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Simplifying PGx SDTM Domains for Molecular biology of Disease data (MBIO)

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ABSTRACT

Pharmacogenomics/genetics peruses how the genetic makeup of an individual affects his/her response to drugs. It deals with the influence of acquired and inherited genetic variation on drug response in patients by correlating genetic expression with pharmacokinetics (drug absorption, distribution, metabolism and elimination) and pharmacodynamics (effects mediated through a drug's biological targets). The purpose of the SDTMIG-PGx is to provide guidance on the implementation of the SDTM for biospecimen and genetics-related data. The domains presented in the SDTMIG-PGx are intended to hold data that fall into one of three general categories: data about biospecimens, data about genetic observations, and data that define a genetic biomarker or assign it to a subject.

The paper will throw some light on the mapping challenges encountered in MBIO data with sample CRF pages illustration.

INTRODUCTION

WHAT DOES MOLECULAR BIOLOGY MEAN?

The study of biology on a molecular level including the structure, function, and makeup of biologically important molecules such as DNA, RNA, and proteins. The field of molecular biology involves many other areas of biology such as biochemistry and genetics.

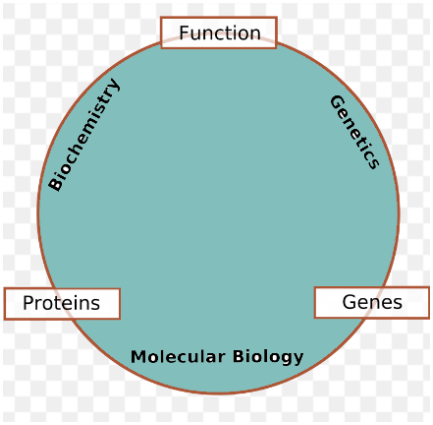

Figure 1. Molecular Biology Concept

The particulars of an individual's genetic sequences affect the response of the individual to drugs. The predictability of safety and efficacy of a drug has increased to a significant level, as both are influenced by the genetic status of the individual, which can be assessed by PG studies. Pharmacogenetics involves the study of single gene mutations and their effect on drug response. The pharmacogenomics involves surveying the entire genome to assess several determinants of drug responses.

The SDTMIG-PGx provides guidance on implementation of the SDTM for biospecimen collection, specimen handling and genetic data, such as genetic variation, gene expression, cytogenetics, viral genetics and proteomics. Depending on the nature of the genetic data collected, one or more SDTM implementation guides need to be used in addition to SDTMIG-PGx, to map to different domains.
Incorporating Pharmacogenomics and pharmacogenetics data that is obtained in clinical trials by testing biological samples collected from the patient and the results of which may have implications for the subject or for a drug is not addressed in the approved SDTMIG. Recently, CDISC PGx team came up with draft guidance SDTMIG for Pharmacogenomics/ Genetics (SDTMIG-PGx) that provides some direction to sponsors.

