CDISC Public Webinar- Huntington's Disease Therapeutic Area User Guide

12 September 2017

Jon Neville – CDISC
Daniel Olson- Critical Path Institute (C-Path)

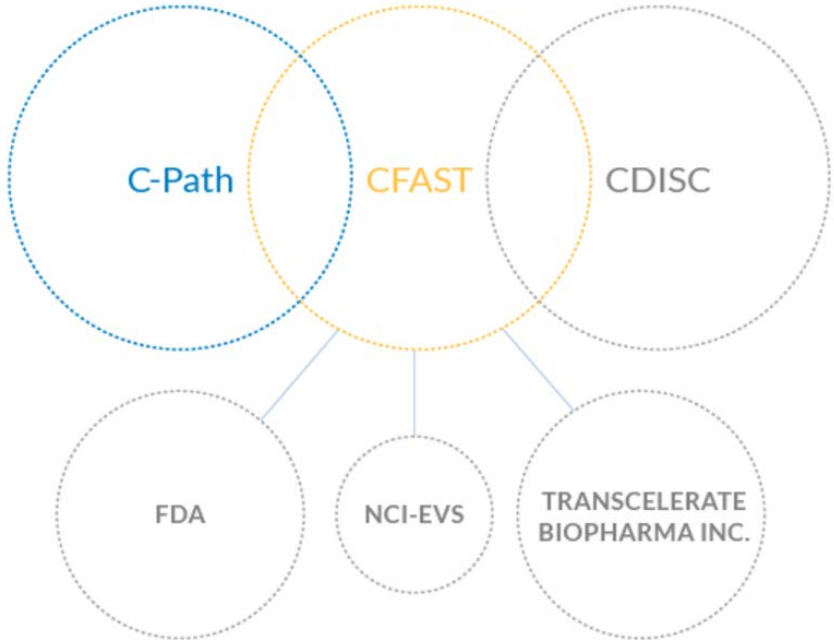
Strength *through Collaboration*

AGENDA

- Project Background
- Introduction to Huntington's disease (HD)
- HD TAUG Overview
  - TAUG Organization
  - Examples
  - Technical Specification details
- Public Review Information
- Q&A

Background

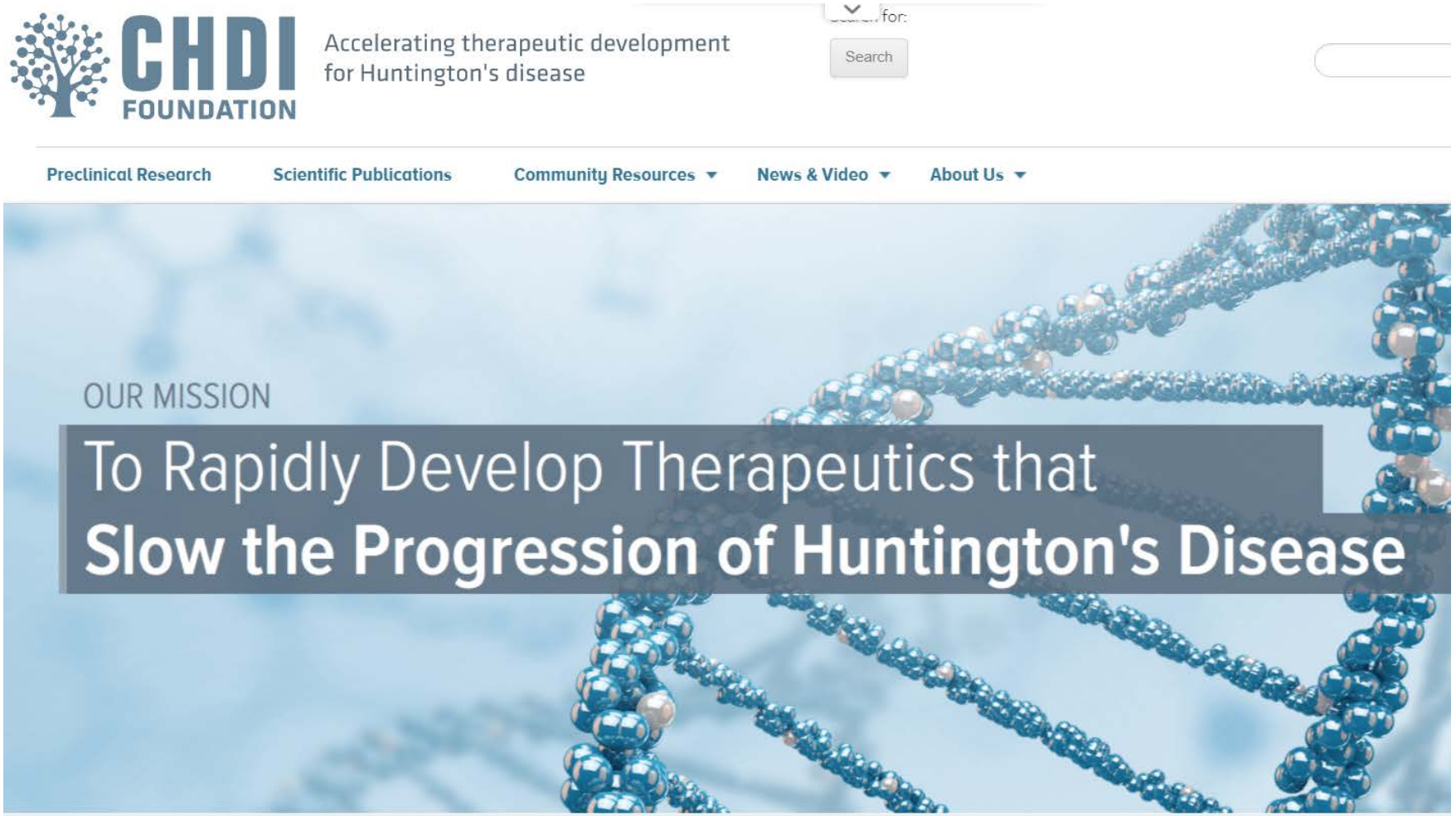
Development of the HD therapeutic area user guide (TAUG-HD) is being conducted under the umbrella of CFAST, a collaboration between CDISC and C-Path, with participation of NCI-EVS, FDA, and TransCelerate BioPharma, Inc



