

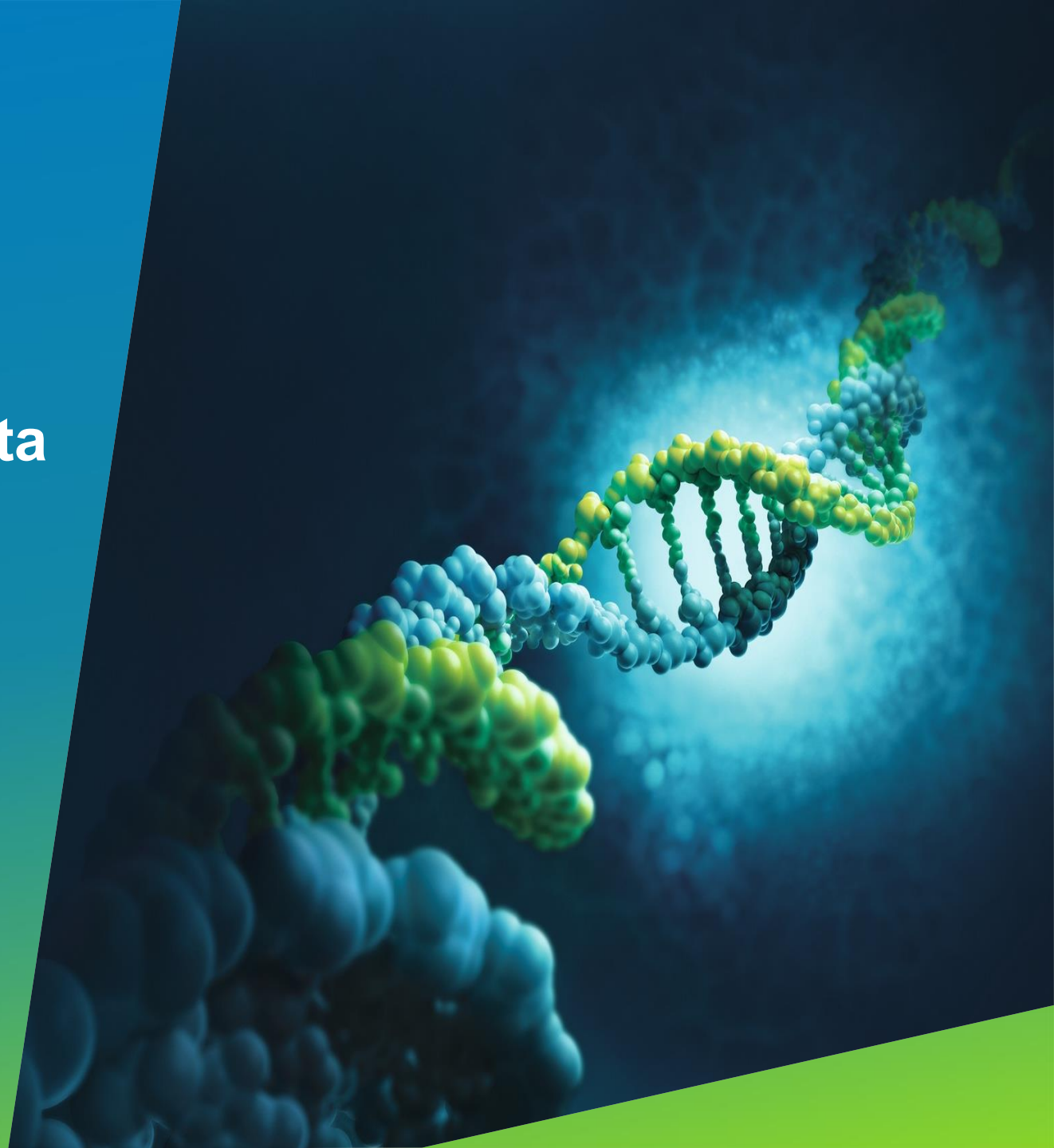


Advancing Precision Medicine and Regulatory Readiness: Data Harmonization and Statistical Methods for Companion Diagnostics Bridging Studies

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Agenda

- **Foundations of Biomarkers and Companion Diagnostics (CDx)**
- **Key Differences: Clinical Trial vs. CDx Bridging Studies**
- **Case Study: End-to-End CDx Bridging Workflow**
- **Genomic Data Harmonization: Challenges**
- **Data Integration, Harmonization and Analysis Workflow**
- **Sensitivity Analyses for Missing CDx Data**
- **Results**
- **Regulatory Readiness & Key Takeaways**



Foundations of Biomarkers and Companion Diagnostics (CDx)

What is a Biomarker?

- Objectively measurable biological characteristic
- Informs disease status, prognosis, or treatment response
- Genomic alterations detected by Next-Generation Sequencing (tissue or plasma)



What is a CDx and role of Biomarker in CDx?

