Cancer Genomic Somatic Reference Samples – A Collaborative Initiative

Public Comment Period Announcement

JD Alvarez, MD, PhD | VP, Head Oncology Diagnostics, Janssen |
Working Group Chair

FDA/IVD Roundtable November 9, 2018

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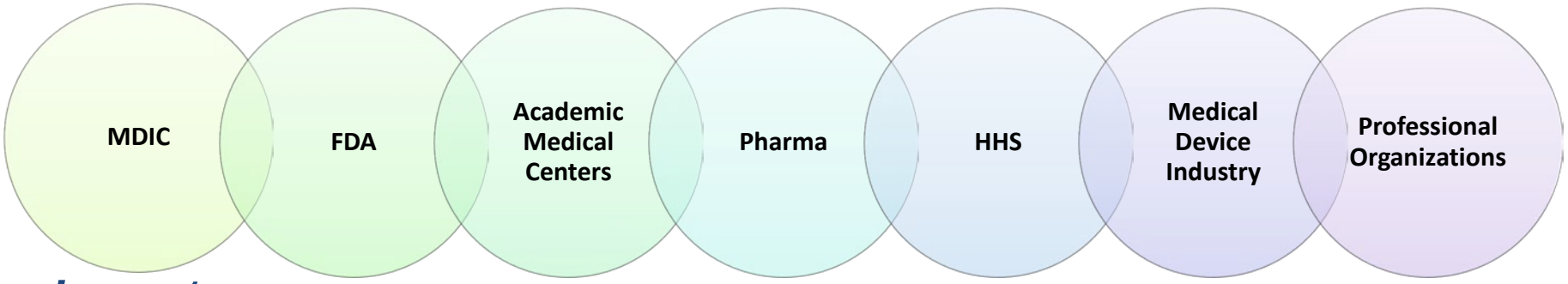
Align. Achieve. Accelerate.

Cancer Genomic Somatic Reference Samples

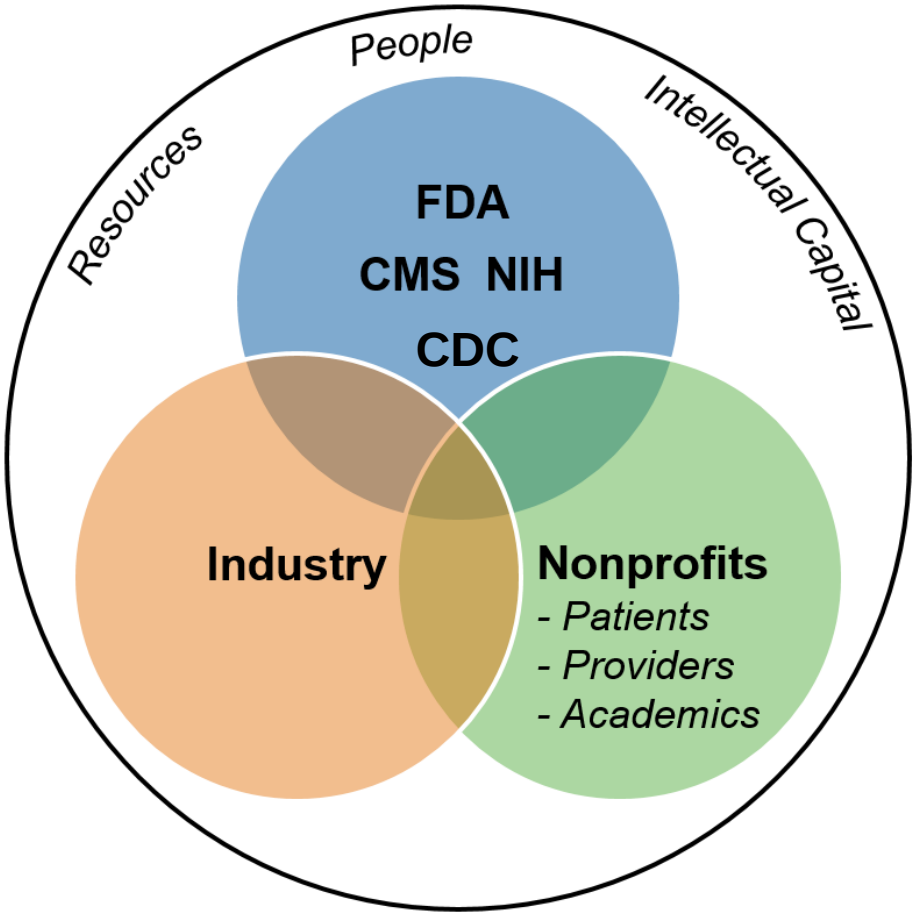
Goal: *Develop reference samples that can be made available to the public to improve the accuracy, reliability and transparency of NGS-based oncology tests.*