CFAST: Coalition for Accelerating Standards and Therapies

NCI-EVS: National Cancer Institute-Enterprise Vocabulary Service

Funding is provided by CHDI Foundation



Sources of Conceptual Input

- CHDI-funded studies
  - Protocols
  - CRFs
- Clinicaltrials.gov
- Medical literature
- TransCelerate member companies
- NINDS CDEs
- Discussions with subject-matter experts

Overview of TAUG Content

•**Section 1**, Introduction, provides an overall introduction to the purpose and goals of the Therapeutic Area Data Standards User Guide for HD.

•**Section 2,** Overview, provides some general information on HD.

•**Section 3**, Subject and Disease Characteristics, discusses the role of family history and genetics in Huntington's disease.

•**Section 4**, Disease Assessments, provides information on data used to evaluate how a subject is progressing over the course of a study.

•**Section 5**, Appendices, provide additional background material and describe other supplemental material relevant to HD.

Introduction to HD

- HD is a genetic disease caused by a mutation in the *Huntingtin (HTT)* gene.
- The disease causes the progressive degeneration of brain cells, resulting in cognitive impairment, psychiatric disorders and motor dysfunction.
- Onset can occur at any age but most often occurs between the ages of 30-50.

Source: http://www.parentprojectmd.org

Introduction to HD – cont'd

- There is no cure; current therapies focus on improving quality of life.
- Typical life expectancy from the time of onset is 15-20 years.
- Prevalence is 5-10 cases per 100,000; similar for men and women.

Source: http://www.parentprojectmd.org

TAUG Content: Examples

1 Introduction
2 Overview
3 Subject and Disease Characteristics
    3.1 Genetics and Family History of Huntington's Disease
4 Disease Assessments
    4.1 Questionnaires, Ratings, and Scales
    4.2 Biofluid Biomarkers
    4.3 Imaging
        4.3.1 Magnetic Resonance Imaging (MRI)
        4.3.2 Positron Emission Tomography (PET)
5 Appendices

Genetics of HD

HD is a *trinucleotide repeat disorder*

The causal mutation is an expansion of the CAG (cytosine-adenine-guanine) repeat region in the *HTT* gene

Characterizing CAG repeat length provides insight into disease risk/burden

HD-causing alleles	
>39 CAG repeats	Full penetrance: This range of CAG repeat length is associated with high certainty of developing HD
36-39 CAG repeats	Reduced penetrance: Subjects are at risk for developing HD, but may never show symptoms, depending on longevity (may die of other causes before developing HD)
Non HD-causing alleles	
27-35 CAG repeats	Intermediate or "mutable normal alleles": Subjects in this range are regarded as not-at-risk for HD, but due to instability in the CAG repeat portion of the gene, they may be at risk of having a child with an HD-causing allele
26 or fewer CAG repeats	Subjects with two alleles in this range of CAG repeat length are regarded as "normal" or not-at-risk

Genetics of HD

Example illustrates how to represent the number of Tandem repeats found in Huntington's using two different methods

- The combination of PFTEST (Number of Tandem Repeats), PFGENRI (HTT) and PFGENLOC (5197_5199) identifies that the focus of the test is the number of times the first CAG repeat (residing at the position identified in PFGENLOC) is repeated.

