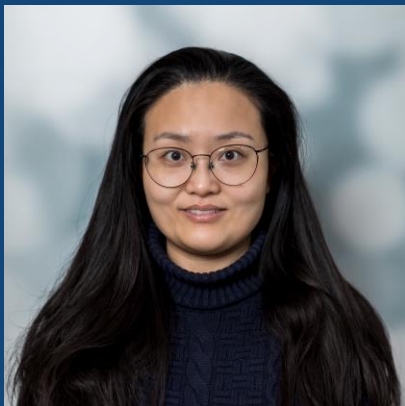cdisc

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US

INTERCHANGE

FALLS CHURCH, VA | 18-19 OCTOBER

Challenges and Solutions in Chromosome Aberration Data Mapping to Genomics Findings (GF) Domain for Oncology Studies

Presented by Shanshan Ma, Senior Manager, Biostatistics, Agenus

Meet the Speaker

Shanshan Ma

Title: Senior Manager

Organization: Agenus

Shanshan has been working in pharmaceutical industrial for nine years and has solid knowledge and hands on experience in conducting data analysis in medical terminology and drug development process from SAP through FDA submission in oncology area. With the participation in in-house SDTM automation process, she built an intensively understanding for CDISC compliance implementation in real data. And this presentation is based on her experience with previous employer, BeiGene.
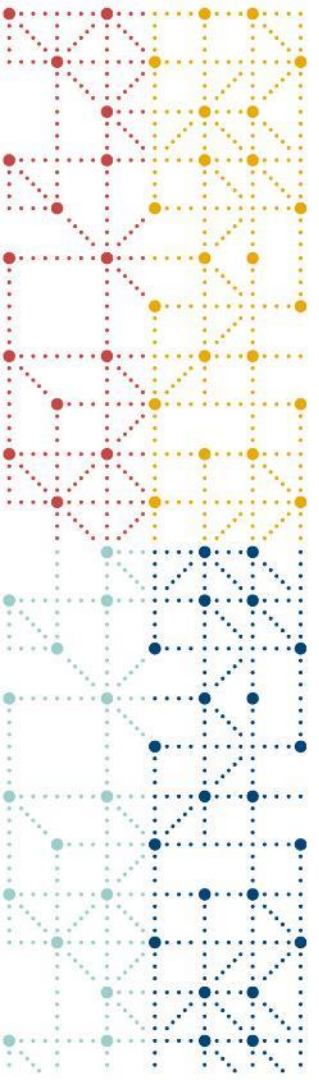
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- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

  - *The author have no real or apparent conflicts of interest to report.*
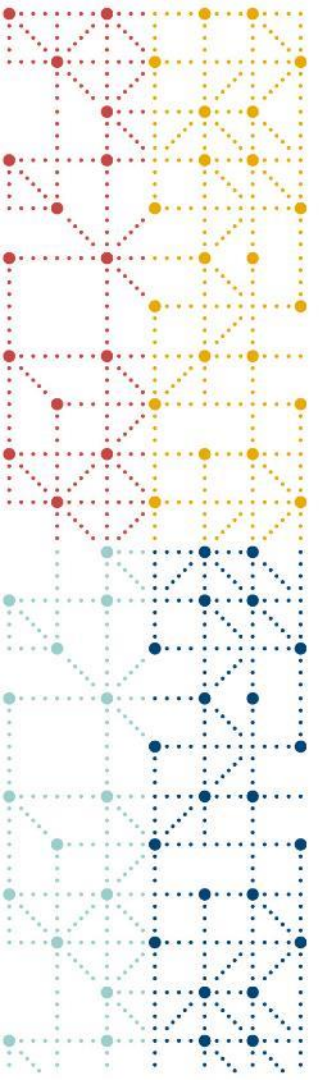
Agenda

Background of Chromosome Aberration

- What is Chromosome aberration
- Main methods used for Chromosome aberration assessment
- Relevant domains used for Chromosome aberration and differentiation in domain mapping

