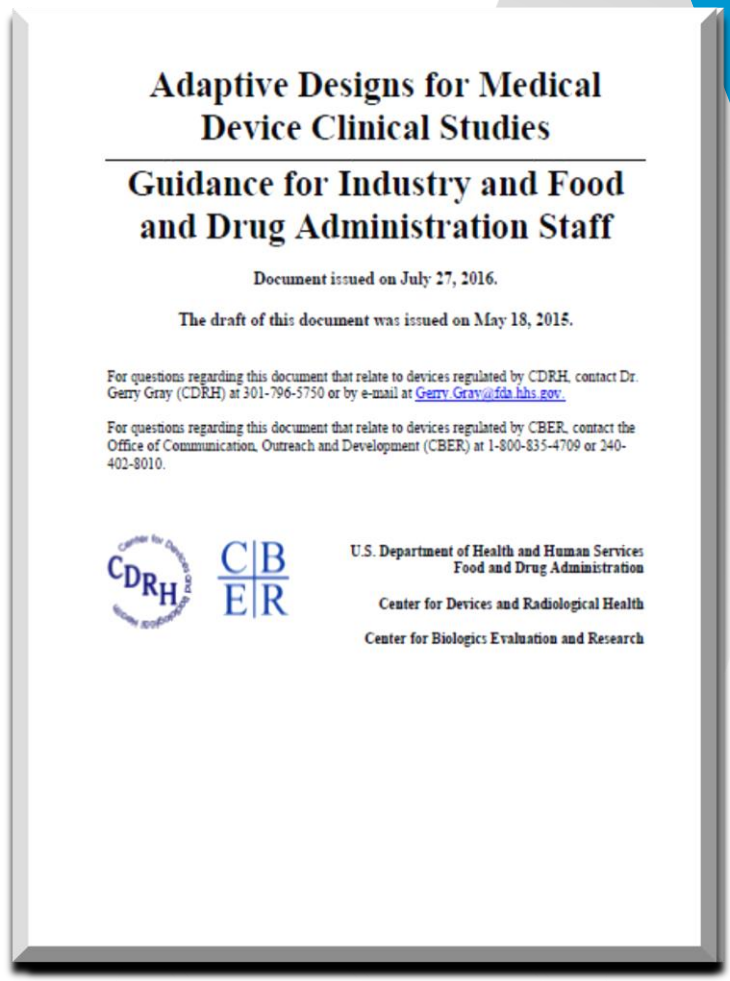
DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical



Adaptive Designs for Medical Device Clinical Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on July 27, 2016.

The draft of this document was issued on May 18, 2015.

For questions regarding this document that relate to devices regulated by CDRH, contact Dr. Gerry Gray (CDRH) at 301-796-5750 or by e-mail at Gerry.Gray@fda.hhs.gov.

