A Public-Private Partnership
collaborating on Regulatory Science
to make patient access to new medical device technologies faster, safer and more cost-effective

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

Align › Achieve › Accelerate

Framework for Surrogate Sample Use in Clinical Diagnostic Test Development and Product Submission

April Veoukas, JD, Director of Regulatory Affairs | Abbott
MDIC Surrogate Samples Work Group Chair,
November 29, 2017

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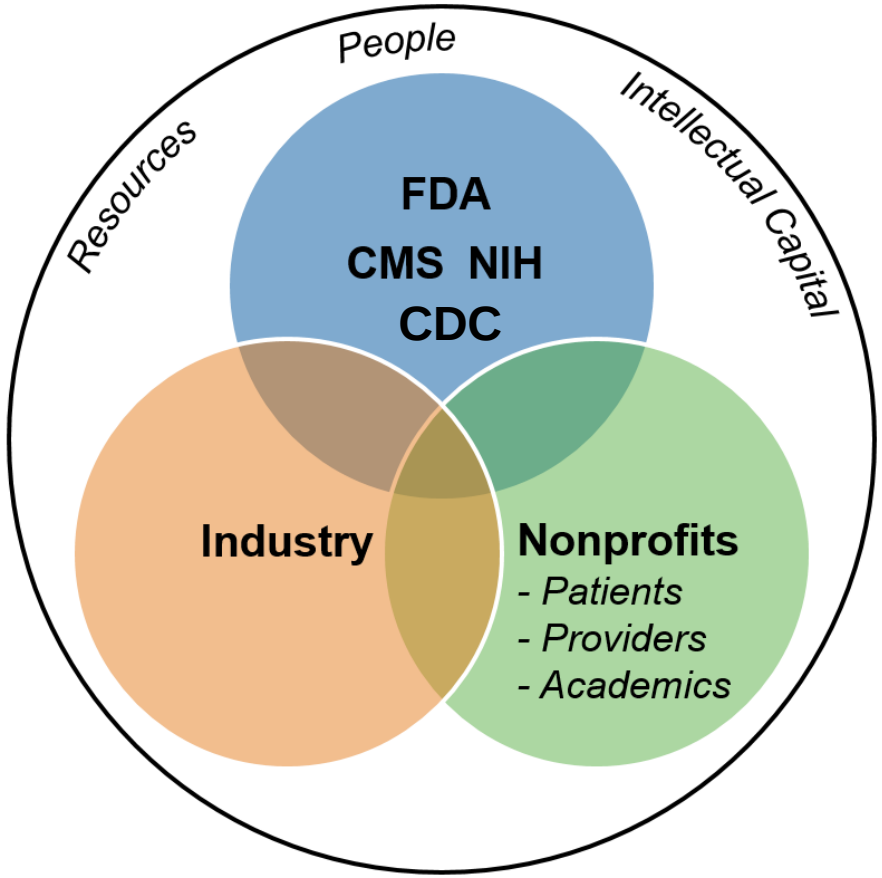
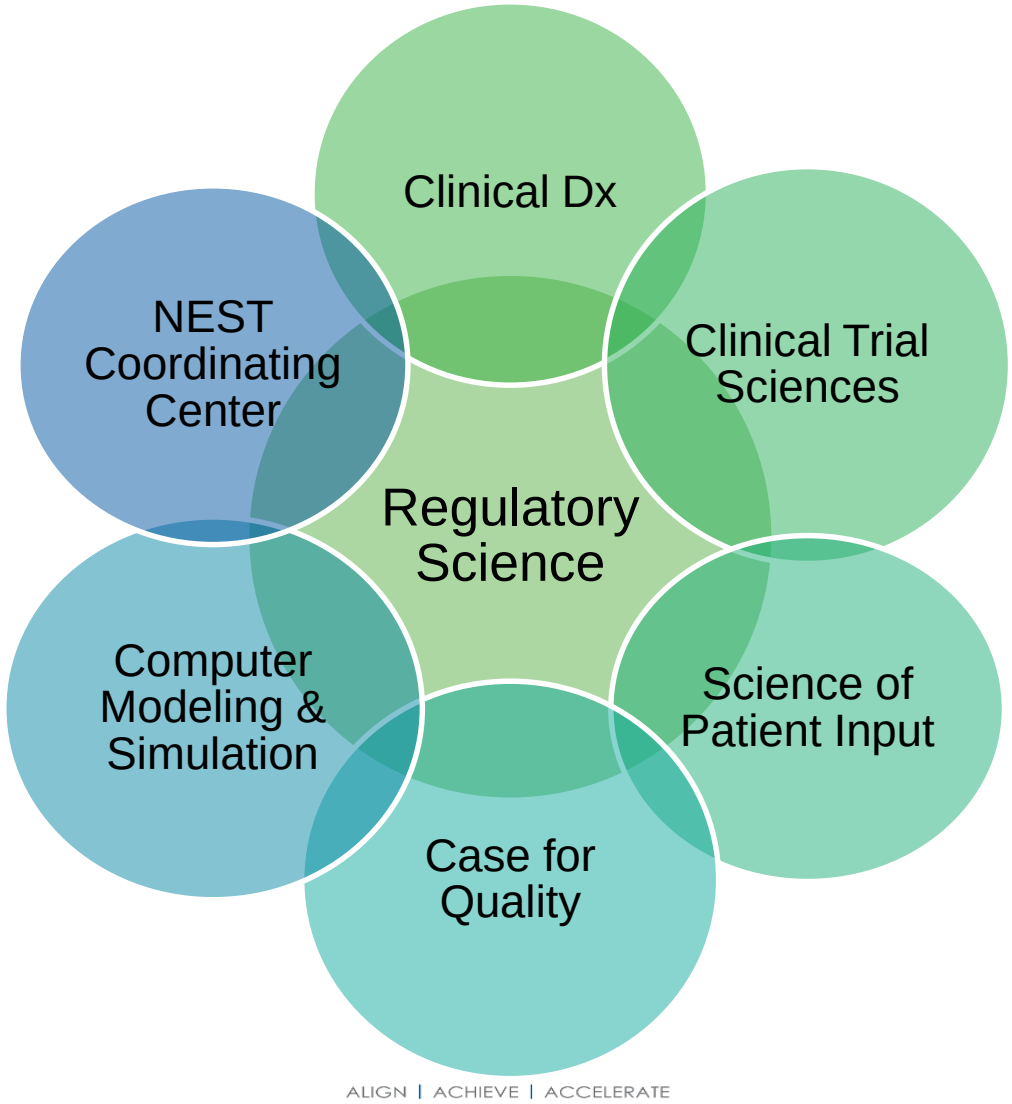