Chromosome aberration

- Chromosomes Structural Variation
  - Deletion (del)
  - Duplication (dup)
  - Inversion (inv)
  - Translocation (trans)
  - Substitution
- Chromosomes Number Variation
  - Trisomy
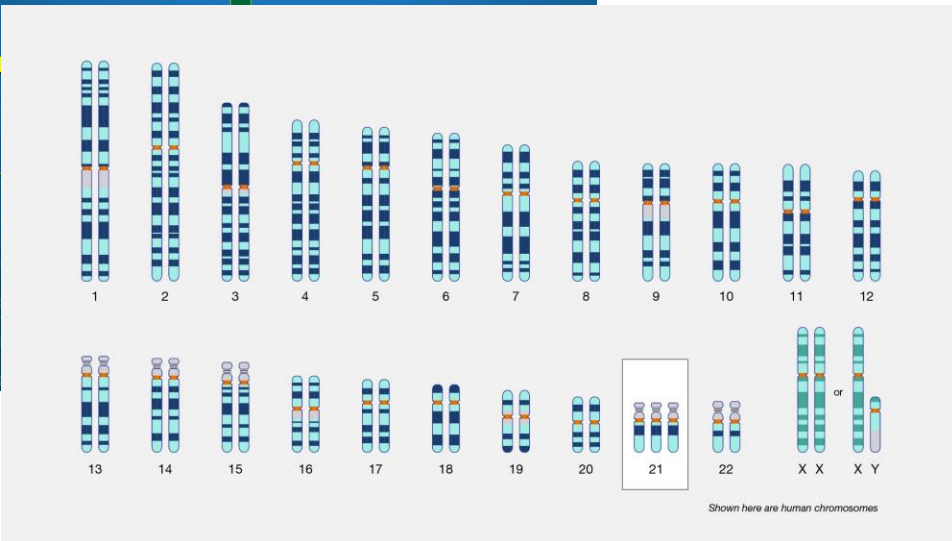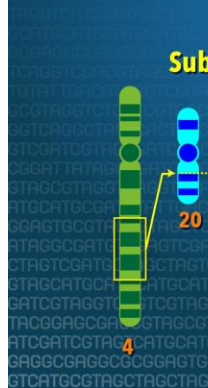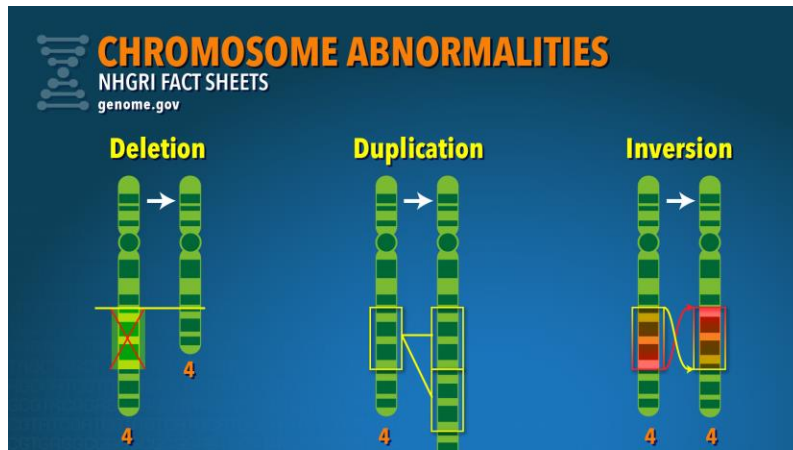
(Images by National Human Genome Research Institution)

Assessment method related to chromosome aberration

- Karyotyping

5 mL venous blood

Add phytohemagglutinin and culture medium

Culture at 37°C for 3 days

Add colchicine and hypotonic saline → Cells fixed

Spread cells onto slide by dropping

Digest with trypsin and stain with Giemsa

Analyze "metaphase spread"

Karyotype

- Fluorescent in-situ hybridization (FISH)