For questions regarding this document that relate to devices regulated by CBER, contact the Office of Communication, Outreach and Development (CBER) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
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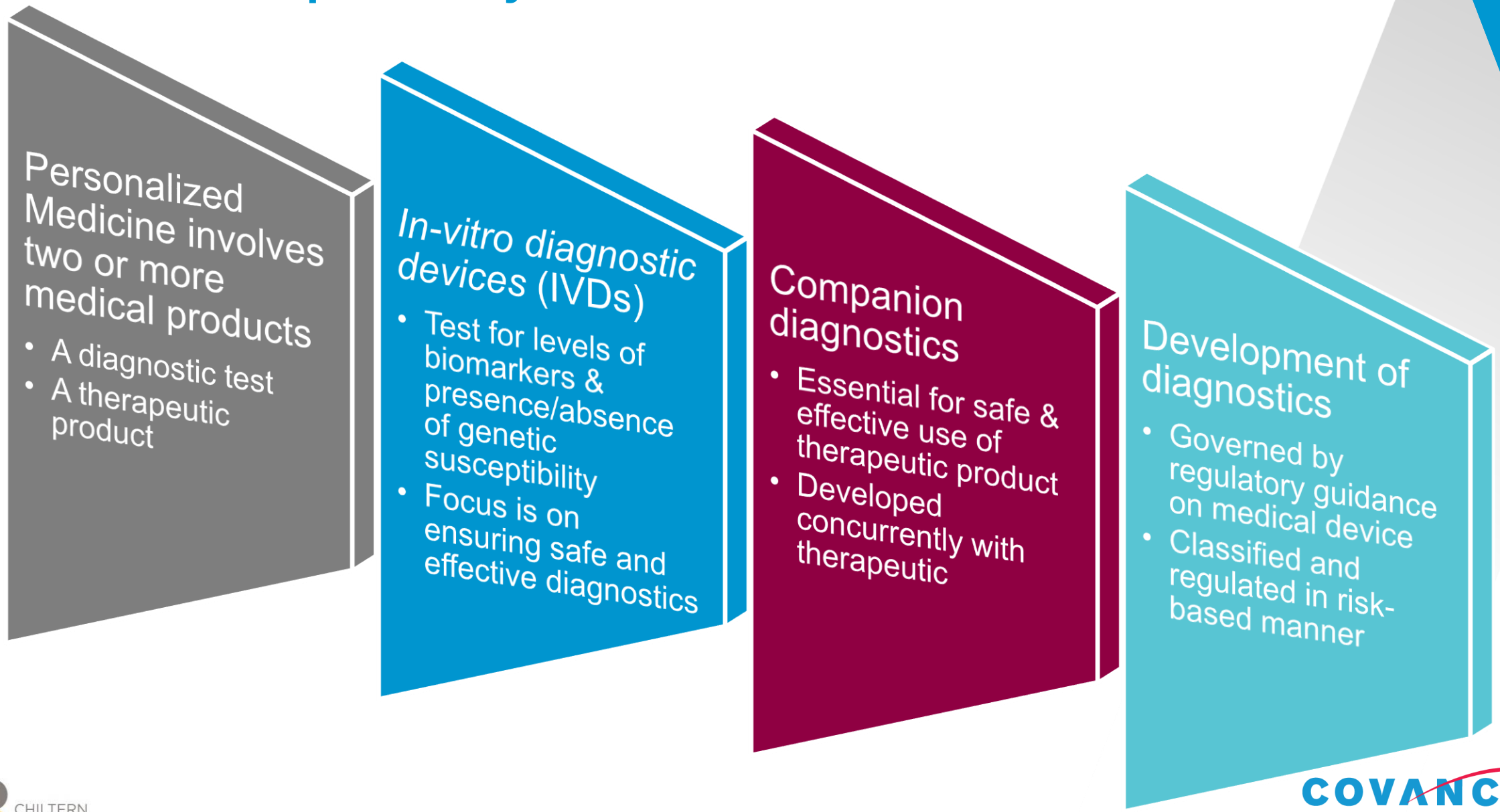
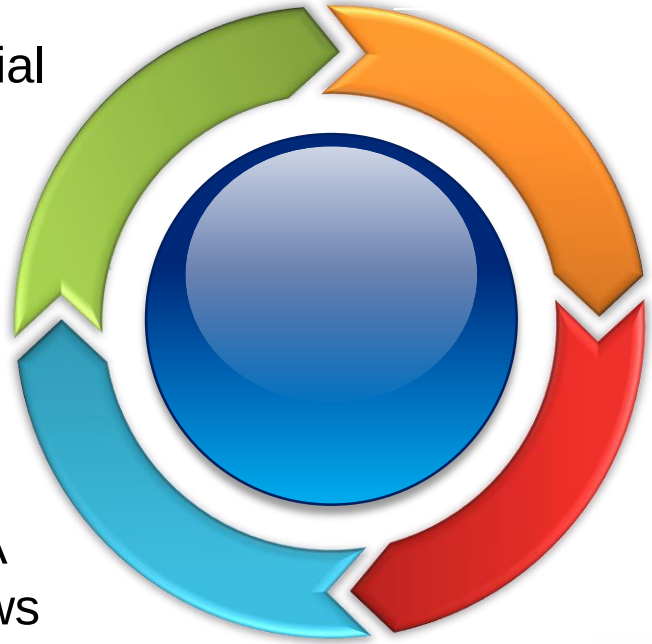
Product Interdependency



Co-development

Cooperation, coordination, and communication between regulatory agency and between sponsors throughout the process are essential for ensuring a successful co-development program