MDIC Program Initiatives



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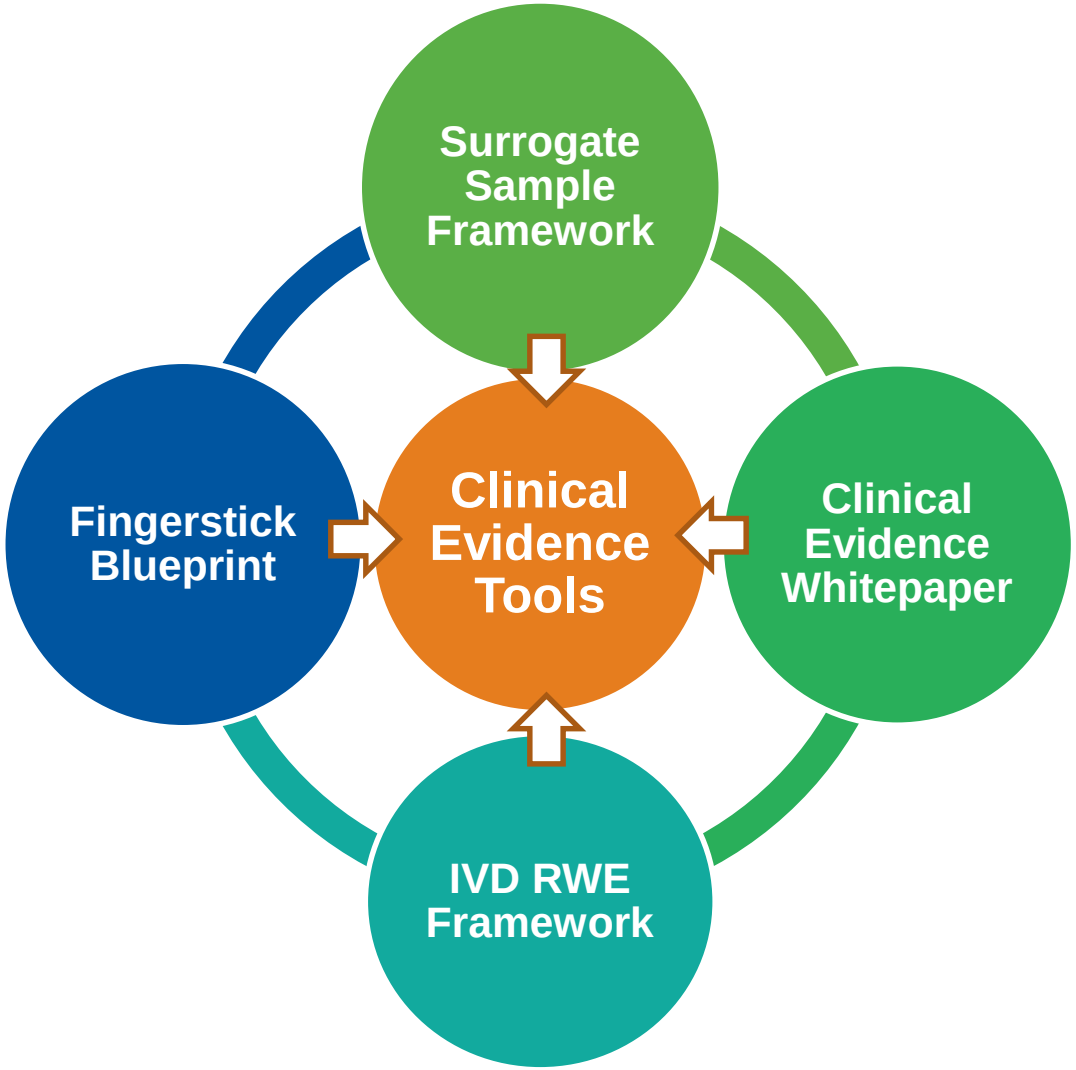
Clinical Diagnostics Program Goal

Foster innovation and speed patient access to new IVD tests by developing new tools and methods that will improve processes to assess safety, effectiveness and the value proposition of diagnostic tests.

Clinical Diagnostic Projects



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Surrogate Sample Framework

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Why this initiative?

- ***Issue:***

  Difficulty obtaining clinical specimens delays the development of innovative and improved diagnostics impacting patient access.

- ***Goal:***

  Establish a foundation for the use of surrogate samples to support IVD product development and the regulatory submission process.

Who worked on this project?

MDIC assembled a work group comprised of member organizations and other subject matter experts to guide work on this project.

Industry:

Khatereh Calleja, JD, AdvaMed
Ronald Freeze, PhD, Abbott
Patrick O'Donnell, Roche
Mark Del Vecchio, BD
April Veoukas, JD, Abbott (Working Group Chair)
Brad Spring, BD
Ian Giles, MD, Sysmex
Maya Mahue, PhD, Hologic

Program Director:

Carolyn Hiller, MDIC

Government:

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Yun-Fu Hu, PhD, CDRH | OIR
Tremel Faison, BARDA

Expert Advisors:

