Time to leave Fiebig staging in the dust?

Estimated Dates of Detectable Infection (EDDIs) as a new and improved method for HIV infection dating

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Disclosures

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1 Why not stick with Fiebig staging?

Why is Fiebig staging outdated?

- Since this method was published in 2003, HIV testing technology has evolved substantially.
  - Fiebig stages were defined using estimated length of time it takes for each of 5 assays to have a reactive result after infection.

Table 1. Laboratory stages of primary HIV infection based on the emergence of viral markers in 51 seroconverting plasma donors.

	Marker					Duration in days (95% CI)[a]	
			Antibody (EIA)				
Stage	RNA	P24 Antigen	NS	S	Western blot	Individual	Cumulative
I	+	–	–	–	–	5.0 (3.1, 8.1)	5.0 (3.1, 8.1)
II	+	+	–	–	–	5.3 (3.7, 7.7)	10.3 (7.1, 13.5)
III	+	+	–	+	–	3.2 (2.1, 4.8)	13.5 (10.0, 17.0)
IV	+	+/–	–	+	I	5.6 (3.8, 8.1)	19.1 (15.3, 22.9)
V	+	+/–	+/–	+	+[b]	69.5 (39.7, 121.7)	88.6 (47.4, 129.8)
VI	+	+/–	+	+	+	Open-ended	Open-ended

[a]Calculations are based on a parametric Markov model.
[b]Without p31 band.
CI, Confidence interval; I, indeterminate; NS, not sensitive, refers to second-generation not IgM-sensitive enzyme immunoassay (EIA); S, sensitive, refers to IgM-sensitive third-generation EIA.

- Today, 3/5 of the assays used for these estimates are no longer in wide use.

Why is Fiebig staging outdated?

- Fiebig stages can only be assigned to people who have discordant test results.
  - Useful for distinguishing people with acute or early infection (partial seroconversion) vs. someone who's fully seroconverted, but not for infection dating with any precision (especially after seroconversion).

But people still use it all the time…?

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Diagnostic delay: (window period)	16.7 days	4.85 days

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				Adjusted calculation
Diagnostic delay:	25.1 days	4.22 days		22.9 days from inf.
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March 31, 2022	**UniGold RT - Negative**	**Aptima Qual RNA - Reactive**		**March 8, 2022**
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Fiebig equivalent:	Abbott IgM-sensitive EIA	Roche Amplicor DT50	*Fiebig stage I-II*	16.2 days from inf.
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More importantly

- The Fiebig staging system only provides meaningful information in cases where a person presents with discordant test results on a single day, indicating incomplete seroconversion.
  - i.e., during Fiebig stages I-IV.
- Most individuals present to clinics or research studies after already reaching Fiebig stage V.
  - Then you know nothing, except that they've fully seroconverted already.
  - This is true even if there is a recent negative result.

2 What is an “EDDI”?

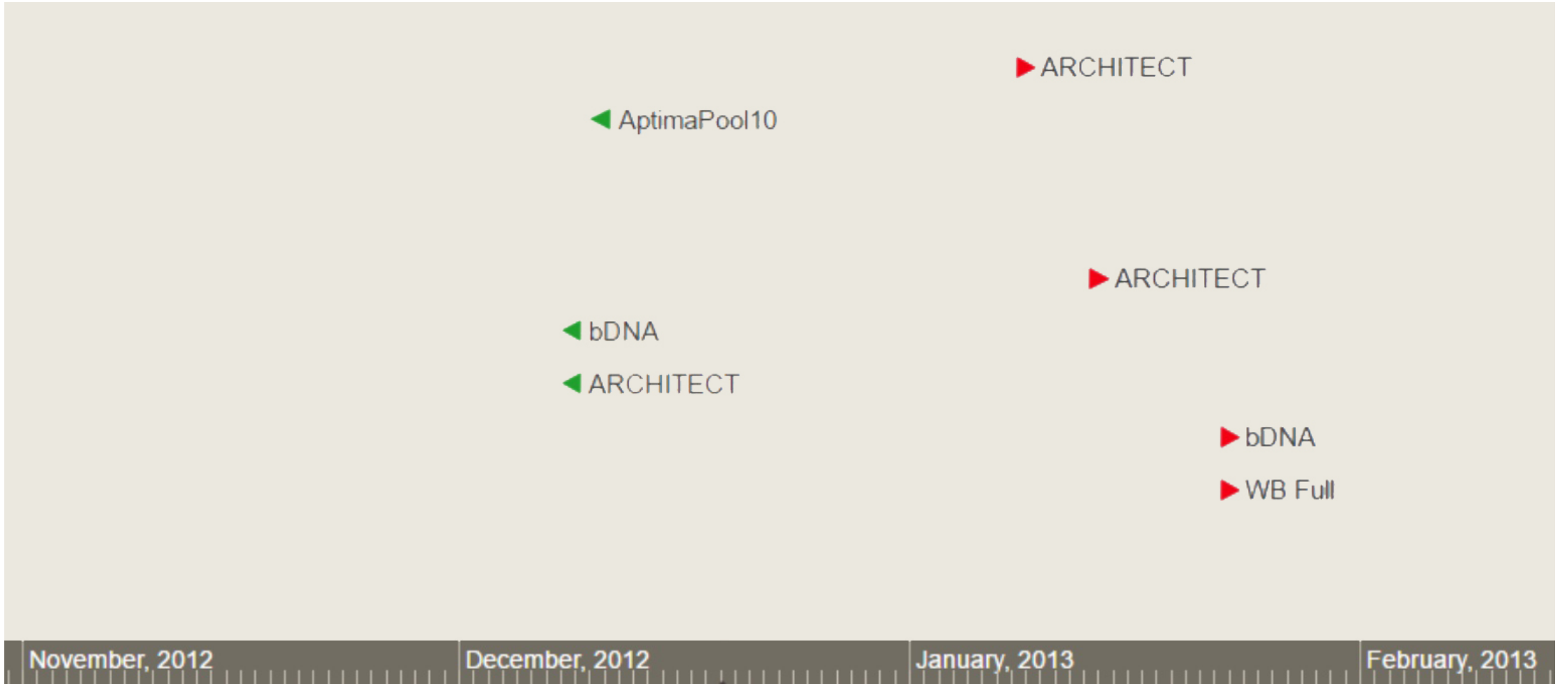
What is an “EDDI”?