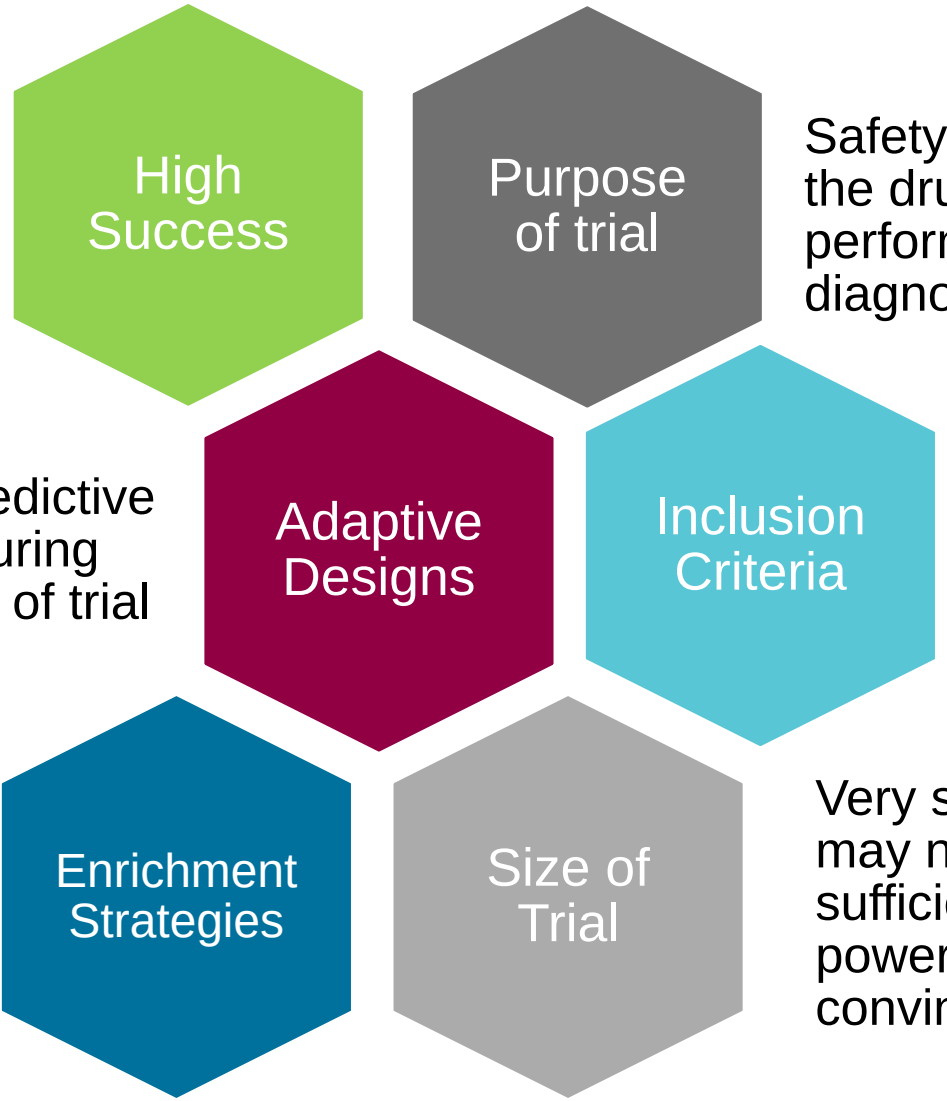


Development of companion diagnostics together with therapeutics allows

- More efficient clinical trials
- Smaller patient populations
- Focused therapies
- Better outcomes
- Fewer treatment delays

Requires expertise and careful coordination between multiple FDA centers to ensure consistent reviews and contemporaneous approval of the two products

Augmenting Clinical Trial Designs



Smaller, faster and less expensive trials