Fluorescently Labeled Probe DNA

Target DNA

Denature to separate DNA strands and allow probe access to target DNA.
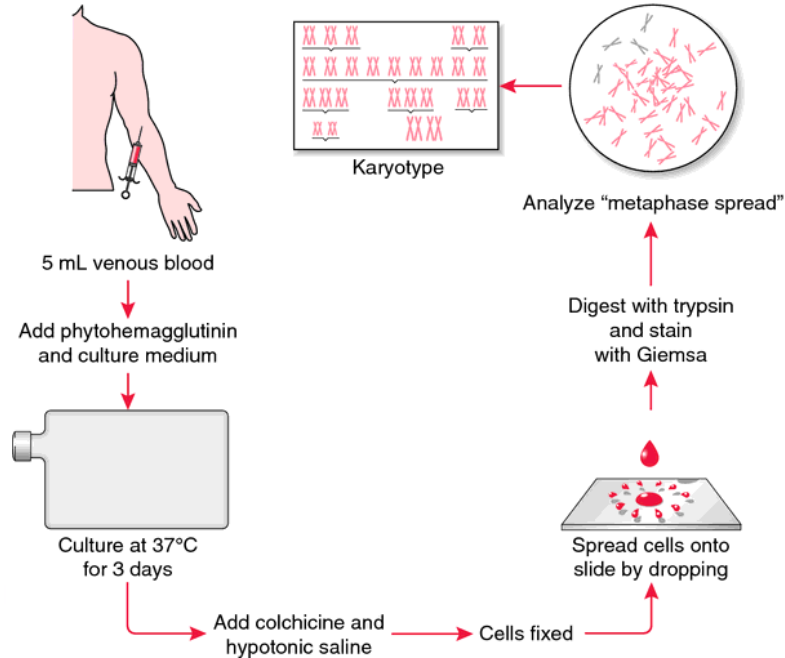
Hybridize together to bind probe to target DNA.

Analyze probe signals using a fluorescent microscope.

What is FISH?
Fluorescence *In Situ* Hybridization
Detects and localizes specific DNA sequences using fluorescently labeled complementary DNA probes.

- Mueller RF, Young ID, Emery AEH (2001) Emery's elements of medical genetics. Churchill Livingstone, Philadelphia.
- https://www.ogt.com/media/wred0xfk/fish-and-cytogenetics-schematic-depicting-each-step-involved-in-fish.png?width=710&height=507&mode=max