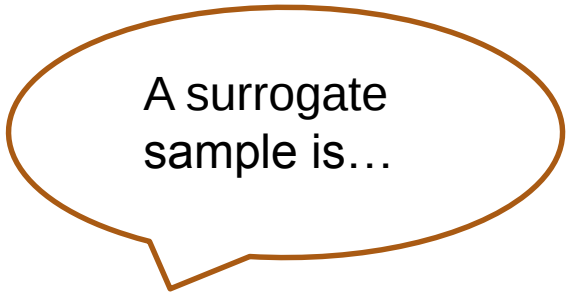
Susan Alpert, MD, PhD
Fred Lasky, PhD

Reasons to Use Surrogate Samples

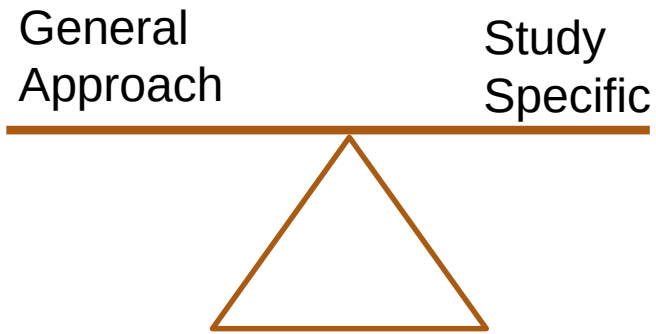
- Naturally occurring specimens rare or difficult to acquire
- Analyte does not naturally occur at level required by study
  - For example, at the extremes of the measurement interval of a test
- Stability of naturally occurring specimens confounds study
- Meet scientific rigor of study when insufficient volume
- Inactivated organisms for highly infectious material
- Introduce variables that can't be studied otherwise
- Ethical considerations
  - For example, reduce the need to conduct invasive sampling procedures or
  - Drawing large volumes or multiple specimens from sick patients

Framework

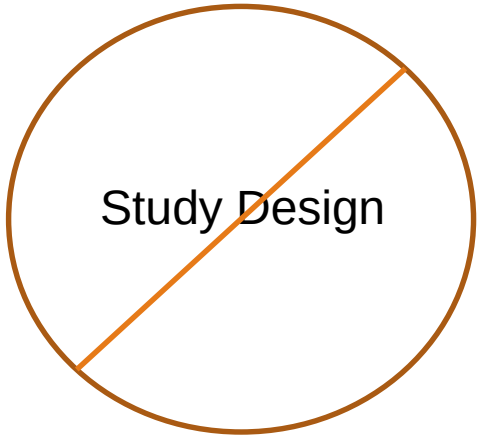
- Common Language



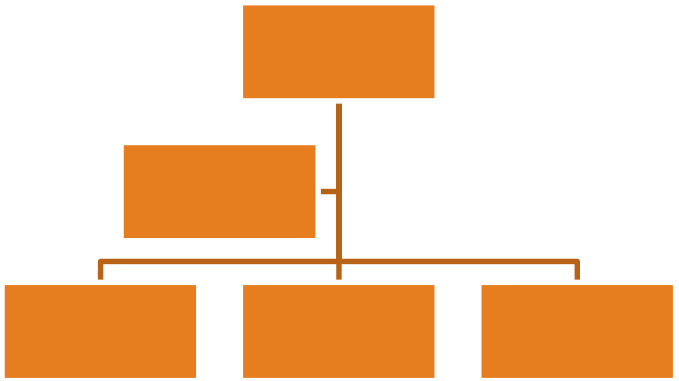
- Balanced



- Focused



- Hierarchy



Framework Elements

- Creates a uniform definition of surrogate sample supplemented with a diverse array of examples
- Outlines general principles and considerations when designing and selecting surrogate samples
- Presents a hierarchy to aid in the selection and design of surrogate samples
- Establishes study specific principles accompanied by a hierarchy for each study type

Surrogate Sample Defined

Material or combination of materials that is used as a substitute for body fluid or tissue taken for examination from a single human subject to study the characteristic of interest.

Examples include, but are not limited to:

- Materials supplemented (spiked) with an analyte of interest
- Pooled patient specimens of biological origin
- Material created to have properties of interest of a body fluid or a tissue
- Material comprised of a combination of an analyte that simulates the analyte of interest, and a material created to have properties similar to or representative of the body fluid or tissue or of the patient/subject.