Impact:

- *Aid in efficient NGS test development and validation*
- *Streamline and possibly obviate steps in the regulatory process for diagnostic companies*
- *Provide transparency*
- *Compress development timelines for targeted therapeutics developers*

MDIC is a 501(c)(3) non-profit organization and is the first-ever public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit



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SRS Project – Two Phases

Phase 1

- Publish a detailed description of a prioritized set of samples and variants to be characterized and made available.
- Plan for their development and characterization in Phase 2.
- MDIC will determine to continue to phase 2 or transfer to 3rd party. (1 year)

Phase 2:

- Contracting and overseeing production and characterization of Phase 1 identified high priority oncology NGS reference samples
- Transfer of outputs to interested commercial entities. The project outputs will be made widely available to allow for scale up, production, and broad public accessibility by interested commercial entities. (1 – ½ years)

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SRS Project Plan – Overview
Multi-stakeholder Approach

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MDIC SRS Team

- JD Alvarez, Janssen R&D, Chair
- Zivana Tevak, FDA - CDRH
- Julie Schneider, FDA - CDER
- Stayce Beck, FDA - CDRH
- Carolyn Hiller, MDIC, Project Director

- Societies
  - AACR
  - AMP
  - CAP
- Pharma
  - Amgen
  - Astra Zeneca
  - BMS
  - Genentech
  - Janssen
  - Merck
  - Novartis
- Government Agencies
  - CDC
  - CMS
  - FDA
- Device Manufacturers
  - Illumina
  - Roche
- Academic Centers
  - Emory
  - TGen
  - UNC
- Suppliers
  - ATCC
  - Horizon*
  - Seracare*
  - NIST*
- Affiliates
  - Palmetto GBA

*Technical Assistance

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SRS Working Groups

- MDIC SRS Kickoff on June 13-14 at FDA campus
- Working groups formed at kickoff

Phase 1

- Landscape Analysis
- Variants
- Sample Definition
- Business Plan

Phase 2

- Sample Quality and Validation
- Data Integration

- Progress meeting Oct 8-9 at MDIC

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Questions and Focus

- Questions
  - What has been done or is ongoing in the space?
  - What variants are most important to develop reference standards for?
  - What are the characteristics of the samples that will serve as reference samples?
  - How to validate those reference samples?
  - How to make those reference samples available?
- Focus
  - Solid tumors
  - Tissue standards - ctDNA is out of scope

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Landscape Analysis

- Chair – Barb Zehnbauer, PhD, Emory
- Goal – Comprehensive summary to identify other efforts for development and evaluation of NGS reference samples which may inform and complement the SRS goals.
- Progress
  - Conducted comprehensive review of ongoing reference material generation projects
  - Surveyed NGS users as to their needs
  - Data to be published and made publicly available.

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Sample Definition

- Chair – Maryellen de Mars, PhD, ATCC
- Goal
  - Define and/or identify desired somatic reference samples (physical and in silico)
  - Develop sample characterization, acceptance criteria and quality control specifications
  - Develop strategies for maintaining supply and stability of reference samples over time.
- Progress
  - Develop minimal requirements for reference samples (consent, availability, licensing, production, distribution)
  - In depth evaluation of current samples and attributes from commercial sources and various initiatives that are related to target areas

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Variant Prioritization

- Chair – Tim McDaniel, PhD, TGen

  Eric Peters, PhD, Genentech
- Goal – Define a list of clinically actionable genomic alterations that would be represented in an ideal set of somatic reference samples.
- Progress – To be discussed today