- FDA-regulated diagnostic tests that measures the biomarker
- Used to identify patients based on biomarker status who are most likely to benefit from a targeted therapy



What does it demonstrate and why it matters?

- Agreement with reference assay (Clinical Trial Assay)
- Reliable patient classification
- Supports regulatory decisions and precision medicine

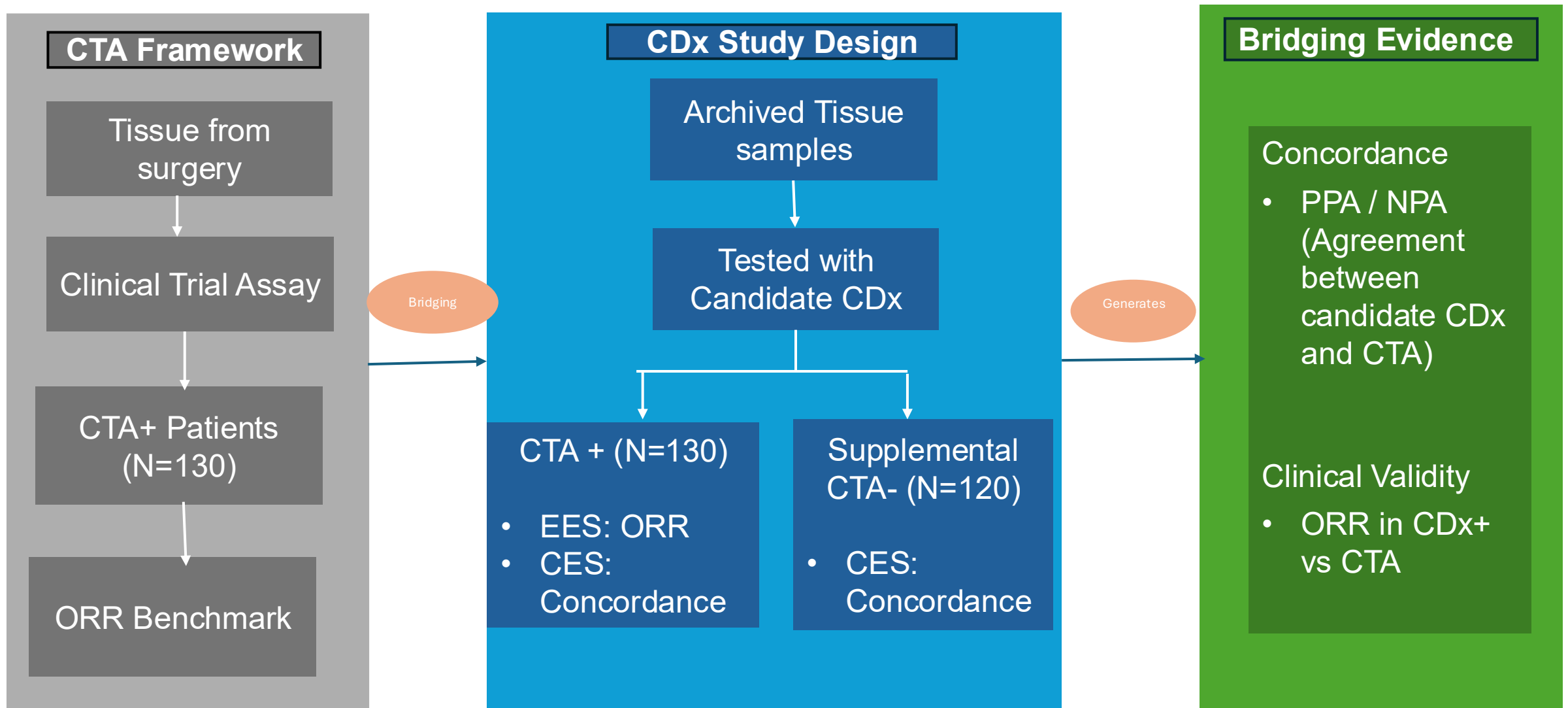




Key Differences: Clinical Trials vs CDx Bridging Studies

Dimension	Clinical Trial	CDx Bridging Study
Primary Objective	Demonstrate drug efficacy and safety	Demonstrate accurate patient selection
Regulatory focus	Drug approval	Diagnostic performance and clinical utility (for regulatory approval)
Role of biomarker	Defines patient eligibility for treatment	Biomarker test performance is evaluated
Study population	Treated, biomarker-positive	Clinical Trial and Supplemental (Often untreated; biomarker-negative)
Endpoints	Objective Response Rate, Progression-Free Survival	Concordance and diagnostic performance metrics