SDTMIG - PGX DOMAINS AND DATASETS

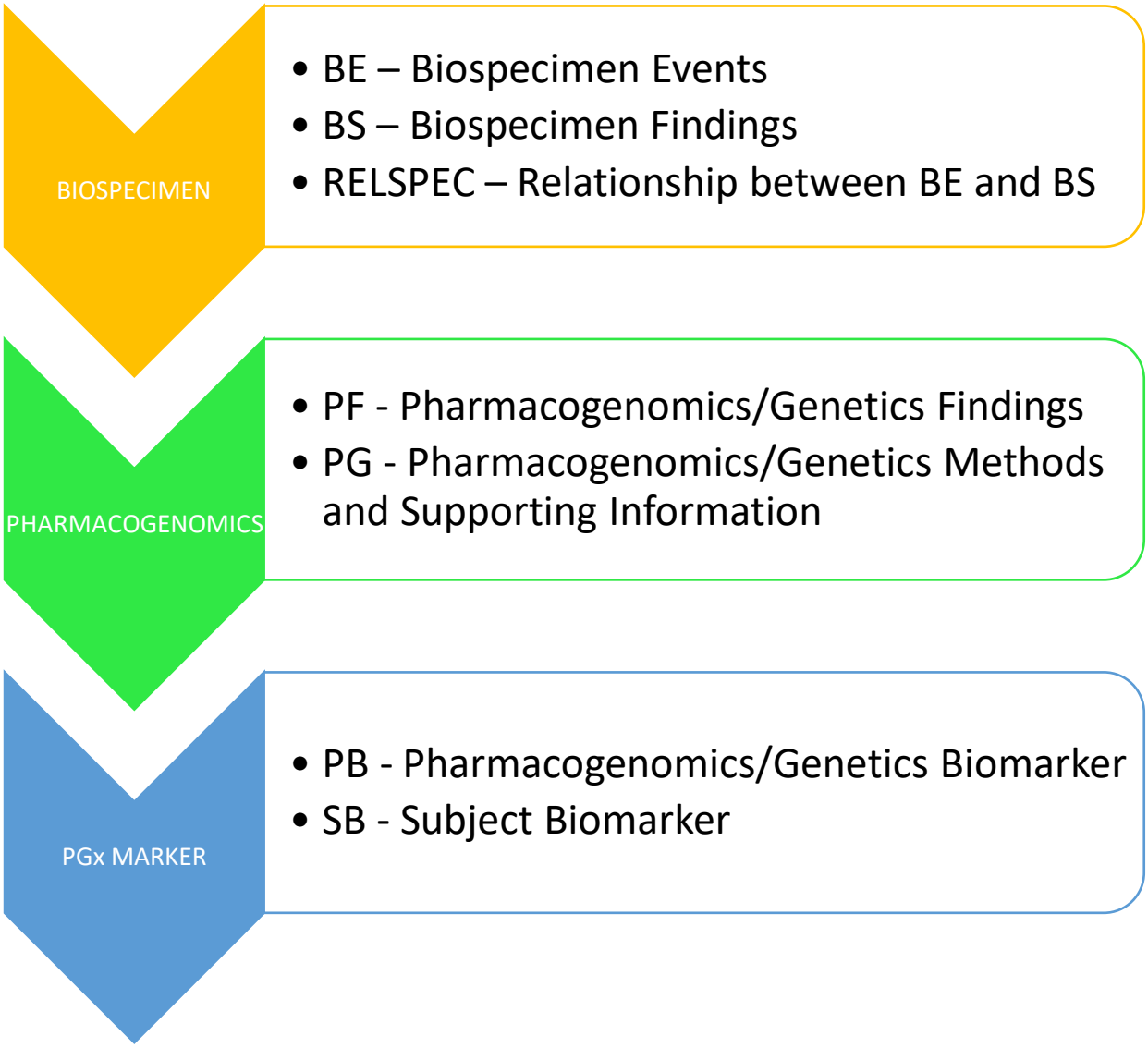

Figure 2. PGx SDTM Domains

In this paper we will be focusing on BE, BS, PF and MI domains. However, MI (Microscopic findings) domains is referenced from SDTM IG.

BIOSPECIMEN EVENTS - BE

BE domain is used to capture information about actions taken that affect a specimen or alter its status. Data may include what the action taken was (e.g., transportation, freezing, thawing), when the action occurred (the date/time associated with it), and who or what party became accountable for the specimen (e.g., site, laboratory).