Surrogate Samples Further Characterized

Supplemented	**Matrix spiked with target analyte**
Pooled	**Combined individual patient specimens that may or may not be spiked with target analyte**
Simulated	**Altered materials of biological origin or artificial materials created to have properties similar to or representative of body fluid or tissue that may or may not be spiked with target analyte**

Surrogate Sample Combinations

			Matrix				
			Biological				Artificial
			Unaltered		Altered		
			Individual	Pool	Individual	Pool	
Analyte	Unspiked		Patient Sample (A1)	Pooled (A2)	Simulated Matrix (C1)	Simulated Matrix (C2)	Simulated Matrix (G)
	Spiked	Biological	Supplemented (B1)	Pooled (B2)	Simulated Matrix (D1)	Simulated Matrix (D2)	Simulated Matrix (H)
		Artificial	Simulated Analyte (E1)	Simulated Analyte (E2)	Simulated Analyte/Matrix (F1)	Simulated Analyte/Matrix (F2)	Simulated Analyte/Matrix (I)

General Principles for Design and Selection of Surrogate Samples

- Identify the objective of using surrogate samples
  - Supplement specimens
  - Replace specimens
- Identify critical factors related to the performance study type, such as:
  - Mimic biological variability of individual patient specimens
  - Meet scientific demands of study type
- Consider factors based on whether the test is qualitative or quantitative

General Principles for Design and Selection of Surrogate Samples

- Consider the effect of sample processing
- Identify most relevant functional characteristics of specimen matrix; test performance
- Consider analyte types; levels of bias
- Assess combinations of matrix and analyte
- Consult existing guidelines
- Consider a hierarchical approach to selection