Case Study: Overview of Bridging Study Design





Challenges in CDx Genomic Integration

- Vendor heterogeneity and CDISC GF harmonization
- Variant Curation and biological annotation traceability
- QC, versioning, and sample accountability
- Regulatory risk if unmanaged (misclassification, unstable concordance)



NGS Vendor Heterogeneity and the Need for Harmonization

	Subject ID	Specimen	Gene	Chromosome	Genomic Position	Coding Change	Protein Change	Variant Consequence
Vendor A	A75-1001	Tissue	HER2	7	55240123	c.145_147delinsGTT	p.Gly49delinsVal	INFRAME_INSERTION

	Subject ID	Specimen	Gene	Chromosome	Genomic Position	Coding Change	Protein Change	Variant Consequence
Vendor B	A75-1001	Tissue	ERBB2	chr7	55240123	145_147delinsGTT	p.G49delinsV	In-frame insertion

Vendor outputs mapped to CDISC-GF

USUBJID	GFSEQ	GFCAT	GFSUBCAT	GFSYM	GFCHROM	GFGENELOC	GFTSTDTL	GFORRES
A75-1001	1	GENETIC_CHANGE	DNA	ERBB2	7	55240123	Predicted Coding Sequence Change (HGVS.c)	c.145_147delinsGTT
A75-1001	2	GENETIC_CHANGE	PROTEIN	ERBB2	7	55240123	Predicted Amino Acid Change (HGVS.p)	p.Gly49delinsVal
A75-1001	3	GENETIC_CHANGE	CONSEQUENCE	ERBB2	7	55240123	Variant Consequence	INFRAME_INSERTION
A75-1001	4	GENETIC_CHANGE	IMPACT	ERBB2	7	55240123	Amino Acid Impact	Non-Synonymous
A75-1001	5	FILTERING	VARIANT_FILTER	ERBB2	7	55240123	Synonymous Variant Indicator	No
A75-1001	6	ANNOTATION	GENE_ROLE	ERBB2	7	55240123	Gene Functional Role	Oncogene
A75-1001	7	ANNOTATION	ANNOTATION_SOURCE	ERBB2	7	55240123	Database Evidence (e.g., COSMIC)	Yes
A75-1001	8	ANNOTATION	CLINICAL_INTERPRETATION	ERBB2	7	55240123	Clinical-Interpretation	Actionable
A75-1001	9	CDX_MAPPING	BIOMARKER_STATUS	ERBB2	7	55240123	CDx- Relevant Variant	Yes



AXCDX: Analysis Dataset for CDx Bridging

Integration of Genomic Findings from standardized GF with XB analysis variables

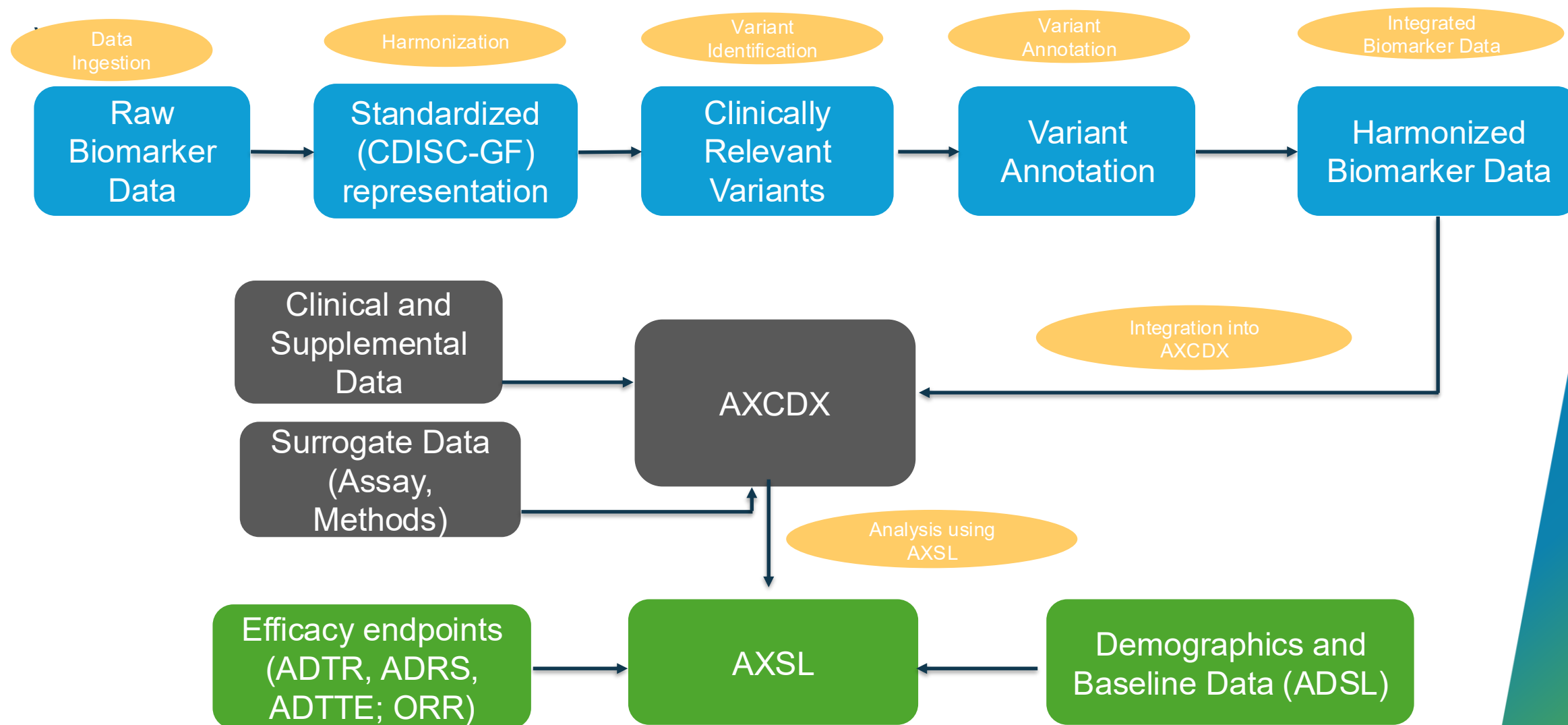
SUBJID	XBTEST	XBSTRESC	XBREASND	XBSBSTRT	RESLCTAC	RESCDXC	CONCORDC	XBSOMSTF	XBAMACCH	XBNUCLCH	XBGENPOS
A75-1001	Quality Control	Pass		Tumor Tissue	Positive	Positive	Concordant				
A75-1001	Genetic Change	CDx Mutation Reported		Tumor Tissue	Positive	Positive	Concordant	INFRAME_INSERTION	p.Gly49delins Val	c.145_147delinsGTT	Chr7:55240123
A75-1003	Quality Control		Sample not sent	Plasma	Positive	.	Not Evaluable				
A75-1006	Quality Control	Fail	Insufficient Quality	Tumor Tissue	Positive	Invalid	Not Evaluable				