- EDDI stands for “Estimated Date of Detectable Infection”
- This method uses an individual’s testing history to generate a plausible interval of calendar days during which earliest detection by a specified reference test (by default, a viral load assay with a detection threshold of 1 copy/mL) would have occurred.
  - Any reference test could be chosen, it doesn’t have to be that default.
- This interval is bounded by the Earliest Plausible Date of Detectable Infection (EP-DDI) and Latest Plausible Date of Detectable Infection (LP-DDI). The midpoint of this “DDI interval” serves as the point estimate, or EDDI.
- Only requirement (other than testing history) is information on the relative “diagnostic delays” of assays in their history.
  - Masciotra *et al*. J Clin Virol Dec 2011; Delaney *et al.* CID Jan 2017; Pilcher *et al.* AIDS 2019
  - Diagnostic delays need to be calibrated to whatever reference test is chosen.

Diagnostic Testing History

Test Date	Adjusted Date	Test Name	Test Estimate	Test Result
Dec. 10, 2012	Nov. 30, 2012	ARCHITECT	CDC calc adjusted	Negative
Dec. 10, 2012	Dec. 2, 2012	bDNA	DT formula	Negative
Dec. 12, 2012	Dec. 5, 2012	AptimaPool10	DT formula	Negative
Jan. 10, 2013	Dec. 31, 2012	ARCHITECT	CDC calc adjusted	Positive
Jan. 15, 2013	Jan. 5, 2013	ARCHITECT	CDC calc adjusted	Positive
Jan. 24, 2013	Jan. 16, 2013	bDNA	DT formula	Positive
Jan. 24, 2013	Dec. 27, 2012	WB Full	CDC calc adjusted	Positive
Jan. 24, 2013	Jan. 14, 2013	ARCHITECT	CDC calc adjusted	Positive
March 26, 2013	March 18, 2013	bDNA	DT formula	Positive
April 23, 2013	April 15, 2013	bDNA	DT formula	Positive

How to calculate an EDDI, and DDI interval (visual illustration)



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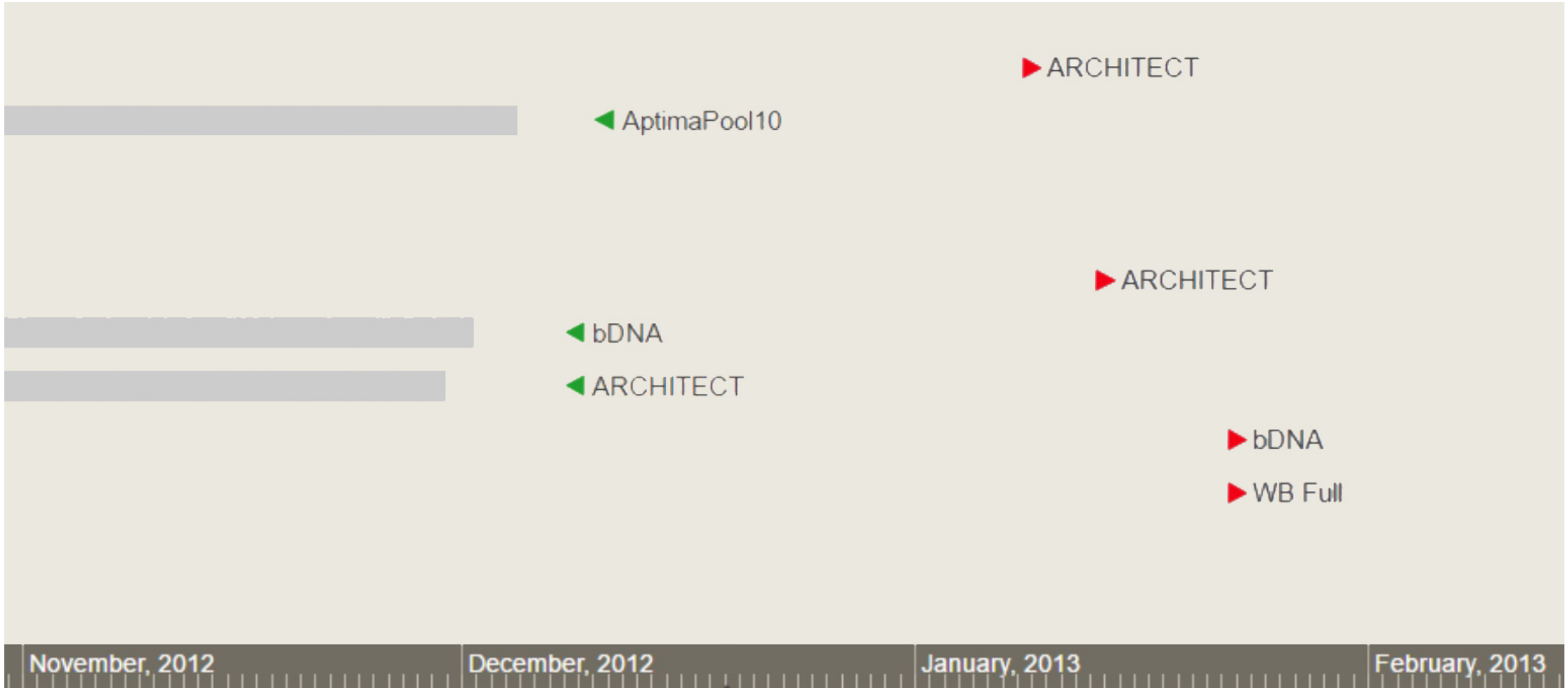