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Data Quality/Validation

- Chair – Jason Merker, PhD, UNC
- Goal – Establish and enact a plan to experimentally verify the presence or absence of somatic variants within defined regions of the reference materials.
- Deliverables
  - Develop an experimental plan
  - Determine experimental methods
  - Plan for quality and usability
  - Plan to confirm quality and stability over time
  - Develop a budget for phase 2

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Data Integration

- Chair – Li Tai Fang, PhD, Roche
- Goal – Integrate raw data and results from different assays and labs to determine the ground truth of the reference samples
- Deliverables
  - Develop a data analysis proposal
  - Report positive (selected) variants for each reference sample, and estimate the variant allele frequencies.
  - Report additional variants in the reference samples beyond the selected variants, but within genomic regions covered by the assays.
  - Report the coverage (and the lack thereof) of different regions and variants by different assays.
  - Report the assays that yield discordant results, and resolve conflicts based on raw data or additional experiments if necessary

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Business Plan

- Chair – JD Alvarez, MD, PhD, Janssen R&D
- Goal – Create a plan that summarizes the framework and lays out the case for investing in the development and characterization of the prioritized set of samples and variants to be characterized and made publicly available
- Progress
  - Gathering data
  - To be started in 2019

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SRS Phase 1 - Timeline

		2018							2019					
		JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN
Kickoff														
Landscape														
Variants														
Sample Definition														
Data Validation														
Data Integration														
Business Plan														

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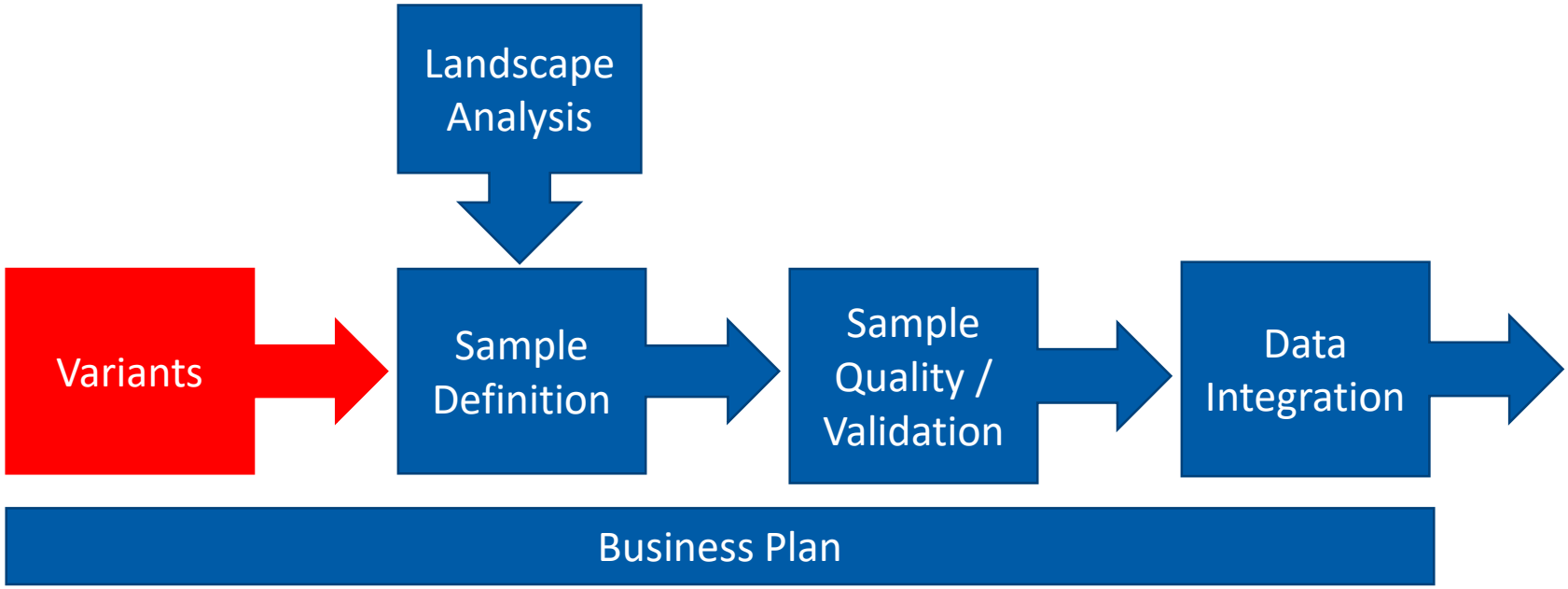
Working Group Workflow