Differences between GF, MI, and CP domains

Subject

↓

Biological Specimen

Tested for

Using FISH *Using karyotyping* *Using flow cytometry*

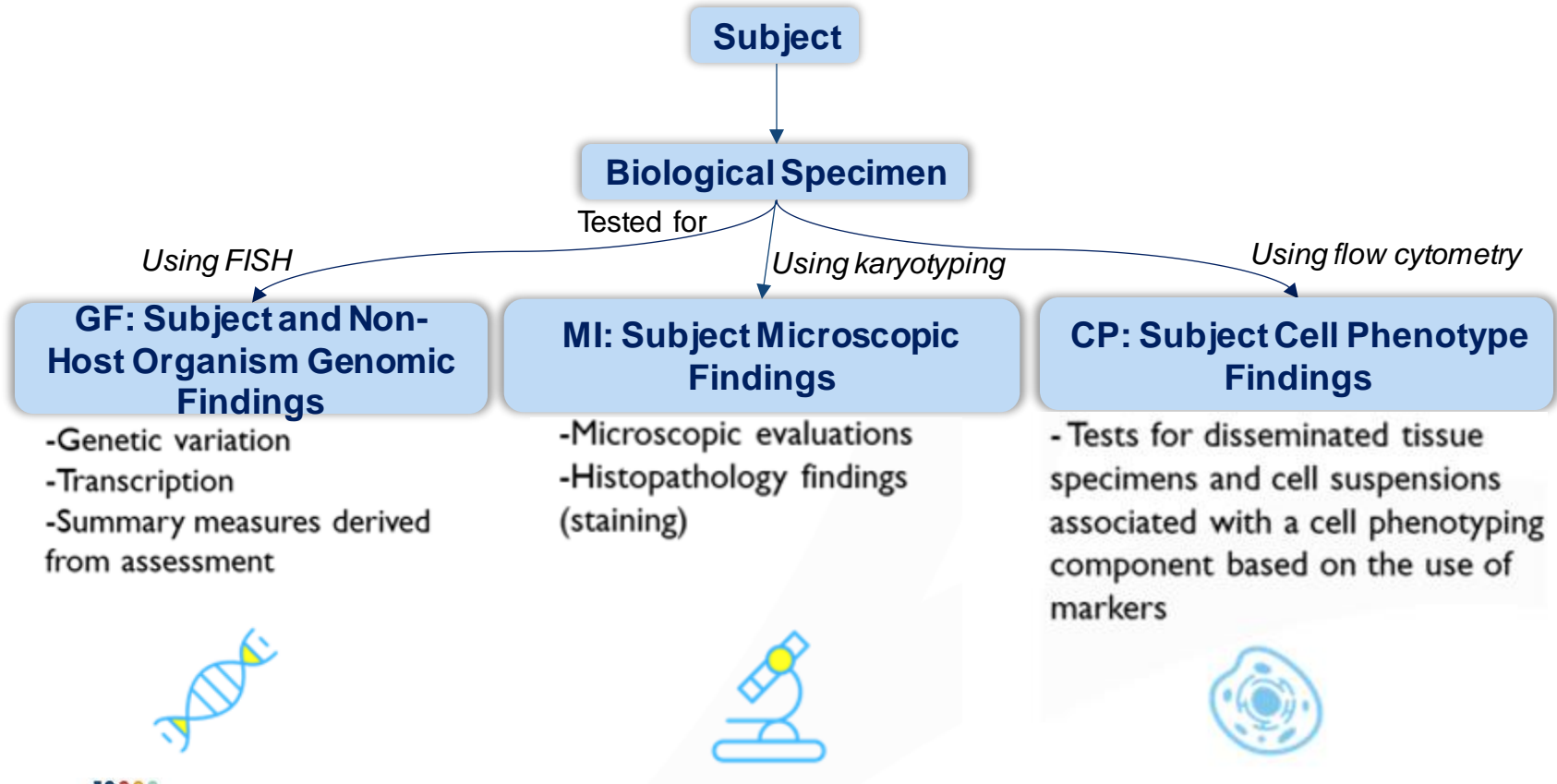| **GF: Subject and Non-Host Organism Genomic Findings**	**MI: Subject Microscopic Findings**	**CP: Subject Cell Phenotype Findings**
-Genetic variation -Transcription -Summary measures derived from assessment	-Microscopic evaluations -Histopathology findings (staining)	- Tests for disseminated tissue specimens and cell suspensions associated with a cell phenotyping component based on the use of markers

GF Domain Introduction

- GF background introduction
- Challenges of mapping chromosome aberration

GF Domain background introduction

Pharmacogenomics Findings (PF) Domain ❌

Genomics Findings (GF) Domain ✅

May 2015

November 2021

✓ SDTMIG-Pharmacogenomics/Genetics (PGx) v1.0
  - Captures results for both genetic variation and gene expression, for both clinical and non-clinical use, and for both study subjects and infectious microbes and viruses

✓ SDTMIG v3.4
  - Includes but is not limited to assessments and results for genetic variation and transcription, and summary measures derived from these assessments
  - Domain renamed and clarified to accurately describe genomic data
  - Variables clarified/added, New concepts added
  - Maintaining a separate implementation guide for genomics does not add value

Challenges of mapping chromosome aberration

- Chromosome aberration broad definition makes it difficult to map properly

| Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	NCI Preferred Term
SDTM Microscopic Findings Test Code	CYEXAM	Cytogenetic Examination	An assessment by microscopic analysis of chromosomal and subchromosomal structure and function.	Cytogenetic Analysis

  - GF or MI(Microscopic Findings) or CP(Cell Phenotype Findings)?

- Lack of examples and accompanying Controlled Terminology

Genomic Findings Test Code (GFTESTCD) (codelist code = C18117)	Genomic Findings Test Name (GFTEST) (codelist code = C181179)		C-code (Concept Code)	Genomic Findings Test Detail (GFTSDTL) (codelist code = C181180)		C-code (Concept Code)	No Yes Response (NY) (codelist code = C6674?)		C-code (Concept Code)
SNV	Single Nucleotide Variation		C45447	GENOTYPE					
SNV	Single Nucleotide Variation		C181343	PREDICTED AMINO ACID CHANGE					
SNV	Single Nucleotide Variation		C181344	PREDICTED CODING SEQUENCE CHANGE					
SNV	Single Nucleotide Variation		C155320	READ DEPTH					
SNV	Single Nucleotide Variation		C181345	VARIANT IMPACT CLASSIFICATION					
SNV	Single Nucleotide Variation		C181346	VARIANT READ DEPTH					
SNV	Single Nucleotide Variation		C181347	VARIANT READ DEPTH/READ DEPTH					C25613