PFTEST	PFGENTYP	PFGENRI	PFREFSEQ	PFGENTRG	PFORRES	PFGENLOC	PFSTRESC	PFSTRESN	PFSPEC	PFALLELC	PFMETHOD
Number of Tandem Repeats	GENE	HTT	NG_009378.1	NUMBER OF CAG REPEATS	43	5197_5199	43	43	DNA	1	CAPILLARY ELECTROPHORESIS
Number of Tandem Repeats	GENE	HTT	NG_009378.1	NUMBER OF CAG REPEATS	25	5197_5199	25	25	DNA	2	CAPILLARY ELECTROPHORESIS
Number of Tandem Repeats	GENE	HTT	NG_009378.1	NUMBER OF CAG REPEATS	41	5197_5199	41	41	DNA	1	SEQUENCING
Number of Tandem Repeats	GENE	HTT	NG_009378.1	NUMBER OF CAG REPEATS	22	5197_5199	22	22	DNA	2	SEQUENCING

QRS Instruments

Full Name and Abbreviation	Copyright Permission Status	Supplement Status
Unified Huntington's Disease Rating Scale (UHDRS)	In progress	Development pending
Huntington's Disease Cognitive Assessment Battery (HD-CAB)	In progress	Development pending
Stroop Color and Word Test	In progress	Development pending
Letter Fluency	In progress	Development pending
Category Fluency	In progress	Development pending
Emotion Recognition*	In progress	Development pending
Hopkins Verbal Learning Test-Revised (HVLT-R)*	In progress	Development pending
One Touch Stockings of Cambridge*	In progress	Development pending
Paced Tapping*	In progress	Development pending
Speed Tapping	In progress	Development pending
Symbol Digit Modalities Test (SDMT)*	Not granted	Developed (total score only)

QRS Instruments Continued

Full Name and Abbreviation	Copyright Permission Status	Supplement Status
Trail Making Test (TMT; both A and B* versions are covered)	Granted	Developed
Clinical Global Impression (CGI)	Public domain	Developed
Columbia-Suicide Severity Rating Scale (C-SSRS)	Granted	Developed
Hospital Anxiety and Depression Scale (HADS)	Granted	Developed
Mini-Mental State Examination (MMSE)	Granted	In progress
Montreal Cognitive Assessment (MoCA)	In progress	Development pending
36-Item Short Form Health Survey (SF-36)	In progress	Development pending
Timed Up and Go (TUG)	Public domain	Developed

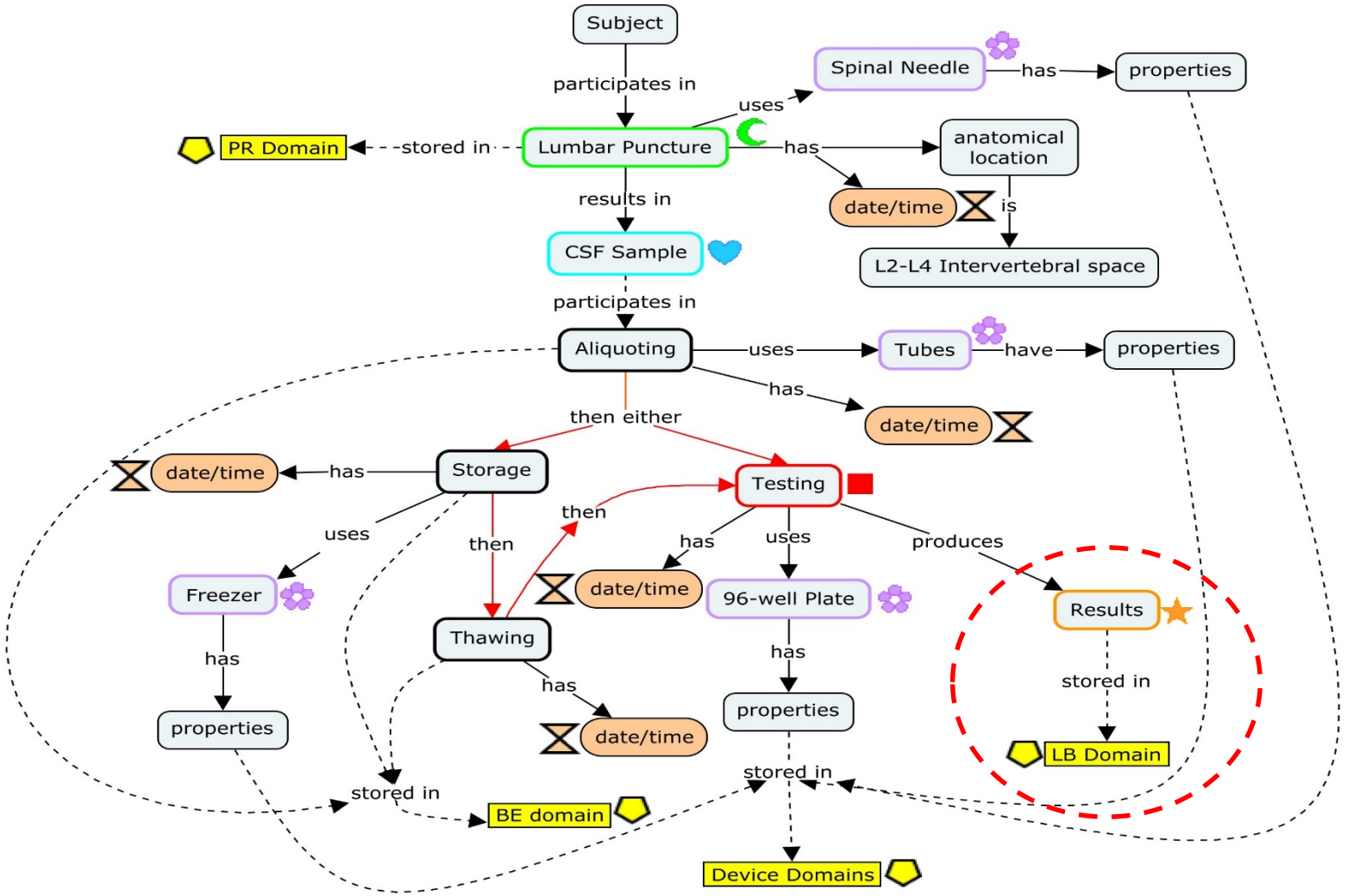
*These instruments are components of the Huntington's Disease Cognitive assessment battery (HD-CAB)