Safety and efficacy of the drug and performance of the diagnostics

Identify predictive markers during the course of trial

Identify patients likely to benefit from drug or biological product

Decreasing heterogeneity

Very small trials may not have sufficient statistical power to yield convincing results

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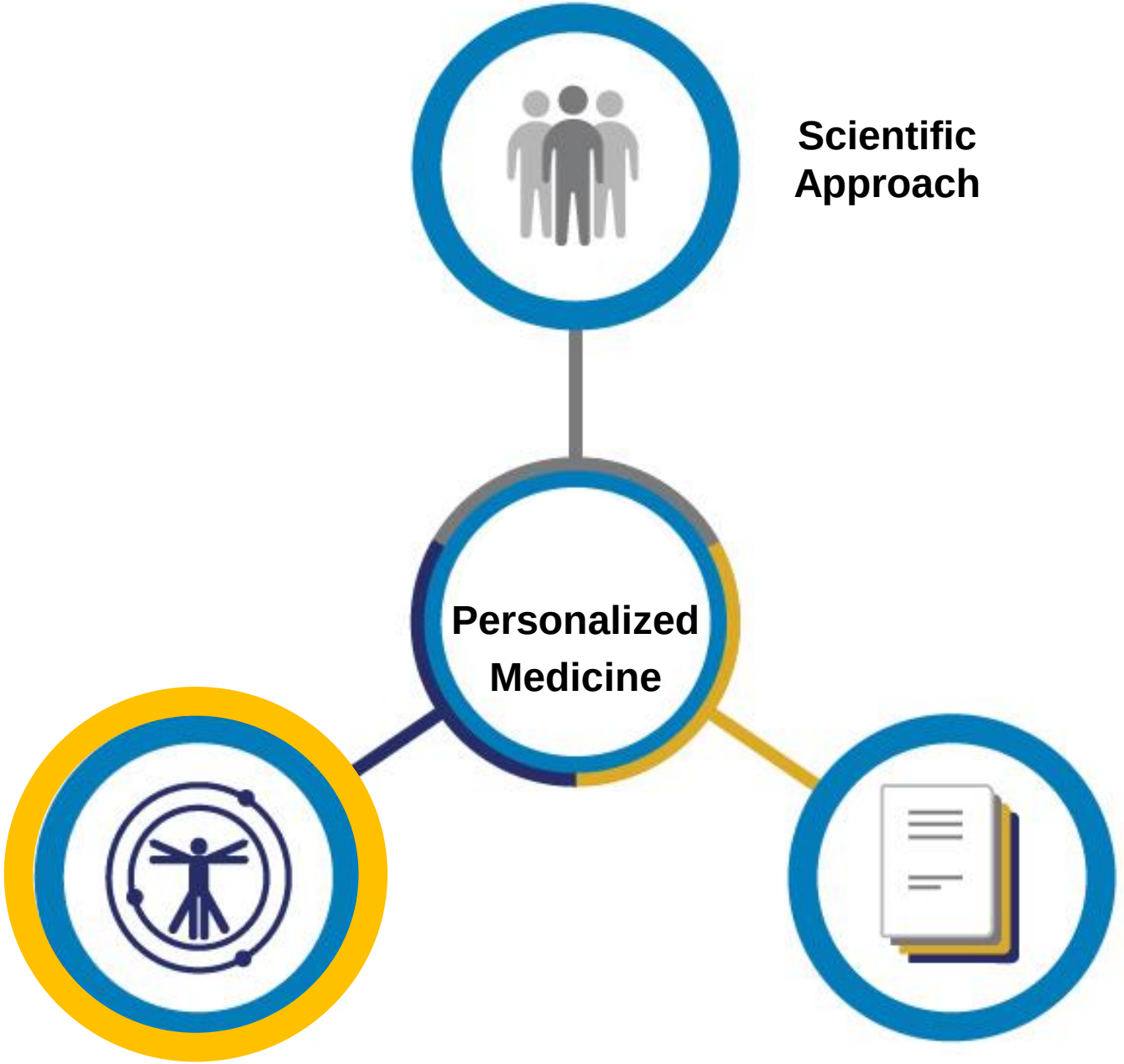
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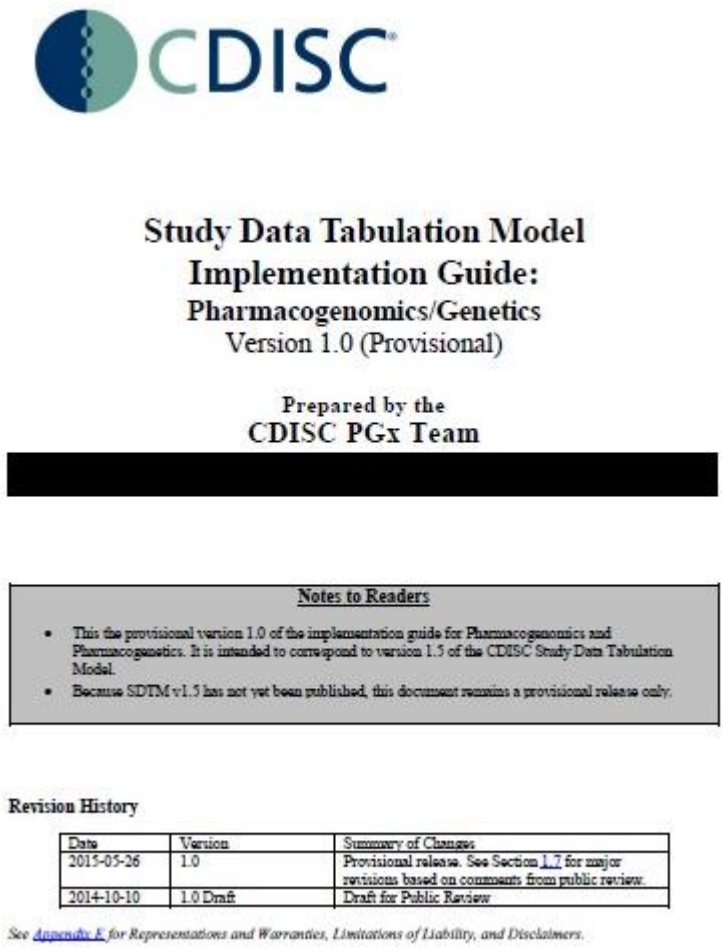
Advent of Pharmacogenomics (PGx)