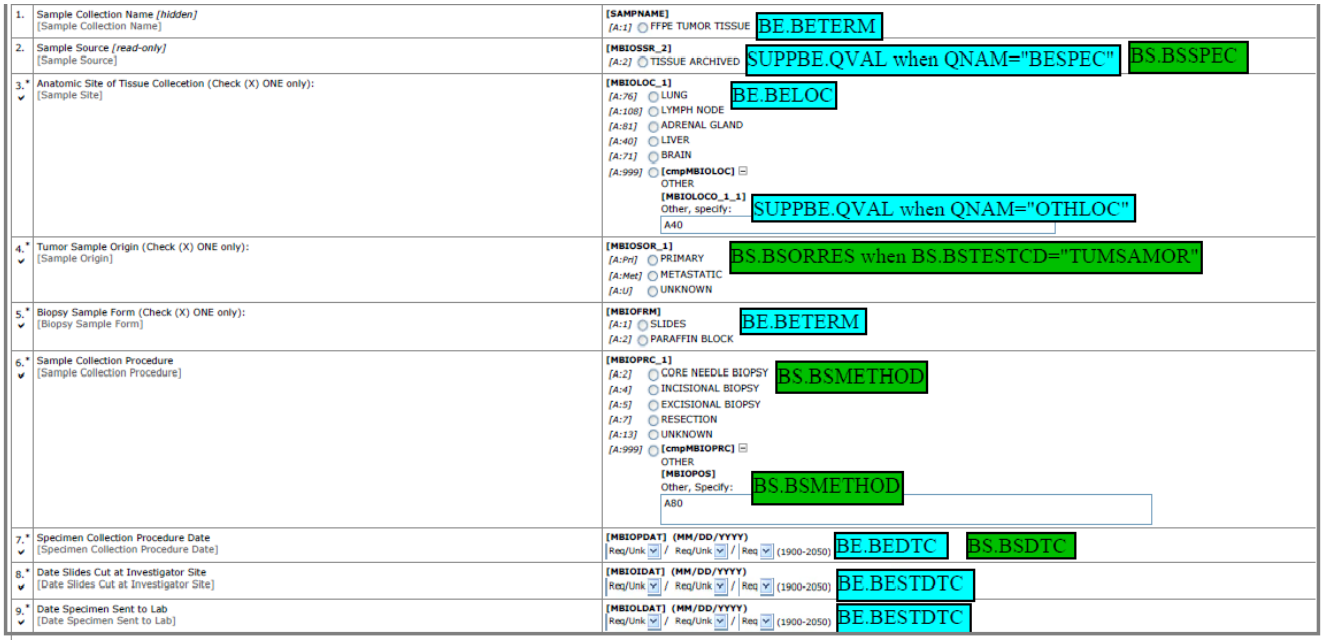

Figure 3.aCRF Showing BE and BS Mapping

	USUBJID	BETERM	BEDECOD	BECAT	BESCAT	BEPRESP	BEOCCUR	BEDTC
1	1001	Alk Sample Collected	COLLECTING	COLLECTION	ALK STATUS	Y	Y	2018-09-17
2	1001	Circulating Nucleic Acid Analysis	COLLECTING	COLLECTION	CIRCULATING...	Y	Y	2019-11-11
3	1001	FFPE Tumor Tissue	COLLECTING	COLLECTION	ARCHIVAL TU...	Y	Y	2018-04-20
4	1001	Slides	MOUNTING	PREPARATION	ARCHIVAL TU...	Y	Y	2018-04-20
5	1001	Slides Cut	SLIDES CUT	PREPARATION	ARCHIVAL TU...	Y	Y	2018-04-20
6	1001	Specimen Sent to Lab	SHIPPED	TRANSPORT	ARCHIVAL TU...	Y	Y	2018-04-20

Figure 4. SDTM BE DATASET

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.

	USUBJID	BSTESTCD	BSTEST	BSCAT	BSSCAT	BSORRES	BSSPEC	BSMETHOD	BSDTC
1	1001	FIXNAM	Fixative Name	SPECIMEN HANDLING	ALK STATUS	FORMALIN FIXED	TISSUE	SURGERY	2018-09-17
2	1001	FIXNAM	Fixative Name	SPECIMEN HANDLING	ALK STATUS	PARAFFIN EMBEDDED	TISSUE	SURGERY	2018-09-17
3	1001	TUMSAMOR	Tumor Sample Origin		ALK STATUS	METASTATIC	TISSUE	THORACENTESIS	2016-06-28
4	1001	TUMSAMOR	Tumor Sample Origin		ARCHIVAL TUMOR TISSUE	PRIMARY	TISSUE	RESECTION	
5	1001	TUMSAMOR	Tumor Sample Origin		ALK STATUS	UNKNOWN	TISSUE	UNKNOWN	2016-11-04

Figure 5. SDTM BS DATASET

PHARMACOGENOMICS/GENETICS FINDINGS - PF

The PF domain 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. The below aCRF captures the information of locally advanced (primary or recurrent) or metastatic solid tumors with a pathogenic or likely pathogenic germline or somatic BRCA1, BRCA2, or ATM gene defect, as determined by local assessment and classification.