- Instruments are published and maintained as standalone supplements; they do not appear in the TAUG itself
- All published instruments are available at https://www.cdisc.org/foundational/qrs

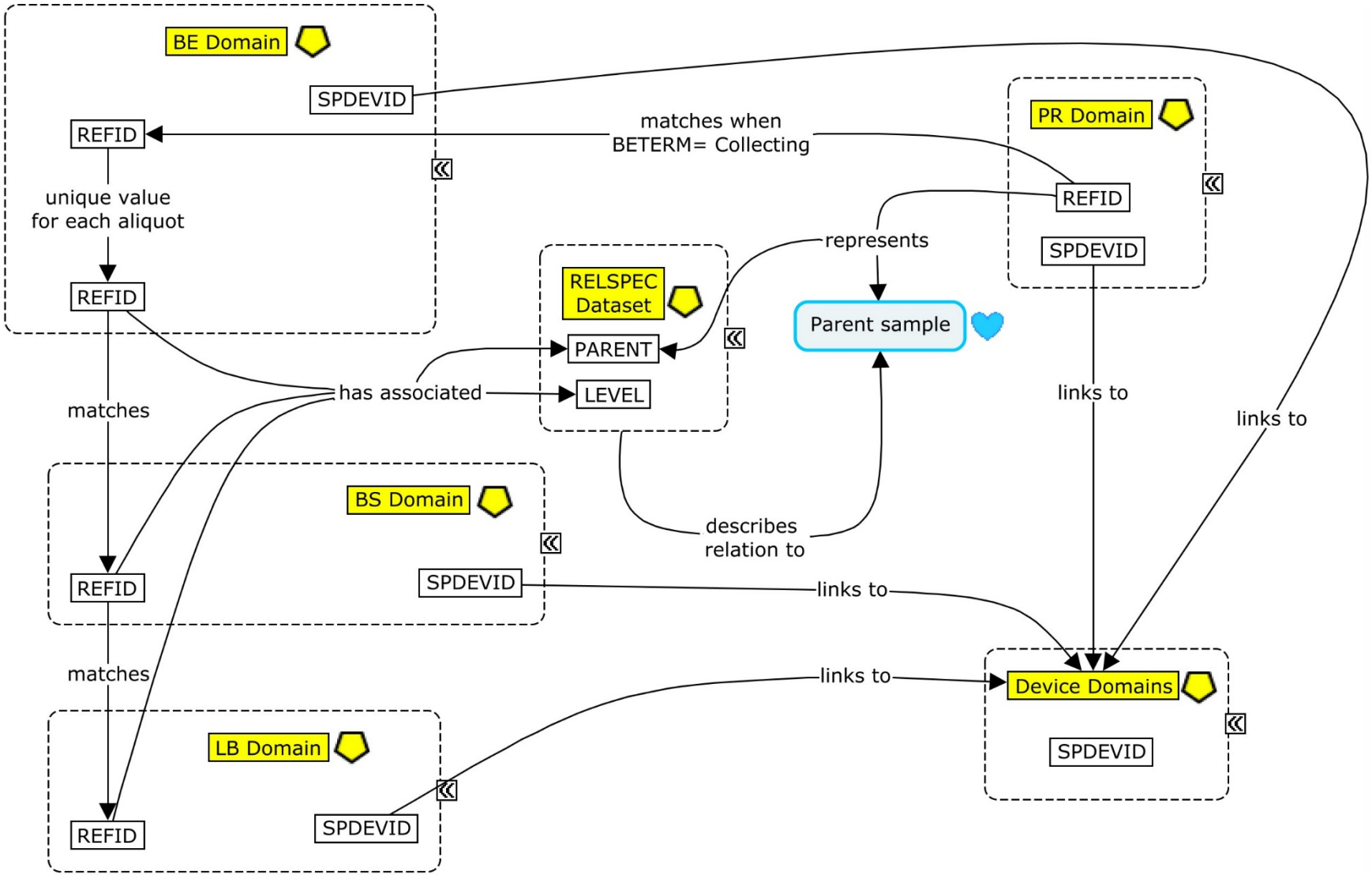
Biofluid Biomarkers

- Sampling of cerebrospinal fluid (CSF) and blood has been identified as an important source of potential biomarkers in HD.
- The TAUG-HD shows how to represent the fluid collection procedure, handling and storage of samples, analyte measurements, and associated device data.

Concept Map: Biofluid Biomarkers



Relating Records: Biofluid Biomarkers



Biofluid Biomarkers for HD

LBTEST	LBTESTCD	LBSPEC	Controlled Terminology Status*
Huntingtin Protein	HTT	CEREBROSPINAL FLUID	Requested
Mutant Huntingtin Protein	MHTT	CEREBROSPINAL FLUID	Requested
Alpha Synuclein	ASYN	CEREBROSPINAL FLUID	Requested
Neurofilament Light Chain	NFL	CEREBROSPINAL FLUID *or* BLOOD	Requested
Tau Protein	TPROT	CEREBROSPINAL FLUID	Published
Phosphorylated Tau Protein	TPROTP	CEREBROSPINAL FLUID	Published
Amyloid Beta 1-42	AMYLB42	CEREBROSPINAL FLUID	Published
Interleukin 6	INTLK6	CEREBROSPINAL FLUID	Published
Interleukin 8	INTLK8	CEREBROSPINAL FLUID	Published
YKL-40 Protein	YKL40	CEREBROSPINAL FLUID	Requested
Cocaine and Amphetamine-Regulated Transcript Protein	CARTPROT	CEREBROSPINAL FLUID	Requested
Ubiquitin	UBQN	CEREBROSPINAL FLUID	Requested

*Refers to the values in the LBTEST and LBTESTCD columns. Values in the LBSPEC column already exist as controlled terminology.