- Pharmacogenomics (PGx) is the study of DNA and RNA characteristics as related to drug response is one of the most exciting areas of personalized medicine today
- The PGx tests most commonly include gene expression analysis using microarrays, SNP or any genetic polymorphism analysis, genotyping and a few more
- These PGx tests yield huge amount of bio-specimen and genetic (DNA, RNA) sample data, along with clinical significance information
- PGx data is heterogeneous, quite large and very noisy
- Quality and accuracy are less controllable with many forms of PGx data. The application of PGx study in clinical trial setting is being challenged by data inconsistencies

Analyzing PGx Data



CDISC

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

Prepared by the
CDISC PGx Team

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.

CDISC published the SDTMIG-PGx 1.0 in May 2015

The PGxIG1.0 provides guidance on the implementation of the SDTM for gene expression and genetic variation data for human and viral studies. Seven domains are used to carry data from three categories

Category\Class	Event	Findings	Special-Purpose
Data about bio-specimens	BE	BS	RELSPEC
Data about genetic observations		PF, PG	
Data defining genetic biomarker			PB, SB

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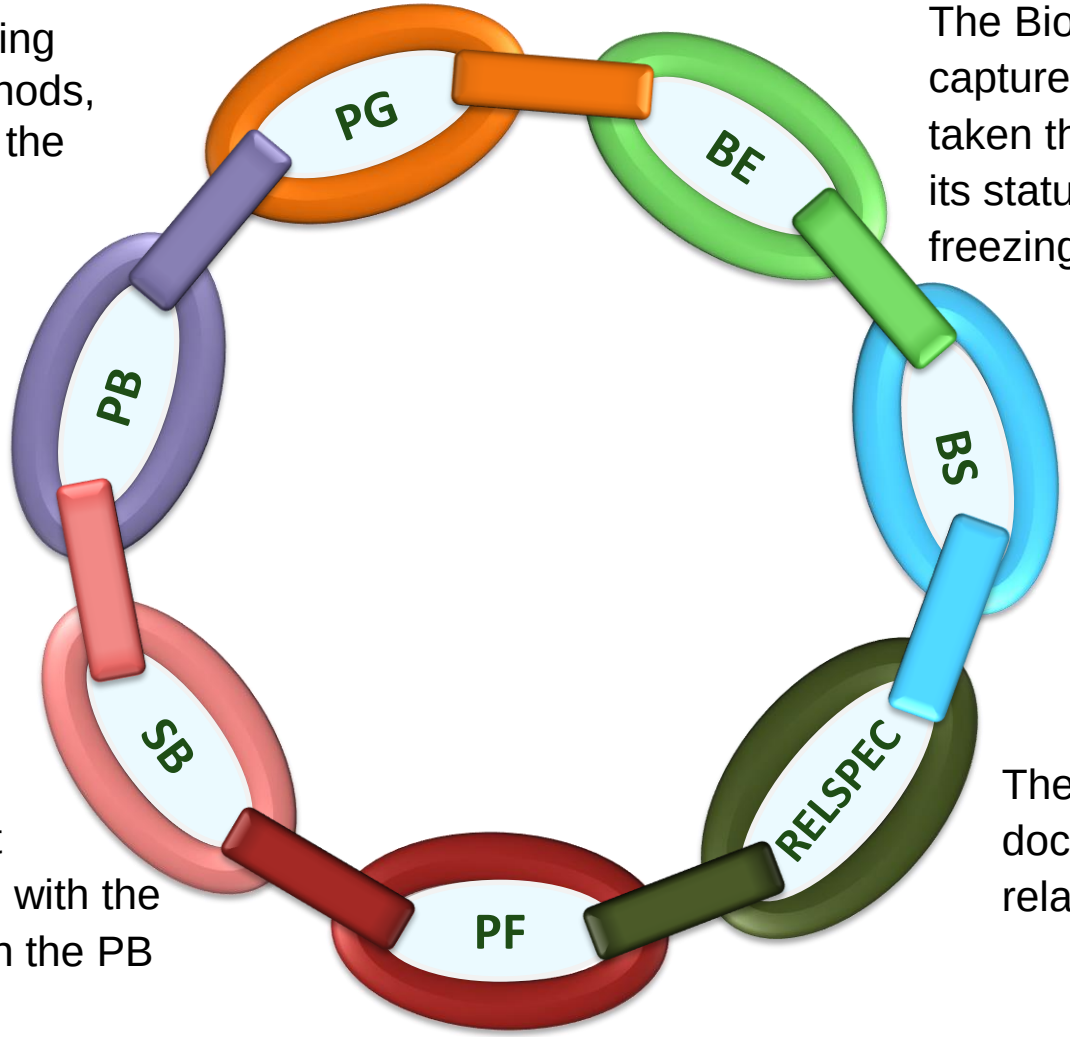
New PGx Domains

PGx/Genetics Methods & Supporting Information domain holds the methods, algorithm and parameters used in the analysis

PGx/Genetics Biomarker domain defines the biomarker and contains known associations between observed biomarkers and medical conclusions (e.g., disease diagnosis, drug resistance)

Subject Biomarker domain connect biomarkers observed in PF domain with the medical conclusions documented in the PB domain for each subject



Data about genetic observations is included in PGx/Genetics Findings domain

The Bio-specimen Events domain captures the details regarding actions taken that affect a specimen or alter its status, such as transportation, freezing, thawing etc.

The findings related to specimen handling, the characteristics of bio-specimens and extracted samples are collected in the Bio-specimen Findings domain

The Related Specimens domain documents the hierarchy of specimen relationships

New Domain, New Learning

Findings Domain

The PGx Findings domain stores key results such as intensity values (both raw and normalized), fold-change, ratio, genetic change, amino-acid change etc. Such data are significantly different from the previously available findings module.

Capturing Heterogeneity

Given the heterogeneity of PGx data, new variables are specified to comply with the dimensions and forms related to genetic variation and gene expression data.

- ✓ --GENRI and --GENTYP are used to annotate the genetic region of interest
- ✓ PFGENLOC and PFGENSR indicate the numeric location and the portion of the genetic variation within the sequence
- ✓ PFRSNUM is assigned to carry 'rs' identifier from dbSNP database or 'cluster' identifier from refSNP database
- ✓ --REFSEQ is given to accession number in RefSeq database to refer genomic DNA, RNA transcripts, and proteins

PGx Mapping Examples – CRF sample

Tumor block/Surgical ID, if applicable	_____
Sample Collection Date	_____
Was this sample sent to the Central Laboratory?	☐ Yes ☐ No
Was corresponding pathology report sent to the Central Laboratory?	☐ Yes ☐ No
Gene or Test	_____
Translocation Status	☐ Positive ☐ Negative ☐ Unknown ☐ Not Determined ☐ Not Applicable
Method Used to Determine Translocation Status	☐ FISH-Break Apart ☐ FISH-Fusion ☐ FISH-Not Specified ☐ Genomics Testing ☐ Other ☐ Not Applicable
Copy Number Status	☐ Amplification