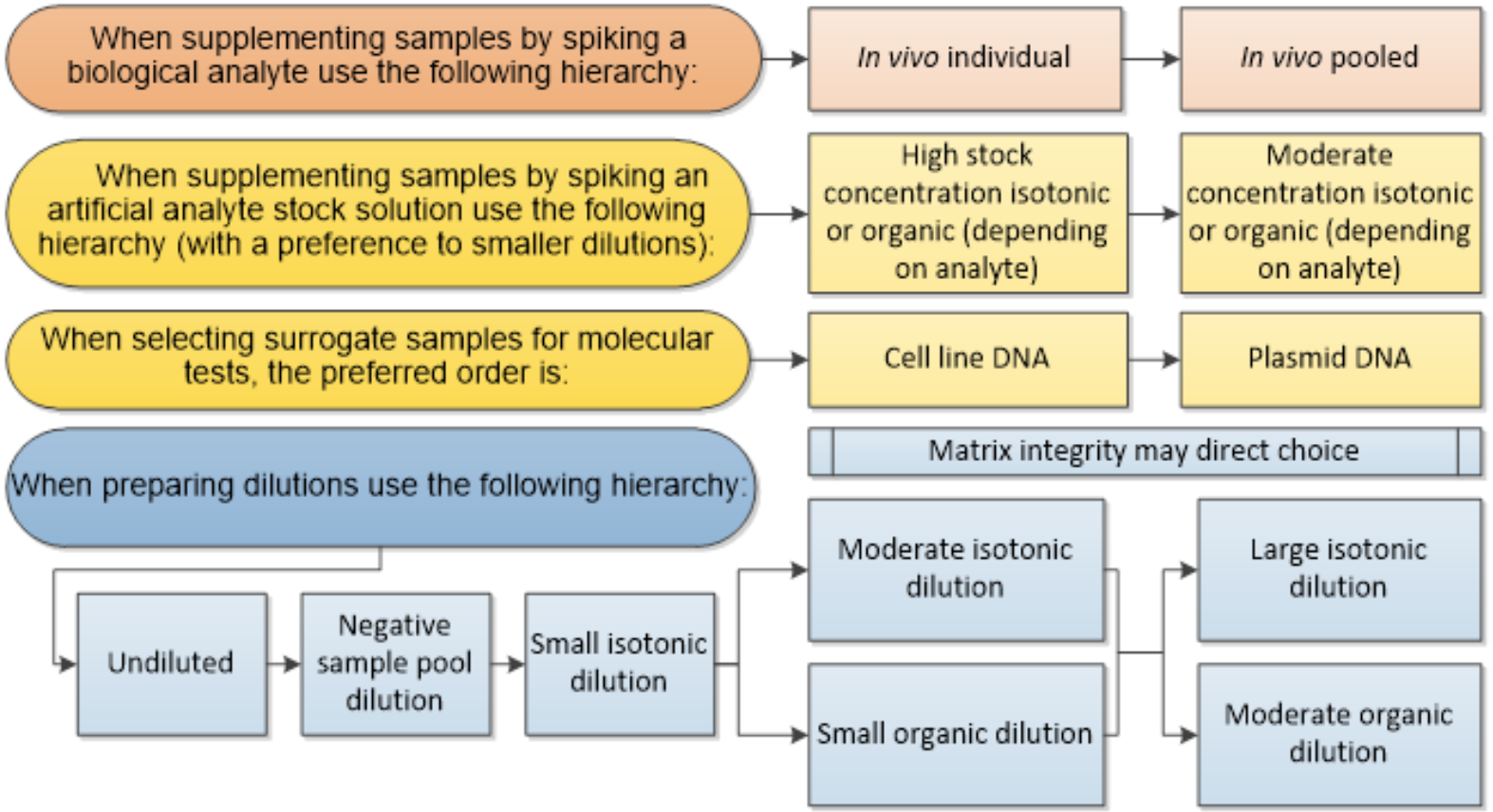
Surrogate Sample Hierarchy

Following a decision to use surrogate samples, the first consideration is a pooled surrogate sample (A2) or a supplemented individual surrogate sample (B1). Use the general principles and study specific principles to make this determination.

			Matrix				
			Biological				*Artificial*
			Unaltered		*Altered*		
			Individual	*Pool*	*Individual*	*Pool*	
Analyte	*Unspiked*		Patient Sample[1] (A1) →	Pooled (A2)	Simulated Matrix (C1)	Simulated Matrix (C2)	Simulated Matrix (G)
	Spiked	*Biological*	Supplemented (B1)	Pooled (B2)	Simulated Matrix (D1)	Simulated Matrix (D2)	Simulated Matrix (H)
		Artificial	Simulated Analyte (E1)	Simulated Analyte (E2)	Simulated Analyte/ Matrix (F1)	Simulated Analyte/ Matrix (F2)	Simulated Analyte/ Matrix (I)

Surrogate Sample Preparation

When supplementing samples or preparing dilutions use the following guidelines.



Performance Studies

- Linearity
- Analytical Specificity/Interference
- Precision/Reproducibility
- Detection Capability
- Matrix Comparison
- Method Comparison
- Specimen Stability
- Reagent Stability
- Instrument Carry-Over Studies

Study Specific Hierarchy

Linearity	Analytical Specificity	Precision	Limit of Blank	Limit of Detection	Limit of Quantitation	Matrix Comparison	Method Comparison	Specimen Stability	Reagent Stability	Instrument Carryover