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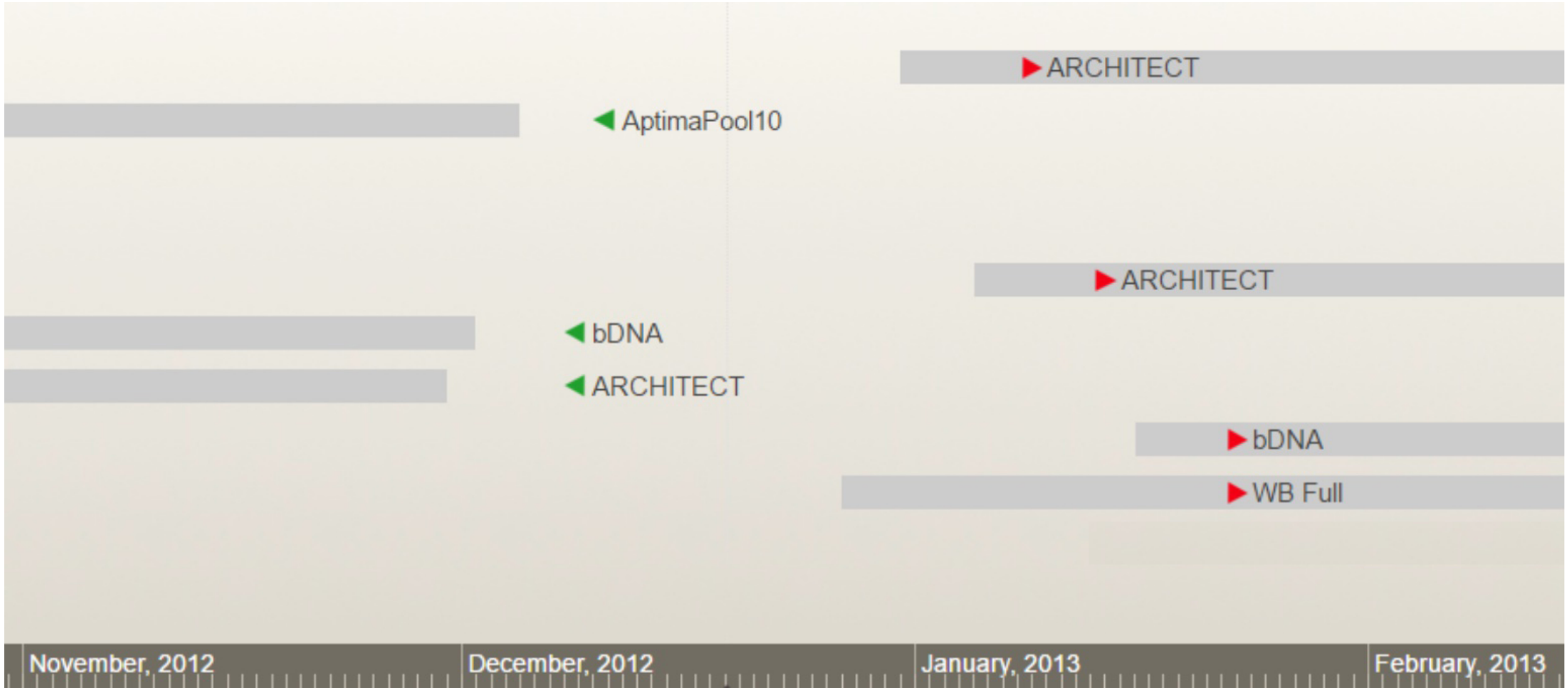