  - SNV including chromosome aberration?
  - What kind of variation belongs to single nucleotide variation?
  - What if we have multiple types of chromosome aberration, can we all map them to SNV?
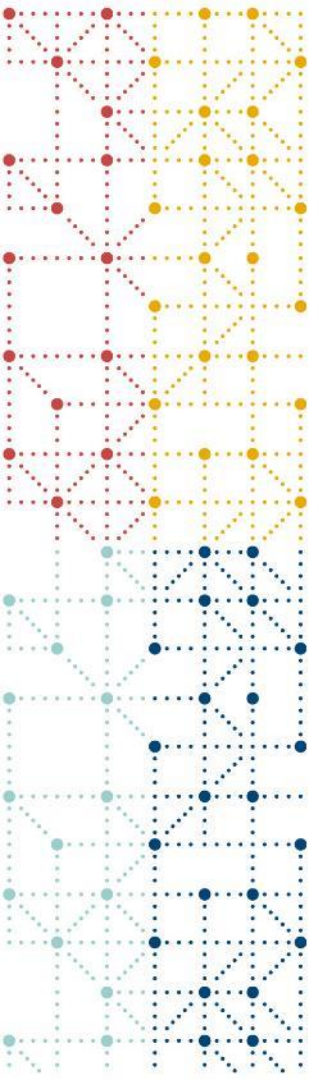
Mapping Chromosome aberration into GF Domain

- Key variables related to GF mapping
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), example from real data
- Mapping illustration

Key variables related to GF mapping

Variable Name	Variable Label	CDISC Codelist	CDISC Notes
GFTESTCD	Short Name of Genomic Measurement	(GFTESTCD)	Short name of the measurement, test, or examination described in GFTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in GFTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g., "1TEST" is not valid). GFTESTCD cannot contain characters other than letters, numbers, or underscores.
GFTEST	Name of Genomic Measurement	(GFTEST)	Long name for GFTESTCD. The value in GFTEST cannot be longer than 40 characters.
GFTSTDTL	Measurement, Test, or Examination Detail	(GFTSDTL)	Description of a reportable qualifying the assessment in GFTESTCD and GFTEST.
GFCHROM	Chromosome Identifier		The designation (name or number) of the chromosome or contig on which the variant or other feature appears (e.g., "17"; "X").
GFINHERT	Inheritability		Identifies whether the variation can be passed to the next generation.
GFGENLOC	Genetic Location		Specifies the location within a sequence for the observed value in GFORRES.
GFGENSR	Genetic Sub-Region		The portion of the locus in which the variation was found. Examples: "Exon 15", "Kinase domain".

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Example: Cytogenetic testing for CLL/SLL

del17p status — Positive ☐ (11) Negative ☐ Unknown ☐

del11q status — Positive ☐ (12) Negative ☐ Unknown ☐

del13q status — Positive ☐ (13) Negative ☐ Unknown ☐

trisomy 12 — Positive ☐ (14) Negative ☐ Unknown ☐

- CLL/SLL background

Example	GFTESTCD	GFTEST	GFTSTDTL	GFCHROM	GFORRES
del(11q)	DEL	Deletion	OVERALL STATUS	11q	NEGATIVE
del(13q)	DEL	Deletion	OVERALL STATUS	13q	POSITIVE
del(17p)	DEL	Deletion	OVERALL STATUS	17p	UNKNOWN
trisomy 12	DUP	Duplication	OVERALL STATUS	12	POSITIVE
t(11; 14)	TRANS	Translocation	OVERALL STATUS	11;14	UNKNOWN

October 18, 2023

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Let's Try to Map It to GF

CLL/SLL (Cytogenetics)