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SRS Variants Working Group

- Eric Peters, Genentech, Co-chair
- Tim McDaniel, TGen/City of Hope, Co-chair
- Dan Klass, Roche, Variants Lead
- Mike Morrissey, Merck, TSG/Signatures Lead
- Carolyn Hiller, MDIC, Project Director

JD Alvarez, Janssen	Jason Merker, UNC
Stayce Beck, FDA - CDRH	Saumya Pant, BMS
Gideon Blumenthal, FDA - CDER	Girish Putcha, Palmetto
Tara Burke, AMP	Banu Sankaran, Novartis
Tracy Bush, Roche	Julie Schneider, FDA - CDER
Maryellen de Mars, ATCC	Katherine Szarama, CMS
Li Tai Fang, Roche	Robyn Temple Smolkin, AMP
Hantash Feras, Sema4 Genomics	Zivana Tezak, FDA - CDRH
Steven Gutman, Illumina	Sarah Thibault-Sennett, AMP
Lisa Kalman, CDC	Patricia Vasalos, CAP
Diane Levitan, Merck	Mary Williams, AMP
Robert Loberg, Amgen	Barbara Zehnbauer, Emory
Sarah Martin, AACR	Mike Zou, Novartis

Pharmas • Labs • Payers • Tech Providers • Government • NGOs • Universities

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Approach to Variant Selection

This team's task is to identify the list of variants or other targets (e.g., genomic signatures) that would be covered in an ideal set of reference materials. In an effort to ensure that this list identifies the most useful targets to benefit the most patients today, we will draw the targets from the work of objective third parties without vested commercial interests in any particular target. Sources should therefore:

- Represent current standard medical practice
- Originate from a public sector or independent non-profit organizations
- Represent the collective opinion of a broad swathe of clinicians and / or laboratory scientists.

Sources used: OncoKB, CIViC Clinical Interpretations of Variants in Cancer, Cancer Genome Interpreter

Initial list will focus on variants relevant to solid tumors

Hotspots Versus TSG/Signatures

Effort broken into two workstreams

- Hotspots (Dan Klass, Roche) } Subject of Current Public Comment Period
- Tumor Suppressor Genes / Signatures (Michael Morrissey, Merck)