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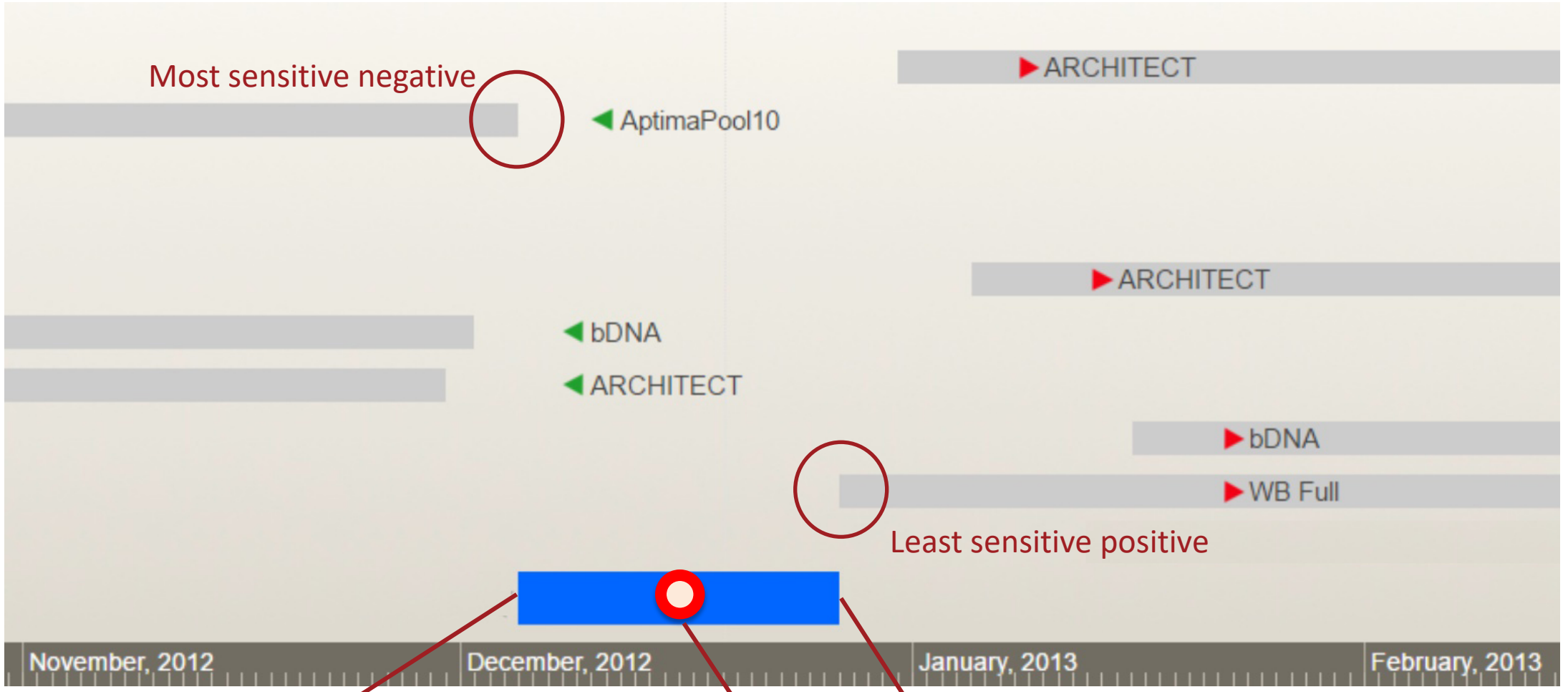