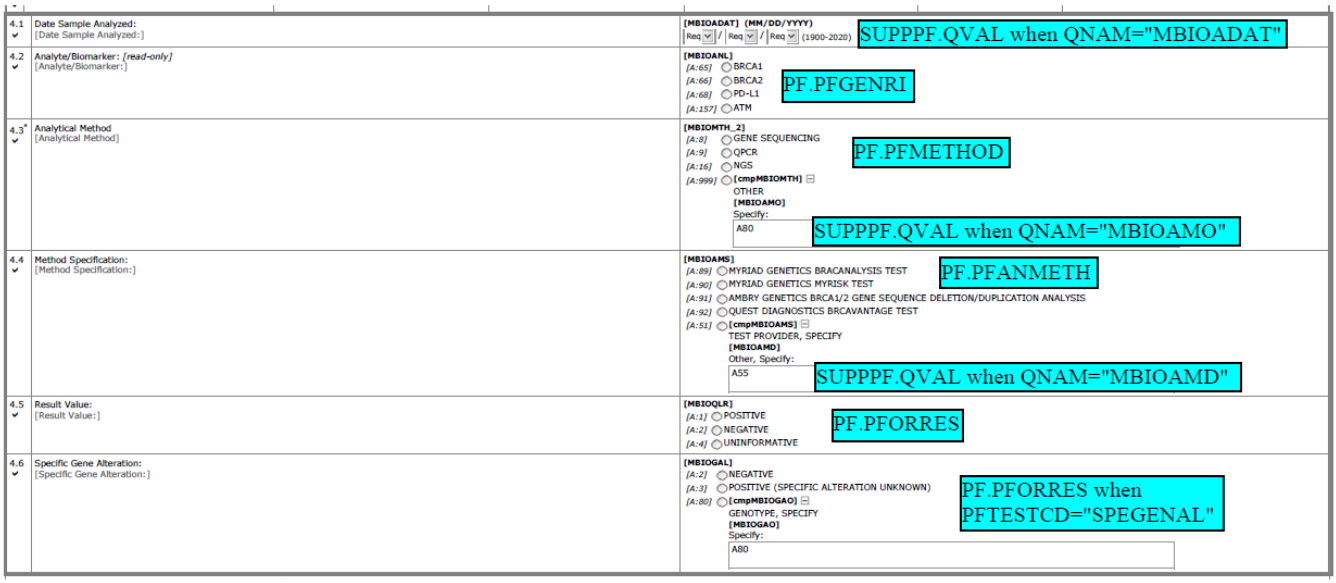

Figure 6. aCRF Showing PF mapping

	USUBJID	PFTESTCD	PFTEST	PFGENRI	PFCAT	PFORRES	PFSTRESC	PFSTAT	PFSPEC	PFMETHOD
1	1001	GENEALT	Gene Alteration		GENETIC/MOL...			NOT DONE	TUMOR TISSUE	
2	1001	GENEALT	Gene Alteration	ATM	GENETIC/MOL...	NEGATIVE	NEGATIVE		TUMOR TISSUE	NGS
3	1001	GENEALT	Gene Alteration	BRCA1	GENETIC/MOL...	NEGATIVE	NEGATIVE		TUMOR TISSUE	NGS
4	1001	GENEALT	Gene Alteration	BRCA2	GENETIC/MOL...	POSITIVE	POSITIVE		BLOOD	GENE SEQUENCING
5	1001	PFALL	Pharmacogenomics Findings		GENETIC/MOL...			NOT DONE		
6	1001	PFALL	Pharmacogenomics Findings	ATM	GENETIC/MOL...			NOT DONE		
7	1001	SPEGENAL	Specific Gene Alteration		GENETIC/MOL...			NOT DONE	TUMOR TISSUE	
8	1001	SPEGENAL	Specific Gene Alteration	ATM	GENETIC/MOL...	NEGATIVE	NEGATIVE		TUMOR TISSUE	NGS
9	1001	SPEGENAL	Specific Gene Alteration	BRCA1	GENETIC/MOL...	NEGATIVE	NEGATIVE		TUMOR TISSUE	NGS
10	1001	SPEGENAL	Specific Gene Alteration	BRCA2	GENETIC/MOL...	POSITIVE (SP...	POSITIVE (SP...		BLOOD	GENE SEQUENCING

Figure 7. SDTM PF DATASET

MICROSCOPIC FINDINGS - MI

MI is for findings resulting from the microscopic examination of tissue samples. These examinations are performed on a specimen. Reflects details of histopathologic examinations which are the microscopic study of characteristic tissue abnormalities by employing various histochemical and immunohistochemical stains. For example, histologic type, histologic grade, stage, diagnosis, and slide stain results from pathology/histopathology examination are MI findings.