BE = Biospecimen

PF = Pharmacogenomics/Genetics Findings

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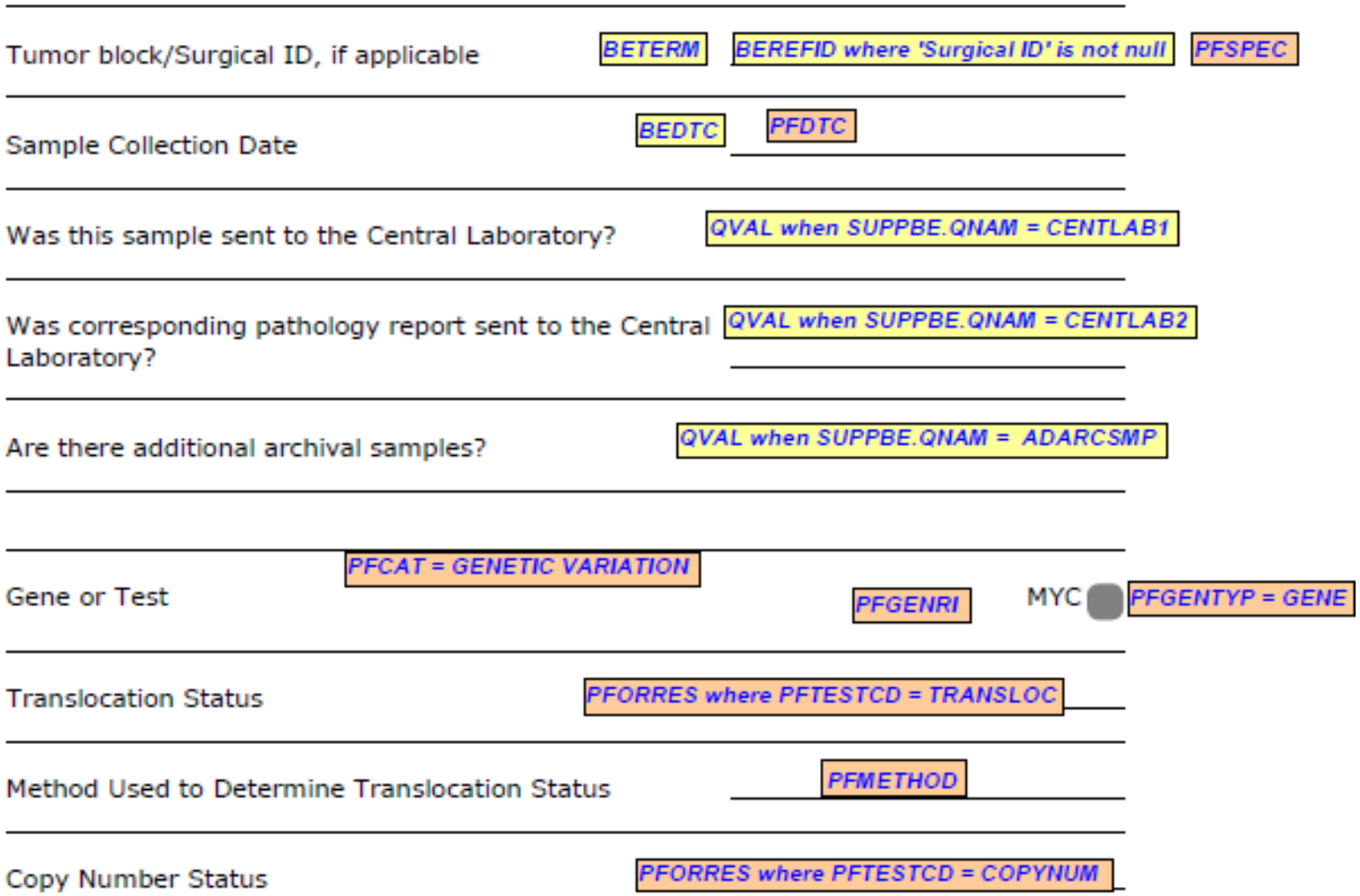
PGx Mapping Examples



PGx Mapping Examples – SDTM Snapshots

USUBJID	BESEQ	BETERM	BECAT	BESCAT	BELOC	VISIT
101-006-1337	1	BONE MARROW	BONE MARROW BIOPSY			SCREENING (DAY -28)
101-006-1337	2	BONE MARROW	BONE MARROW BIOPSY_DE			SCREENING (DAY -28)
101-006-1337	3	PLASMA	PLASMA BIOMARKER COLLECTION			CYCLE 1 DAY 1
101-006-1337	4	SALIVA	SALIVA SAMPLE COLLECTION			CYCLE 1 DAY 1
101-006-1337	5	TUMOR BIOPSY	TUMOR BIOPSY	CORE	BONE MARROW	SCREENING (DAY -28)
101-006-1337	6	WHOLE BLOOD	WHOLE BLOOD EX VIVO COLLECTION			CYCLE 1 DAY 1
101-006-1337	7	WHOLE BLOOD PBMC	WHOLE BLOOD PBMC & CFDNA COLLECTION			CYCLE 1 DAY 1

BE = Biospecimen

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
101-006-1337	BESEQ	3	BESPEC	Specimen Type	CYTOKINES
101-006-1337	BESEQ	3	SPECTPT	Scheduled Time Point	PREDOSE
101-006-1337	BESEQ	4	SAMPCOLL	Sample Collected	N
101-006-1337	BESEQ	4	SPECTPT	Scheduled Time Point	PREDOSE
101-006-1337	BESEQ	6	BESPEC	Specimen Type	WHOLE BLOOD EX VIVO STIMULATION
101-006-1337	BESEQ	6	SPECTPT	Scheduled Time Point	PREDOSE
101-006-1337	BESEQ	7	SAMPCOLL	Sample Collected	Y
101-006-1337	BESEQ	7	SPECTPT	Scheduled Time Point	PREDOSE