GFCHROM = 11q

del(11q)   ☐ Yes   ☐ No   ☐ Unknown

del(13q)   ☐ Yes   ☐ No   ☐ Unknown

del(17p)   ☐ Yes   ☐ No   ☐ Unknown

GFTESTCD = DEL
GFTEST = Deletion

GFCHROM = 13q

GFORRES = POSITIVE

GFORRES = NEGATIVE   **GFORRES = UNKNOWN**

GFCHROM = 17p

CLL/SLL (Cytogenetics)

trisomy 12   ☐ Yes   ☐ No   ☐ Unknown

GFTESTCD = DUP
GFTEST = Duplication

GFCHROM = 12

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Additional step after mapping

- Another challenge – no CT term available for chromosome aberrations
  - Suggestion: propose the sponsor custom terms and submit new term requests to CDISC (link here)
- BeiGene has submitted the related terms of GFTESTCD/GFTEST/GFTSTDTL to CDISC, which will be considered for CDISC CT package 55 to be released on 29Sep2023.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1		Your term request has been received by																				
	Status	Date of Submission	Request Code	Submitter Name	Submitter Affiliation	Submitter E-mail	Submitter Phone	Conf. E-mail sent?	Date	Request Type	CDISC Codelist	New Term or Codelist/Existing Term or Code Number (Summary)	Detailed Description	File uploaded? If yes, enter file name.	NCI Decision	Date of Implementation	Date sent to CDISC	CDISC Decision	Date	Team (codelist)	CDISC back to requester	Date of Final Implementation
2																						
8	Open	2023/4/19	CDISC-6021	Shanshan Ma	Beigene	shanshan.ma@beigene.com	n/a	Y	2023/4/19	Create New Term	Multiple	Add Chromosomal abnormalities related terms into GFTEST and GFTESTCD code list with suggested GFTSTDTL.	File emailed separately Multiple term request spreadsheet supplement to term suggestions request of "Add Chromosomal abnormalities related terms into GFTEST and GFTESTCD code list with suggested GFTSTDTL.". Thanks! Regards, Shanshan Ma Senior, Statistical Programmer Scientific Programming BeiGene USA, Inc.	Y(2023-04-21_Multiple Term Request Spreadsheet_Shanshan_04192023)	Send to CDISC for review		2023/4/21	Consider for P55	2023/4/29	Genomics (GFTEST-CD); (GFTSTDTL)		

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Additional examples for Genetic variation

GFINHERT

Example	GFTESTCD	GFTEST	GFTSTDTL	GFORRES	GFSYM	GFINHERT
Germline BRCA1 Mutation	SNV	Single Nucleotide Variation	DETECTION	DETECTED	BRCA1	**GERMLINE** VARIATION
Somatic BRCA1 Mutation	SNV	Single Nucleotide Variation	DETECTION	DETECTED	BRCA1	**SOMATIC** VARIATION

GFGENLOC and GFGENSR

Example	GFTESTCD	GFTEST	GFTSTDTL	GFSYM	GFGENLOC	GFGENSR
EGFR mutation with S768I	SNV	Single Nucleotide Variation	PREDICTED AMINO ACID CHANGE	EGFR	S768I	Exon20

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Reference

- CDISC SDTMIG v3.4
- CDISC Controlled Terminology
- CDISC GF Codetable Mapping File, CDISC Rules for Genomics
- CDISC Webniar - Introduction to the SDTM Genomics Findings (GF) Domain
- NCI – Chromosomes Fact Sheet, Fluorescence-In-Situ-Hybridization
- OSMOSIS – Chromosomal Aberrations - What Are They, Causes, and More
- PharmaSUG China 2022 SR145 Time to Get in the Genomics Findings (GF) Domain
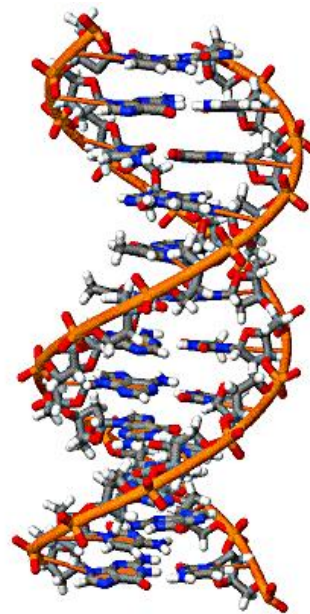
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- Thank you all who helped in reviewing and giving comments to the paper and slides!

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Q & A >

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Thank You!