From this harmonized data, a comprehensive set of analysis flags were derived for downstream analyses

- CDx Evaluability Flags (CEHERFL, CNEHERFL)
- CTA Population Flags (HPASFL, HNASFL)
- Concordance Set Flags (HPCESFL, HNCESFL)



Data Integration, Harmonization and Analysis Workflow





Sensitivity Analyses for Missing CDx Data



- Missing CDx results could bias concordance (PPA / NPA) and clinical validity
- Multiple Imputed datasets were generated to reflect uncertainty
- Nested Bootstrap resampling (MI-Boot) captured both imputation and sampling variability
- Final estimates and Confidence Intervals were robust to missing data assumptions



Sensitivity Analysis Results

Sensitivity Analysis: Complete-Case vs. MI-Boot Imputed Data

Analysis Type	Endpoint	Complete-Case Analysis (95% CI)	Analysis with Imputed Data (95% CI)
Efficacy	ORR (%)	60.8% (48.8%, 72.0%)	59.2% (47.5%, 70.6%)
Concordance	PPA (%)	85.0% (75.5%, 92.2%)	84.1% (74.9%, 91.6%)
	NPA (%)	96.4% (91.1%, 98.9%)	96.0% (90.8%, 98.7%)

- Consistent results between complete-case and imputed data
- Supports robustness of primary conclusions



Key Results: Concordance and Clinical Efficacy

	CTA Positive	CTA Negative	Total
CDx Positive	68	4	72
CDx Negative	12	106	118
Total	80	110	190

- Positive Percent Agreement (PPA): 85.0%
- Negative Percent Agreement (NPA): 96.4%

Subgroup	N	ORR (%)	95% CI (%)
CTA positive	86	58.1%	47.0%, 68.7%
CDx positive	74	60.8%	48.8%, 72.0%

- ORR in CDx+: 60.8%
- ORR in CTA+: 58.1%
- Lower bound of 95% CI above threshold



Regulatory Considerations

Submission Package (Master Analysis File)

Analysis Datasets

- ADaM datasets (SAS® XPT v5)

Analysis Programs

- Annotated SAS® programs

Listings

- Patient-level listings (e.g., *.xlsx)

Documentation and Metadata

- ADS and ARM for traceability



Key Take Aways



➤ **CDx integration is inherently multi-dimensional**



➤ **Genomic Literacy is now essential**



➤ **Multidisciplinary collaboration drives success**



➤ **Early alignment drives consistency and traceability**



➤ **Statistical programmers act as integrators across domains**



Questions?

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Thank You!