A1	A1	A1	A1	A1	A2	A1	A1	A1	A1	A1
A2	A2	A2	A2	B1	B2	B1	B1	B1	A2	A2
B1	B1	B1	C1	E1	E2	E1	A2	A2	B1	B1
B2	B2	B2	C2	A2	D2	A2	B2	B2	B2	B2
E1	E1	E1	G	B2	F2	B2	E1	E1	E1	E1
E2	E2	E2	*	E2	H	E2	E2	E2	E2	E2
C1	C1	C1		C1	I	*	C1	*	C1	*
C2	C2	C2		D1	*		C2		C2	
D1	D1	D1		F1			D1		D1	
D2	D2	D2		C2			D2		D2	
F1	F1	F1		D2			F1		F1	
F2	F2	F2		F2			F2		F2	
H	H	H		H			H		H	
I	I	I		I			I		G	
G	*	G		*			*		I	

	Use general principles and study specific guidelines to select surrogate type in a downward linear fashion. Ensure you have well-thought out rationale before considering the next surrogate sample type.
	Consider unique properties of your assay type, study design, patient sample type, and the importance of whether altering an analyte or matrix more closely mimics a patient sample, in addition to the general principles and study specific guidelines to select surrogate sample type. Ensure you have well-thought out rationale before considering the next surrogate sample type.
	Consider only after exhausting other options.
*	Remaining surrogate sample types may not be suitable for this study type.

Accessing the Framework

- How do I access the Surrogate Sample framework?

http://mdic.org/ClinicalDx/