EP-DDI = December 5, 2012

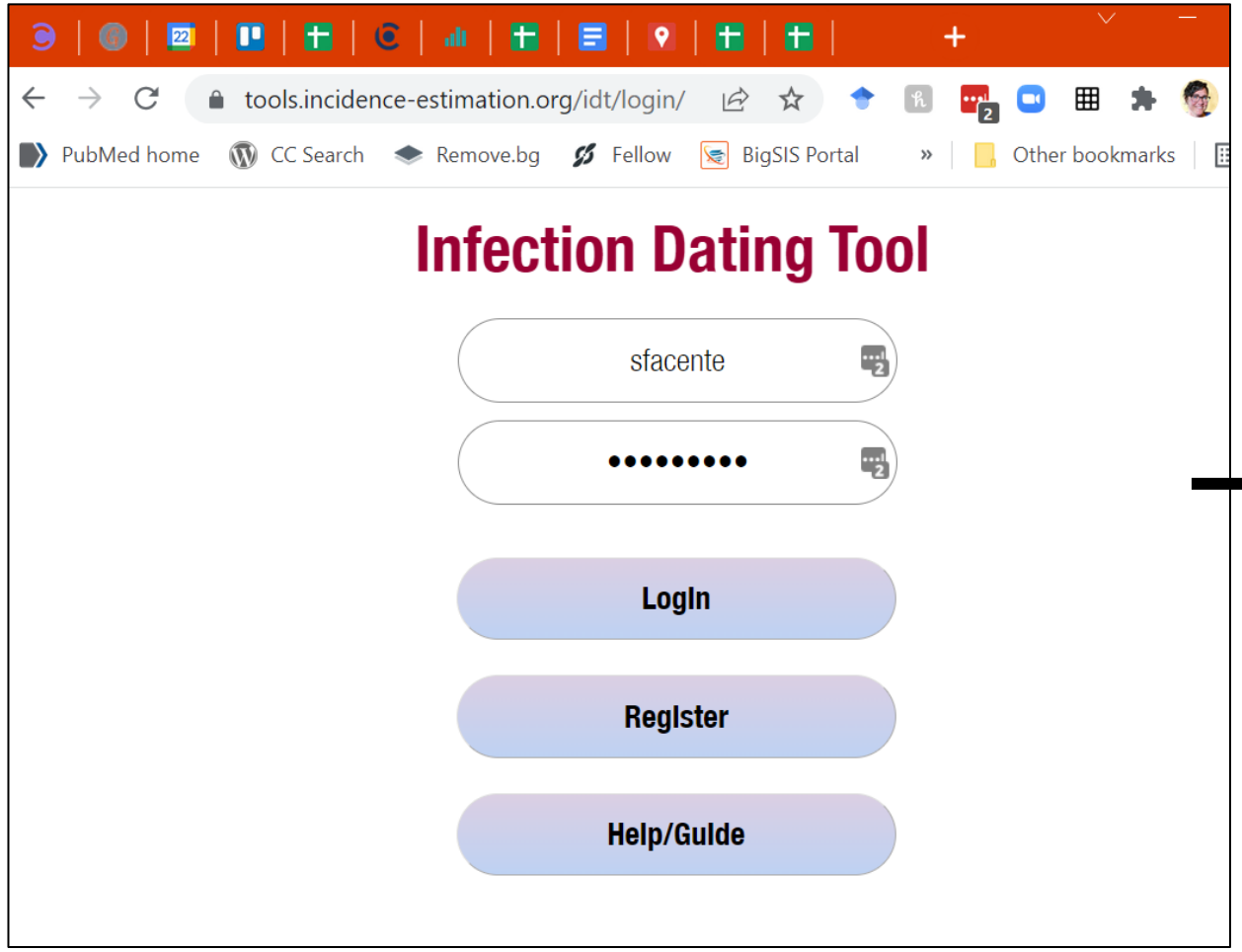
DDI interval = 22 days

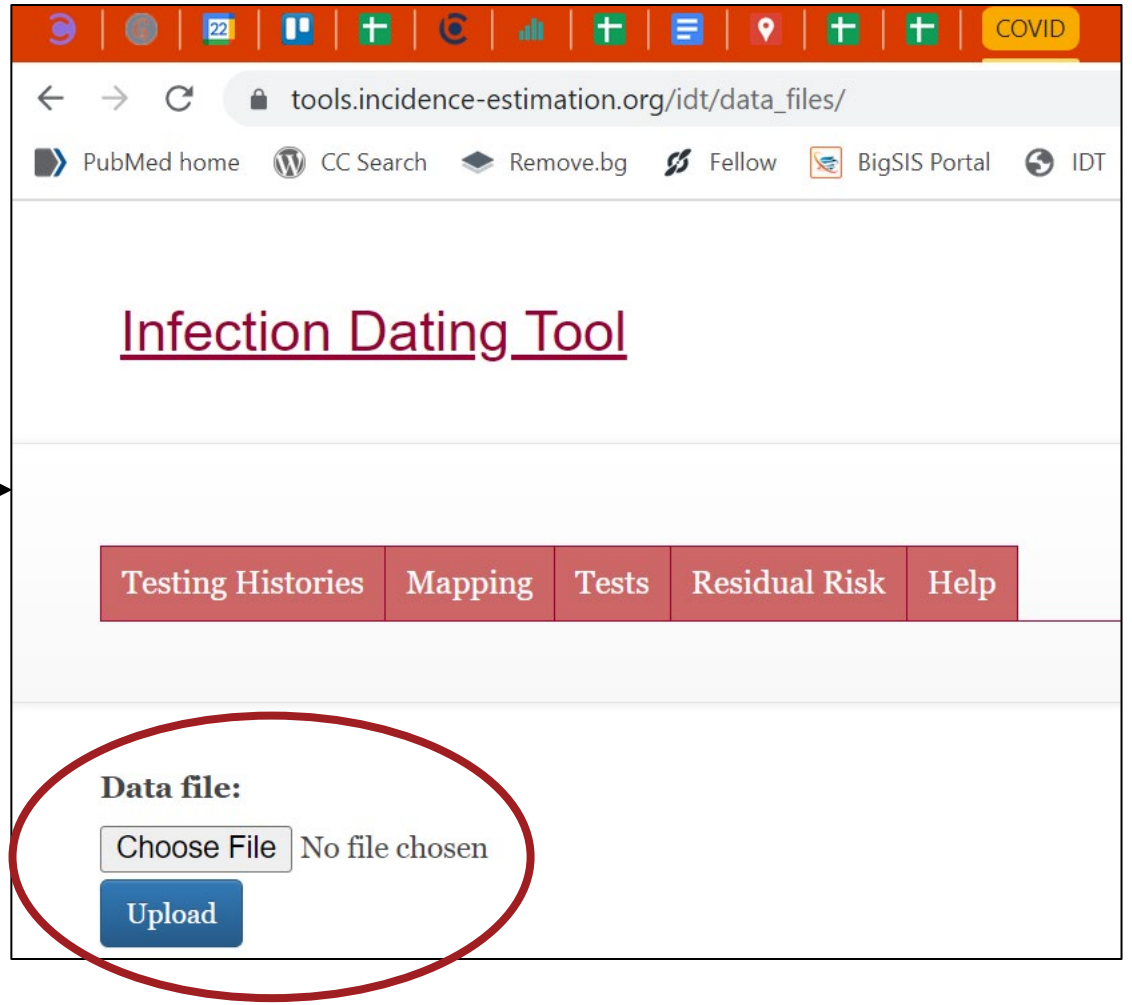
EDDI = December 16, 2012

LP-DDI = December 27, 2012

3 So how can I calculate EDDIs?

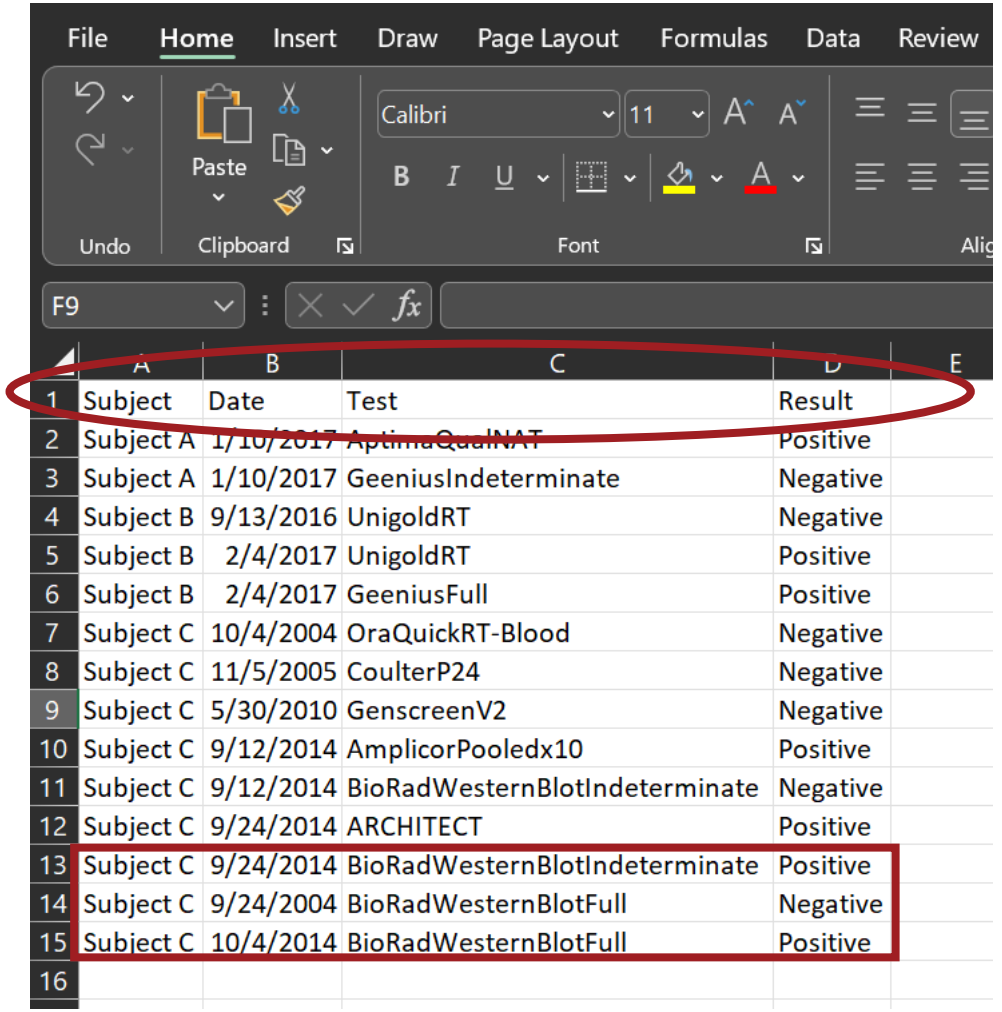