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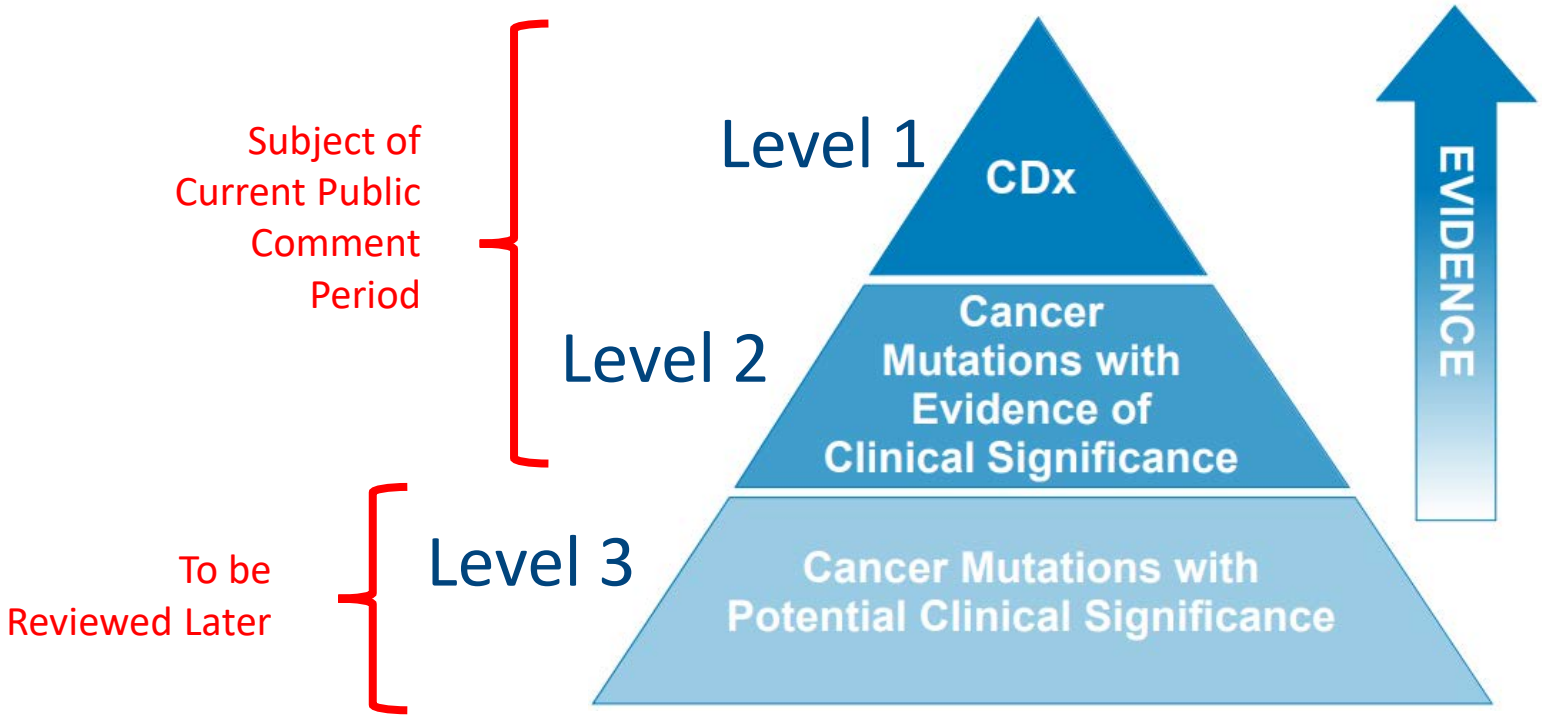
Hotspot Variant Evidence Levels



https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm584603.pdf

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Process for Creating Hotspot Variant List

- June 13-14
  - First MDIC Somatic Reference Samples F2F Meeting, FDA White Oak
  - Variants Working Group Formed
- July – October
  - Biweekly teleconferences
  - Lists drafted—Dan Klass (Roche) leads
- October 9-10
  - Second MDIC Somatic Reference Samples F2F Meeting
  - Finalization of Level 1 & 2 Variants List

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Current Snapshot

- Nov 8 — Draft Level 1 & 2 Variants list made publicly available
  — Public comment period opens
- Dec 6 — Public comment period closes
- Dec-Jan — Public comments reviewed by SRS Variants Team
- Jan 23, 2019 — MDIC Variant Public Workshop at FDA
  — Final Levels 1 &2 Variants List to be made public
- Later in 2019 — Level 3 Variants & TSG/Signatures Lists to be developed

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Process for Accessing Levels 1&2 Variant List & providing feedback

- ACCESS the draft Levels 1&2 Variant List
  - http://mdic.org/clinicaldx/somatic-reference-samples/
- REVIEW the list
- SHARE your comments - **December 6 deadline**
  - Please email your comments to SRS-Variants@mdic.org
- VIEW the final list once released on January 23

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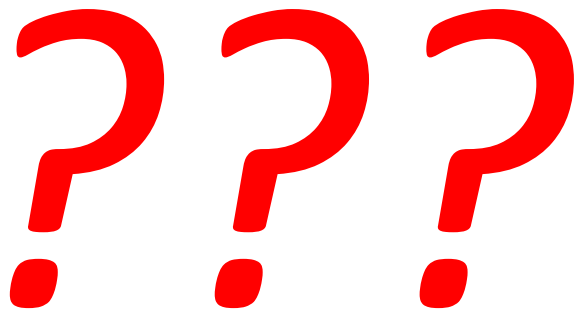
Questions for Public Comment Period

1. Are there any variants missing? Rationale why?
2. Is there a variant on the list that should not be on the list? Rationale why?
3. Are any of the variants mis-categorized? Rationale why?