PF = Pharmacogenomics/Genetics Findings

USUBJID	PFSEQ	PFSPID	PFTESTCD	PFTEST	PFCAT	PFORRES	PFORRESU	PFMETHOD
101-006-1337	1	4809	COPYNUM	Copy Number Status	COO	Amplification		FISH-Fusion
101-006-1337	2	4809	IHCOTHR	Other Results	COO	Activated B-cell-like (ABC)		IHC
101-006-1337	3	4804	IHCPOSIT	IHC, Percent Positive Cells	BCL2	4	%	
101-006-1337	4	4809	IHCPOSIT	IHC, Percent Positive Cells	COO	23	%	
101-006-1337	5	4803	IHCPOSIT	IHC, Percent Positive Cells	MYC	93	%	
101-006-1337	6	4809	IHCSTAT	IHC Status	COO	Not Determined		
101-006-1337	7	4809	MUTSTAT	Mutation Status	MYD88	Abnormal		PCR
101-006-1337	8	4809	TRANSLOC	Translocation Status	CD10	Negative		FISH-Break Apart

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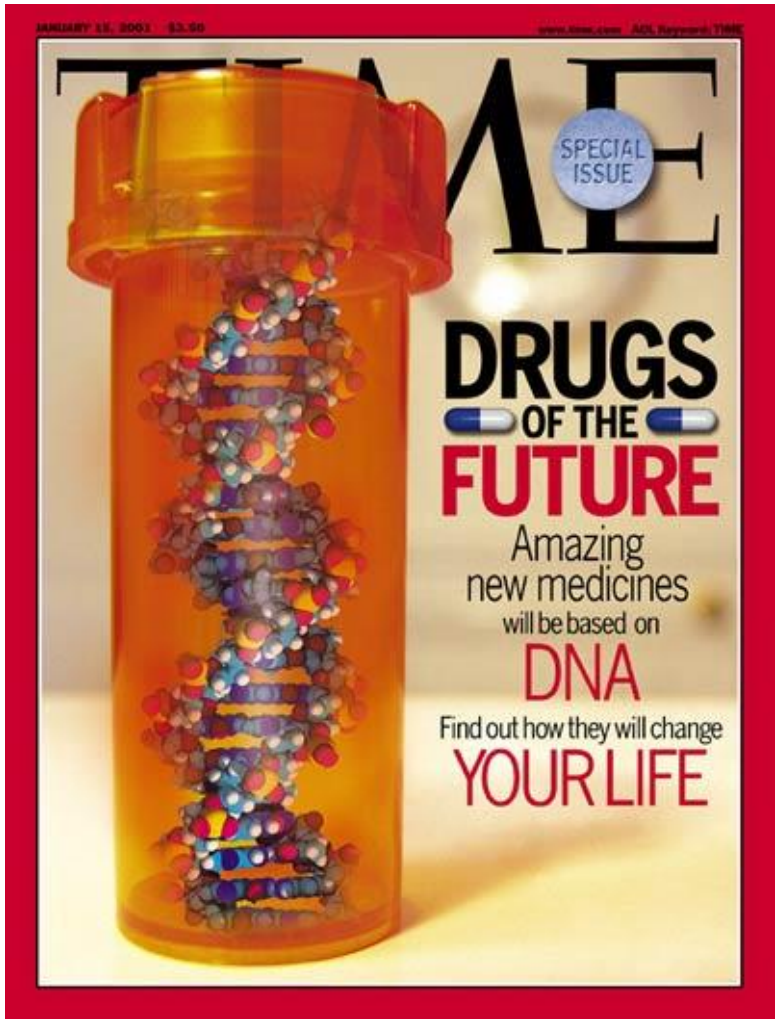
Analysis Dataset and Sample Report