The Infection Dating Tool (IDT)





The Infection Dating Tool (IDT)

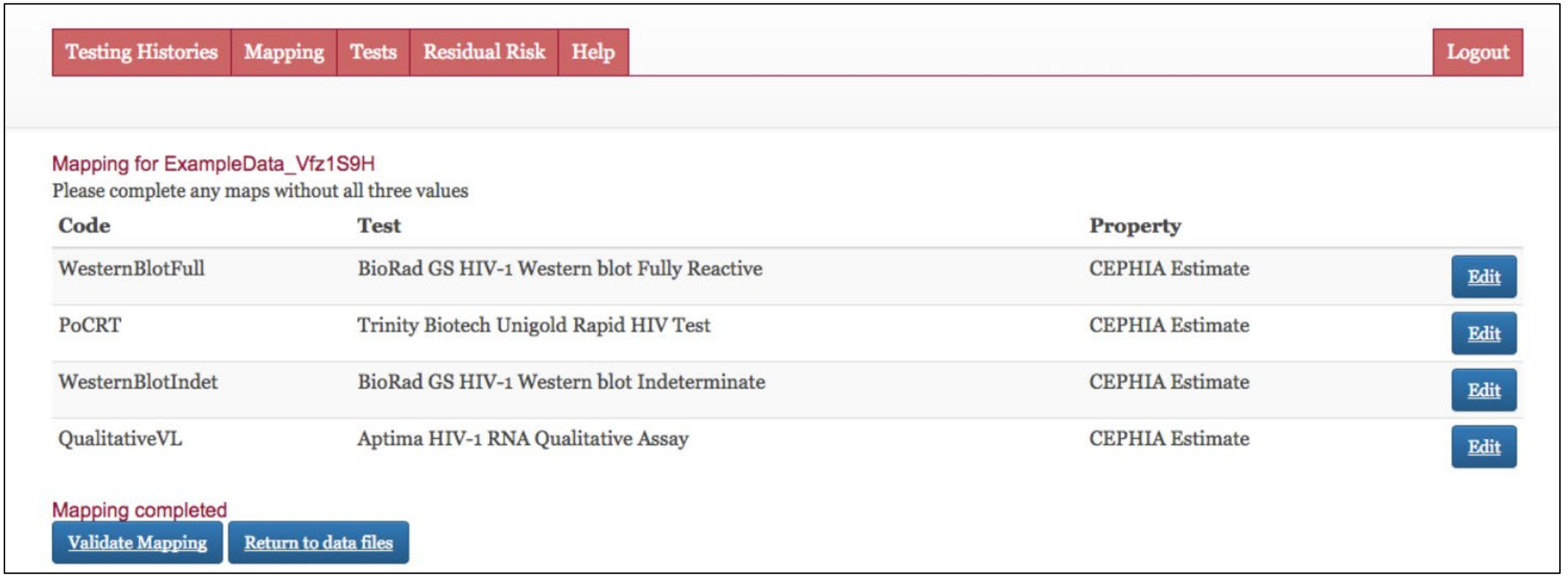
- Upload a .csv or .xslx file with 4 columns
  - Long format
  - Call tests whatever you want (you'll map them the first time)
  - Results are always positive or negative