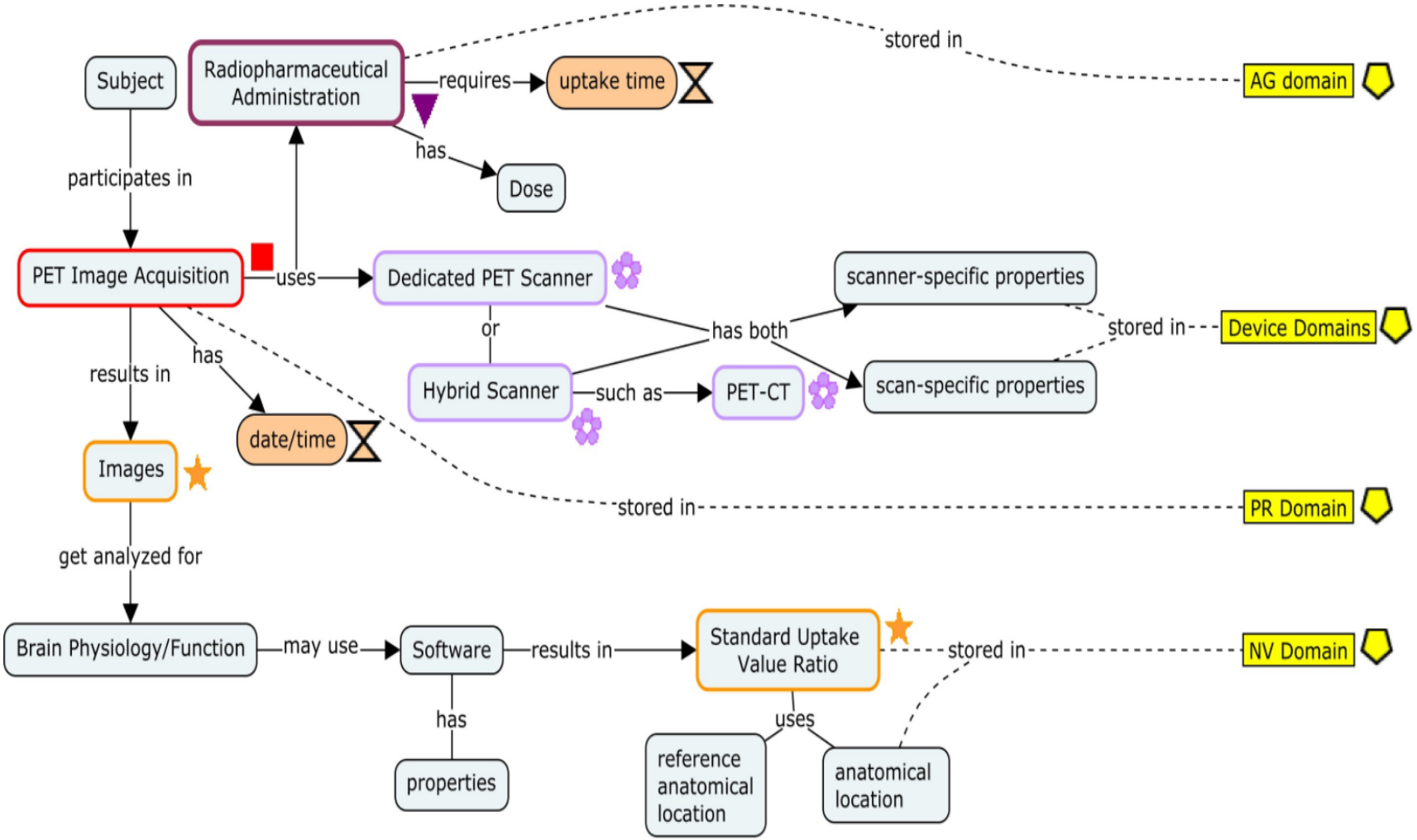
Imaging: PET

- PET imaging is used to characterize molecular and/or functional processes in the brain.

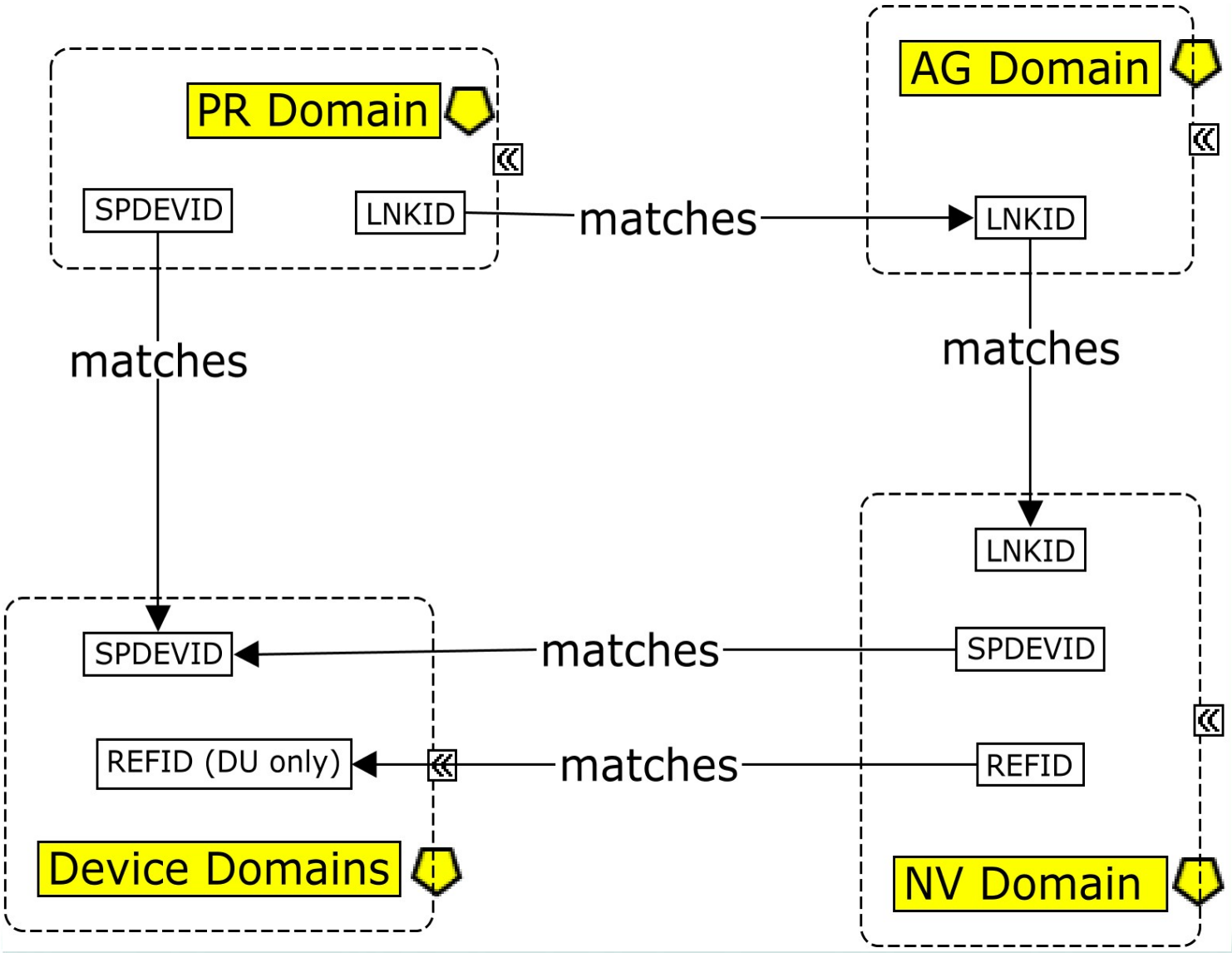
- The ultimate endpoint generated by a PET procedure is a *Standard Uptake Value* (SUV) or *Standard Uptake Value Ratio* (SUVR), both of which are based on the uptake of a radiolabeled tracer, an exogenous agent administered to the subject that is designed to bind a specific target