PD-L1 status is a Non-invasive assessment of tumor which is captured in MI in the below CRF page

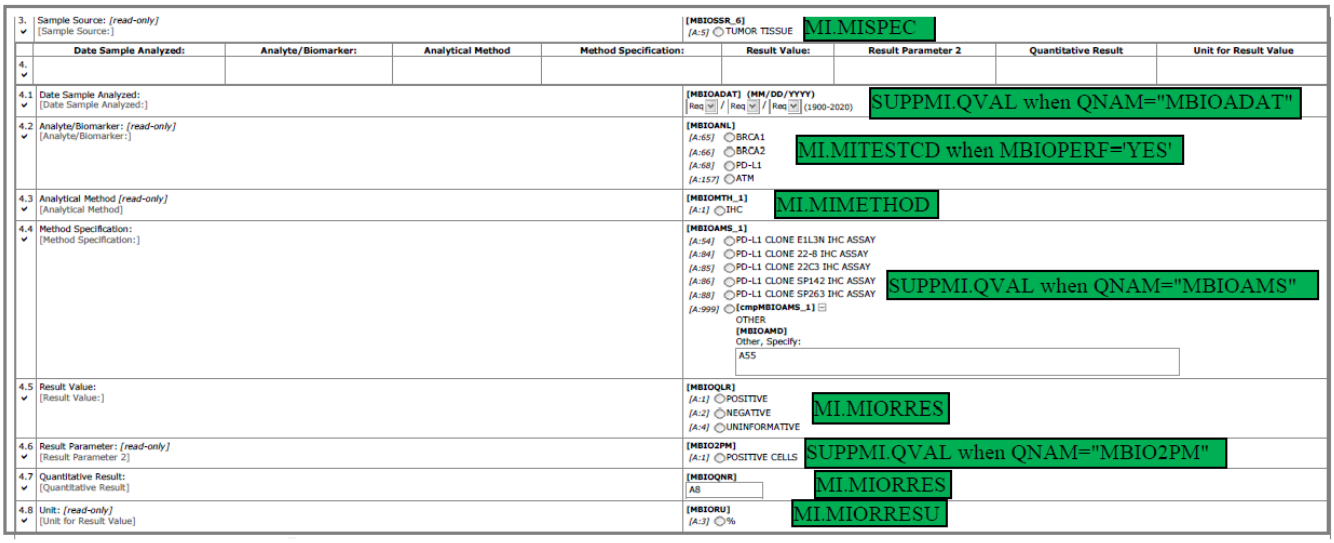

Figure 8. aCRF showing MI mapping

	USUBJID	MITESTCD	MITEST	MITSTDTL	MICAT	MIORRES	MIORRESU
1	1001	ALK	Anaplastic lymphoma Kinase	GENE REARRANGEMENT	ALK	30-40	%
2	1001	ALK	Anaplastic lymphoma Kinase	PROTEIN EXPRESSION	ALK	POSITIVE	

Figure 9. SDTM MI DATASET - 1

	USUBJID	MITESTCD	MITEST	MITSTDTL	MICAT	MIORRES	MIORRESU	MISTAT
1	1001	CTC	CIRCULATING TUMOR CELL	PERCENT POSITIVE CELL	Circulating Tumor Cells	58	CTC/7.5 ML	
2	1001	MIALL	Microscopic Findings					NOT DONE
3	1001	PDL1	Programmed Cell Death Ligand 1	OVERALL STATUS	PD-L1	NEGATIVE		
4	1001	PDL1	Programmed Cell Death Ligand 1	PERCENT POSITIVE CELL	PD-L1	6	%	

Figure 10. SDTM MI DATASET - 2

CONCLUSION

The role of biomarkers data in clinical trials is rapidly growing; with this, the generation of a submission compliant dataset becomes very important. The draft CDISC SDTMIG-PGx defines a standard for mapping gene related biomarker data. Working towards implementing these standards will help in standardizing the data and collaborative efforts with the industry clinical and data-standards experts will result in new SDTMIG-PGx domains supporting various biomarkers data. Above all, just like mapping any other data we are more familiar with, understanding the biomarkers data is crucial to allow proper capture of the values collected into SDTM domain.

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RECOMMENDED READING

- *Study Data Tabulation Model Implementation Guide: Human Clinical Trials, Version 3.2, CDISC Submission Data Standards Team (November 26, 2013).*
- *Study Data Tabulation Model, Version 1.4, CDISC Submission Data Standards Team*
- *Study Data Tabulation Model Implementation Guide: Pharmacogenomics/Genetics, Version 1.0 (Provisional), CDISC PGx Team*

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