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Draft Levels 1&2 Variants List

First 14 Lines…

Variant UID	Variant Type	Evidence Level	Gene Symbol	Variant	Source
V001	CNV	1	ERBB2	Amplification	OncoKB
V002	CNV	2	CDK4	Amplification	OncoKB
V003	CNV	2	MET	Amplification	OncoKB
V004	CNV	2	MYCN	AMPLIFICATION	CIViC
V005	Indel	1	ALK	ALK inframe insertion (1151T)	CGI
V006	Indel	1	EGFR	Exon 20 insertion	OncoKB
V007	Indel	1	EGFR	A763_Y764insFQEA	OncoKB
V008	Indel	1	EGFR	E709_T710delinsD	OncoKB
V009	Indel	1	EGFR	Exon 19 deletion/insertion	OncoKB
V010	Indel	2	PDGFRA	PDGFRA inframe deletion (I843)	CGI
V011	MNV	1	BRAF	V600K	OncoKB
V012	SNV	1	ALK	G1269A	CGI
V013	SNV	1	ALK	I1171T	CGI
V014	SNV	1	ALK	L1196M	CGI

When providing comments about a variant, please reference the "Variant UID" identifier number to avoid ambiguity

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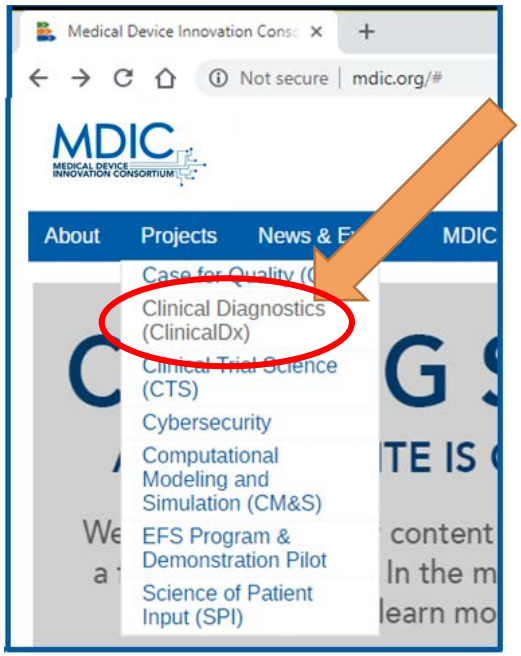
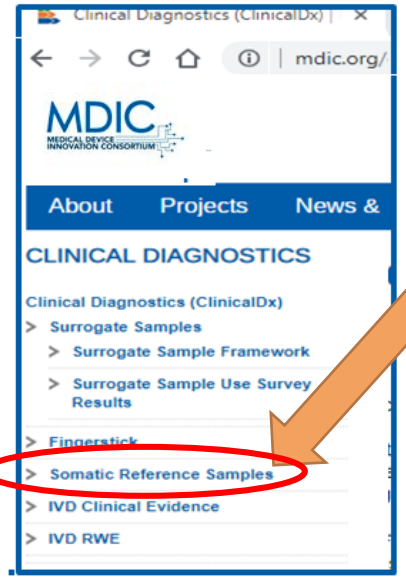
Draft Levels 1&2 Variant List On MDIC.org



1. On MDIC homepage (www.MDIC.org) – select Clinical Dx from Projects drop down menu



2. On Clinical Dx page – select Somatic Reference Samples

3. On the webpage mdic.org/clinicaldx/somatic-reference-samples you will find:

- Comment instructions
- Variant List
- MDICx Archive Link
- Project overview

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Public Comment Period

- **Draft Level 1 & 2 Variants List:** http://mdic.org/clinicaldx/somatic-reference-samples/
- **Address Comments to:** SRS-Variants@mdic.org
- **Please reference Variant UID Number for comments on any existing variant**

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