- The examples in TAUG-HD focus on tracers that bind Phosphodiesterase 10 (PDE10), a molecule expressed almost exclusively in brain regions affected by HD

Concept Map: PET Imaging



Relating Records: PET Imaging



Imaging: MRI

- In TAUG-HD, MRI is limited to volumetric brain measurements.
- HD is characterized pathologically by neurodegeneration of specific brain regions.
- The example in the TAUG represents the MRI procedures in the PR domain, the volumetric endpoints in the NV domain and the associated device proprieties and settings in the DI and DU domains respectively.

TA Specification- selected details

Domains

- No new domains were requested for this version of the TAUG
- The following Domains are used TAUG:

Datasets	Description
AG	Procedure Agents
LB	Laboratory Data
NV	Nervous System Findings
PR	Procedures
RELREC	Related Records
DO	Device Properties
DU	Device In-Use
DI	Device Identifiers
BE	Biospecimen Events
BS	Biospecimen Findings
PF	Pharmacogenomics/genetics Findings
RELSPEC	Related Specimens

New Variables

No new variables were requested for this user guide

Non-Standard Variables

Parent Domain	Variable	Label
PF	DEGACC	Degree of Accuracy

Known Issue: The non-standard variable Degree of Accuracy (DEGACC) needs further review by the Modeling Review Committee before publication.

Public Review: 11 Sep – 10 Nov

Stage 3b: Public Review

Stage 0	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 3c	Stage 4
Scoping & Planning	Modeling of Biomedical Concepts	Development of Draft Standards	Internal Review	Public Review	Publication	Standard Maintenance

CDISC and the TAUG-HD development team are seeking comment for the next 60 days

Public Review Information

- Review package available only on the CDISC WIKI
  - Links/Instructions were provided in the Public Review announcement email
  - https://www.cdisc.org/public-review/huntingtons-disease-therapeutic-area-user-guide-v10-available-public-review

- Reviewers are requested to make any comments directly via JIRA
  - Detailed instructions are provided on the TAUG-HD WIKI page
  - Wiki and JIRA use the same credentials, so if you can access the TAUG in the WIKI, then you can use JIRA.

Accessing and Reviewing the TAUG

Therapeutic Area User Guide for Huntingtons Disease

Created by Joe Ben Clark, last modified by Alana St. Clair on Sep 07, 2017

This is the landing page for the TAUG-HD. What would you like to do?

- **Read the TAUG-HD**
  There are two options, depending on your reading preference:
  - TAUG-HD compiled — This lets you view the entire document as a single web page, but is more prone to errors with the JIRA Connector.
  - TAUG-HD sections — This displays each section on its own page, and comprises the source of the content displayed on the compiled view.
    - Jump to a specific section:
- **Look at examples**
  - Huntington's Disease examples — This is where all examples used in the TAUG-HD live.

> ⚠ Note: Readers are recommended to use this directory only *after* reading the TAUG-HD in its entirety at least once.

- **Provide feedback**
  - Instructions for Reviewers — Detailed instructions for how to use JIRA to provide feedback on the TAUG-HD are given here.

Other resources you may find helpful:

- Introduction to Therapeutic Area Standards — This provides an overview of what to expect, and what *not* to expect, from a therapeutic area user guide.
- Reading on the Wiki — This page touches on some of the ways the Wiki edition of the TAUG-HUNT has been optimized for web use, with which a reader new to the CDISC Wiki may be unfamiliar.
- Draft Standards of Interest to TAUG-HUNT — These are CDISC standards-in-development that have influenced the development of the TAUG-HUNT, and are used in examples and/or modeling advice.
- TA Specification — This is a spreadsheet that provides information, for newer and proposed domains and

Security
This space is currently visible to team members. Team members can also edit pages.