	A	B	C	D	E
1	Subject	Date	Test	Result	
2	Subject A	1/10/2017	AptimaQualNAT	Positive	
3	Subject A	1/10/2017	GeeniusIndeterminate	Negative	
4	Subject B	9/13/2016	UnigoldRT	Negative	
5	Subject B	2/4/2017	UnigoldRT	Positive	
6	Subject B	2/4/2017	GeeniusFull	Positive	
7	Subject C	10/4/2004	OraQuickRT-Blood	Negative	
8	Subject C	11/5/2005	CoulterP24	Negative	
9	Subject C	5/30/2010	GenscreenV2	Negative	
10	Subject C	9/12/2014	AmplicorPooledx10	Positive	
11	Subject C	9/12/2014	BioRadWesternBlotIndeterminate	Negative	
12	Subject C	9/24/2014	ARCHITECT	Positive	
13	Subject C	9/24/2014	BioRadWesternBlotIndeterminate	Positive	
14	Subject C	9/24/2004	BioRadWesternBlotFull	Negative	
15	Subject C	10/4/2014	BioRadWesternBlotFull	Positive	
16					

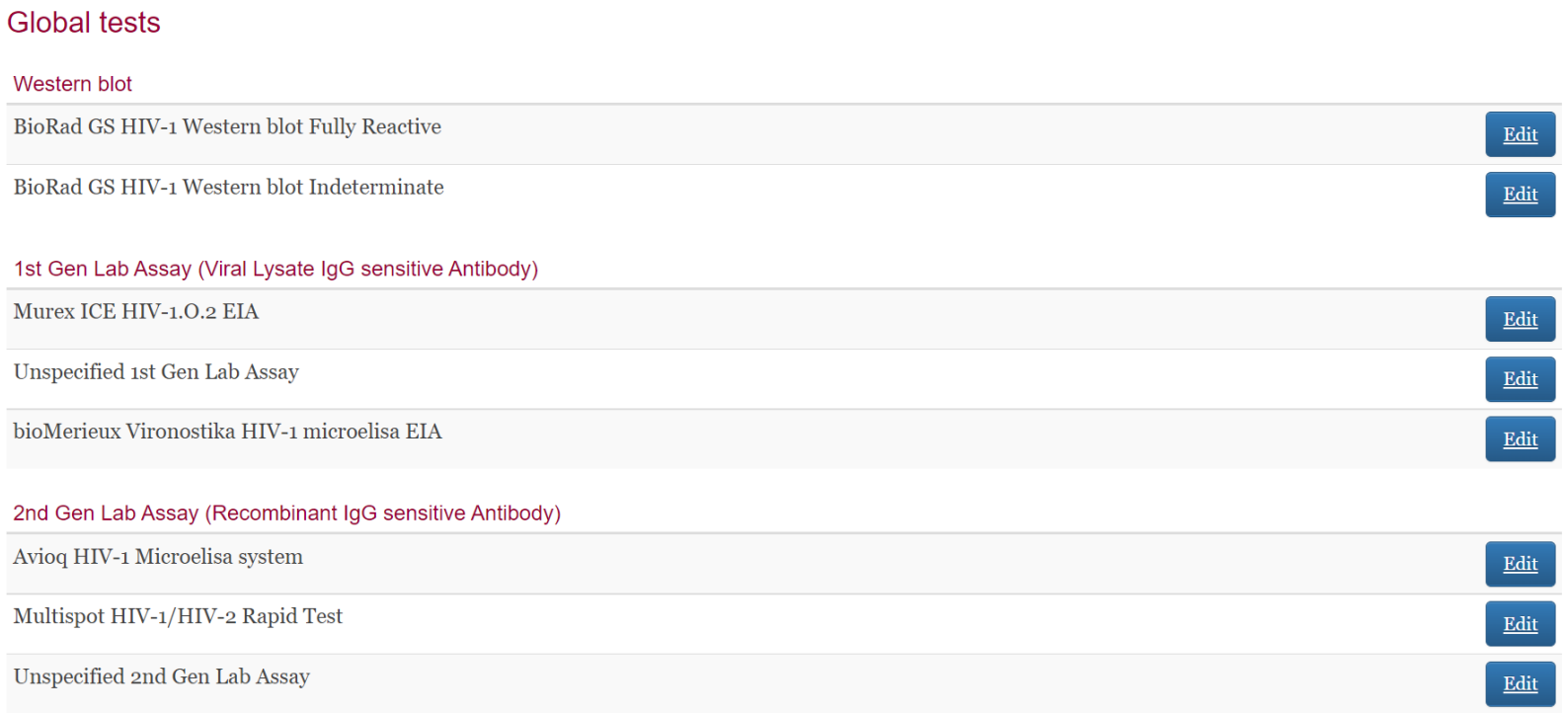
The Infection Dating Tool (IDT)