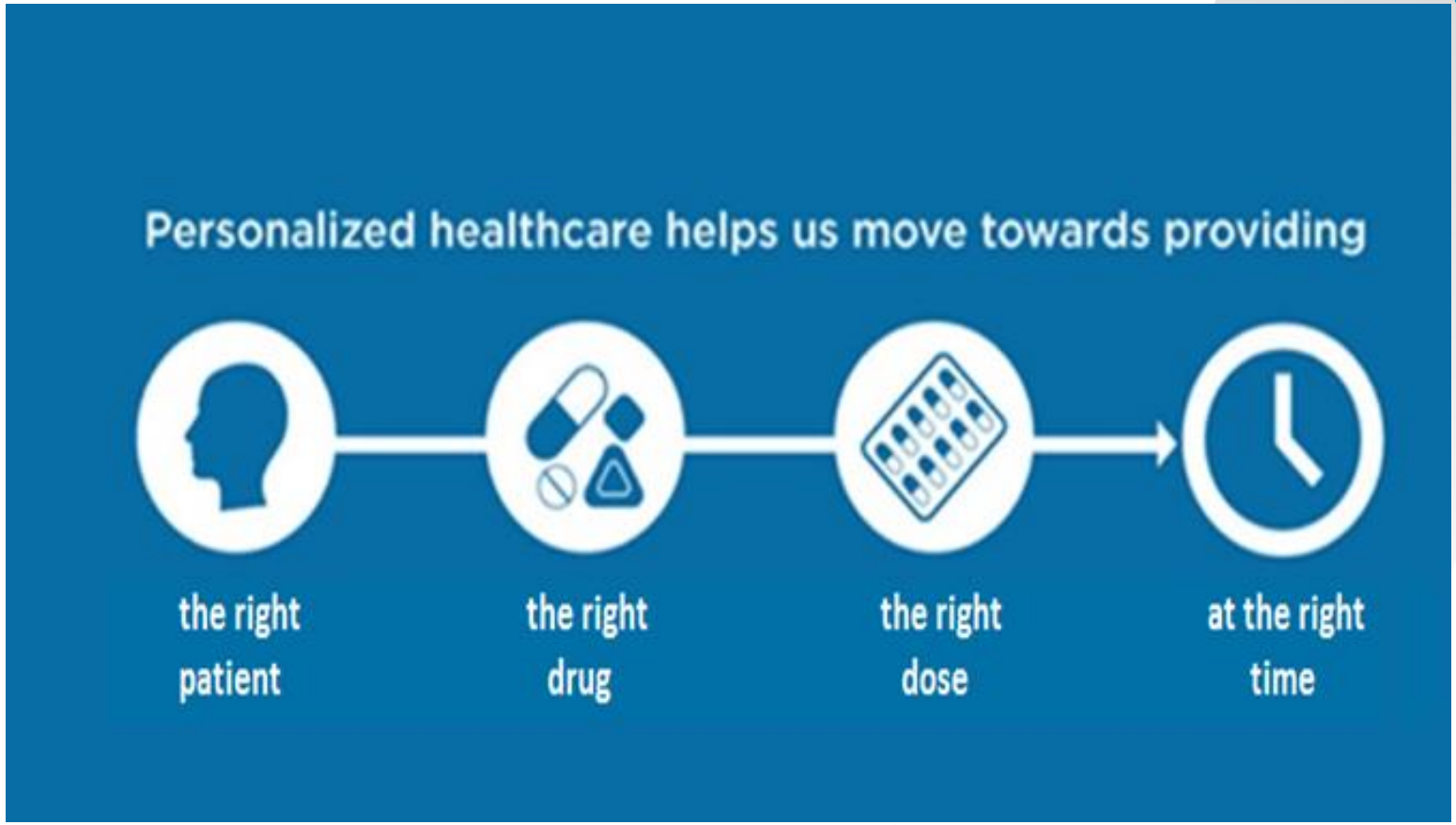
USUBJID	GENE	GENMUTAT	GENOTYPE	PGMUTE	GTESTYN
101-006-1337	Complement C3- Mutation	c.3343G>A	Heterozygous	Yes	Yes
101-006-1337	Complement CD46 (MCP) - Mutation	c.3343G>A substitution p.Asp1115Asn(D1115N) Mutation D1093N	Heterozygous	Yes	Yes
101-006-1337	Complement Factor B - Mutation	c.3470T>Cp(Il57THR)	Heterozygous	Yes	Yes
101-006-1337	Complement Factor H - Mutation	c.3478G>A in exon 27	Heterozygous	Yes	Yes
101-006-1337	Complement Factor I - Mutation	c.463A>C,p.Lys155Gln		Yes	Yes
101-006-133				Yes	Yes
101-006-133				Yes	Yes

Table 3.2.1.1
Genotype of Patients – Pediatric/Adult at Enrollment
UK
Full Analysis Set

	Pediatric (<18 Years at Initial Symptoms)			Adult (>=18 Years at Initial Symptoms)		
Genotype	N with Genotype Data	Result	N with Mutation (%)	N with Genotype Data	Result	N with Mutation (%)
Anti-CFH Antibody	xx	Yes	xx (xx.x)	xx	Yes	xx (xx.x)
		No/Unk	xx (xx.x)		No/Unk	xx (xx.x)
Complement C3 Mutation	xx	Yes	xx (xx.x)	xx	Yes	xx (xx.x)
		No/Unk	xx (xx.x)		No/Unk	xx (xx.x)
Complement Factor H Mutation	xx	Yes	xx (xx.x)	xx	Yes	xx (xx.x)
		No/Unk	xx (xx.x)		No/Unk	xx (xx.x)
Complement Factor I Mutation	xx	Yes	xx (xx.x)	xx	Yes	xx (xx.x)
		No/Unk	xx (xx.x)		No/Unk	xx (xx.x)
Complement CD46 (MCP) Mutation	xx	Yes	xx (xx.x)	xx	Yes	xx (xx.x)
		No/Unk	xx (xx.x)		No/Unk	xx (xx.x)

Personalized Medicine is the ……. “Future”





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- Genomic Data Commons (GDC): https://portal.gdc.cancer.gov/
- The Video shown with permission from GDC
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- "*Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*" – US FDA, October 2013

- CDISC SDTM IG v1.0 Pharmacogenomics/Genetics

https://www.cdisc.org/standards/foundational/pgx

- "*Implementation of STDM Pharmacogenomics/Genetics Domains on Genetic Variation Data*" - Linghui Zhang, PharmaSUG 2017

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Gaurab and Pritish would like to thank Chiltern colleagues, especially Yash Sonak, Lekshmanan Subbiah and Neha Srivastava for their help in making this presentation a better one.