This space is NOT visible to the general public, or to users who are not team members.

Status
This is a DRAFT standard, which means that it is still in development and not yet ready for provisional or general use.

This document is best read online.

Public Review Information – cont.

- We recommend reading the TAUG-HD in its entirety at least once before jumping to specific sections or examples
- Keep the JIRA-HD page and the WIKI HD Therapeutic User guide open in separate window
  - Comments can be entered without navigating back and forth between the Wiki and JIRA.
  - Always check to make sure the project selected in JIRA is HD.

Public Review Information – cont.

You can also make scope suggestions for future versions

If you have no edits or comments on a page, click 'Like' at the bottom of the page. This will help us determine who has read each page.

Q&A

Upcoming Webinars

Topics	Presenters	Webinar Date
CDISC Members Only Mini-Training - Define-XML 2.0 Completion Guidelines & Stylesheet Recommendations	Sally Cassells, Owner, Next Step Clinical Systems LLC Prafulla Girase, Principal Analyst, Biogen Marcelina Hungria, Data Submission Consulting Services, Dlcore Group, LLC Lex Jansen, Principal Software Developer, SAS Institute Inc. Dmitry Kolosov, Principal Statistical Programmer, PAREXEL	WED, 28 SEP 2017 10:00 AM - 11:30 AM CDT

Webinar details and registration at
www.cdisc.org/webinars

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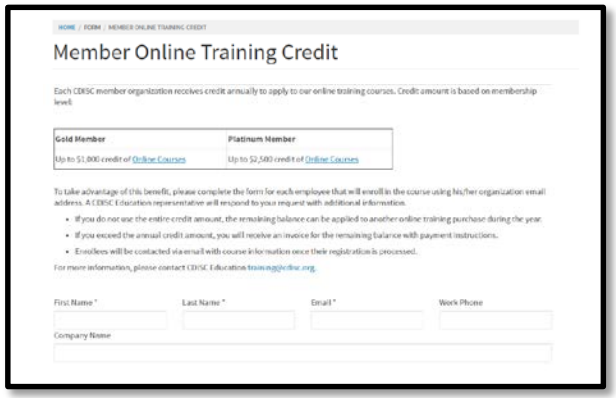
  - **Platinum Member** - Up to $2,500 credit of Online Courses
- To take advantage of this credit, visit:

www.cdisc.org/form/member-online-training-credit



For more information, please contact CDISC Education training@cdisc.org.

UPCOMING NORTH AMERICA PUBLIC COURSES

Location	Dates	Courses Offered:	Discount period ends:	Late fees kick(ed) in:	Host
Seattle, WA	25-29 Sep 2017	SDTM, CDASH, ADaM Primer, ADaM T&A, Define-XML	25 Jun 2017	25 Aug 2017	Axio
Austin, TX	13-17 Nov 2017	SDTM, CDASH, ADaM Primer, ADaM T&A, Define-XML, Controlled Terminology, SEND, Standards from the Start, ODM, SDTM for Medical Device	13 Aug 2017	3 Nov 2017	CDISC

Visit cdisc.org/public-courses for information on other CDISC Public Training events.

UPCOMING EUROPE PUBLIC COURSES

Location	Dates	Courses Offered:	Discount period ends	Late fees kick(ed) in:	Host
Copenhagen, Denmark	2-10 Nov 2017	SEND, SDTM, ADaM Primer, ADaM T&A, Define-XML	2 Aug 2017	3 Oct 2017	
London (Reading), United Kingdom	22-26 Jan 2018	SDTM, ADaM Primer, ADaM T&A, CDASH, Define-XML	22 Oct 2017	22 Dec 2017	

Visit cdisc.org/public-courses for information on other CDISC Public Training events.

UPCOMING ASIA PUBLIC COURSES

Location	Dates	Courses Offered	Discount period ends:	Late fees kick(ed) in:	Host
Beijing, China	19-20 Sep	SDTM, CDASH, ADaM Primer, ADaM T&A, ODM, Define-XML	19 Jun	1 Sep	Croit
Tokyo, Japan	4-8 Dec 2017	SDTM, CDASH, ADaM Primer, ADaM T&A, Define-XML	4 Oct	4 Nov	PAREXEL PPD
Seoul, South Korea	5-14 Mar 2018	Standards from the Start, SDTM, CDASH, ADaM Primer, ADaM T&A, Define-XML	5 Dec 2017	5 Feb 2018	C&R RESEARCH

Visit cdisc.org/public-courses for information on other CDISC Public Training events.

Any more questions?

Thank you for attending this webinar.

CDISC's vision is to:
Inform Patient Care & Safety Through Higher Quality Medical Research