- Then you proceed to mapping (saves within your profile)



The Infection Dating Tool (IDT)

- The *Tests* tab lets you view and edit options for each test (connected to your profile, not the global database)
- You can also add your own tests, if you like
- The *Edit* button shows you more detail, and you can add info



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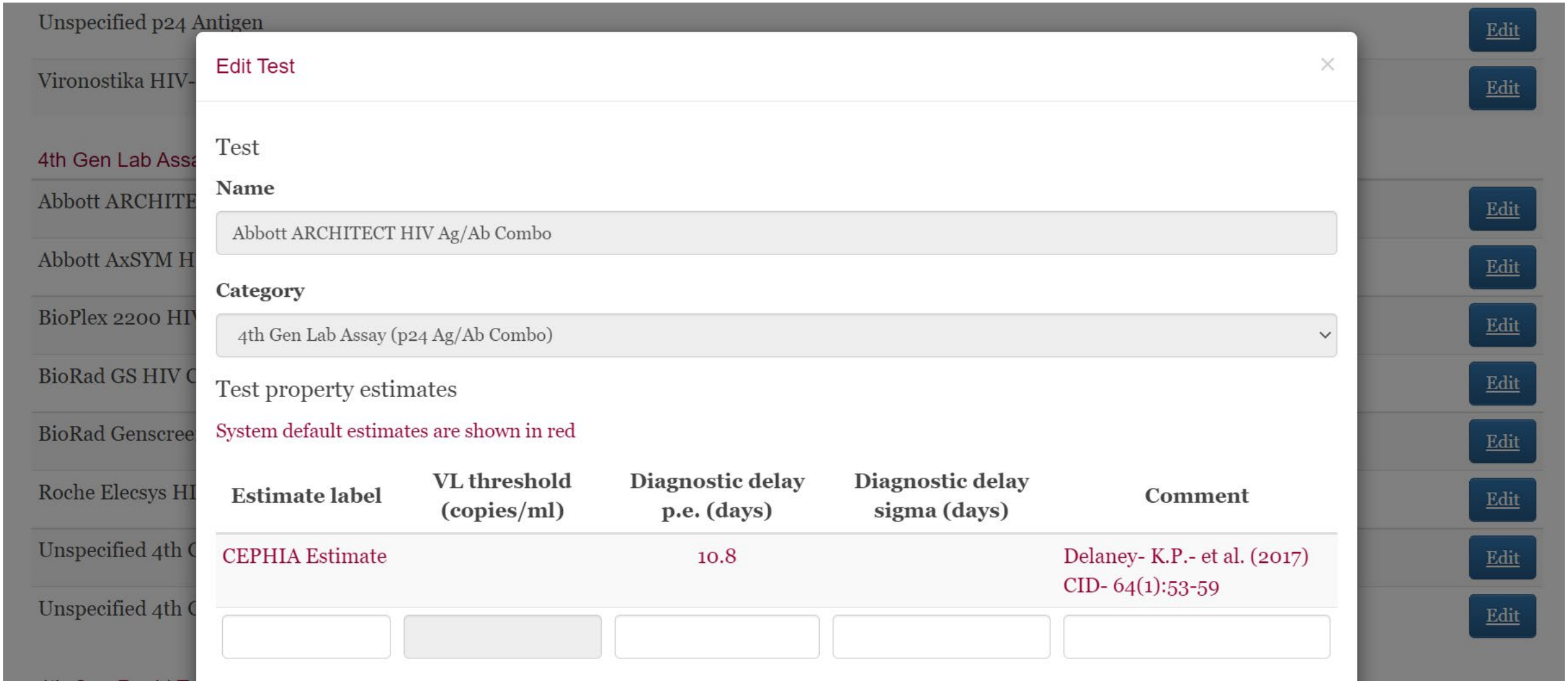

The Infection Dating Tool (IDT)

- Once mapping is complete, a *Process* button appears.

Subject	EP DDI	LP DDI	DDI Interval	EDDI	Flags
Subject A	Dec. 16, 2016	Jan. 6, 2017	21	Dec. 26, 2016	All tests reported are on same date EP-DDI & LP-DDI based on median diagnostic delays Subject has a discordant test date
Subject B	Aug. 19, 2016	Jan. 6, 2017	140	Oct. 28, 2016	EP-DDI & LP-DDI based on median diagnostic delays
Subject C	Aug. 28, 2014	Sept. 4, 2014	7	Aug. 31, 2014	EP-DDI & LP-DDI based on median diagnostic delays Subject has a discordant test date EPDDI and LPDDI less than 10 days apart

3 Bottom line

Bottom line…

- Fiebig staging is familiar, and an easy way to categorize people by evolution of infection.
    - But, it's a 20-year-old system based on technology that is outdated.
- The EDDI system is adaptable, flexible, and useful beyond seroconversion to help estimate someone's infection timing.
    - And there's a free tool to help calculate EDDIs easily!
    - You can still categorize people's infection timing if you choose.
- Just like our technology, it's time to update the way we think about how we use that technology to better understand a patient or research participant's HIV story.

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