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Tumor Profiling Assays

A Representative Approach in Analytical Accuracy Study

ASA Biopharmaceutical Section Regulatory-Industry Statistical Workshop 9/23/2020 11:30am-12:45pm

Disclaimer Statement

The views expressed during this presentation are those of the presenter and do not necessarily reflect finalized policy or position of the US FDA.

Outline

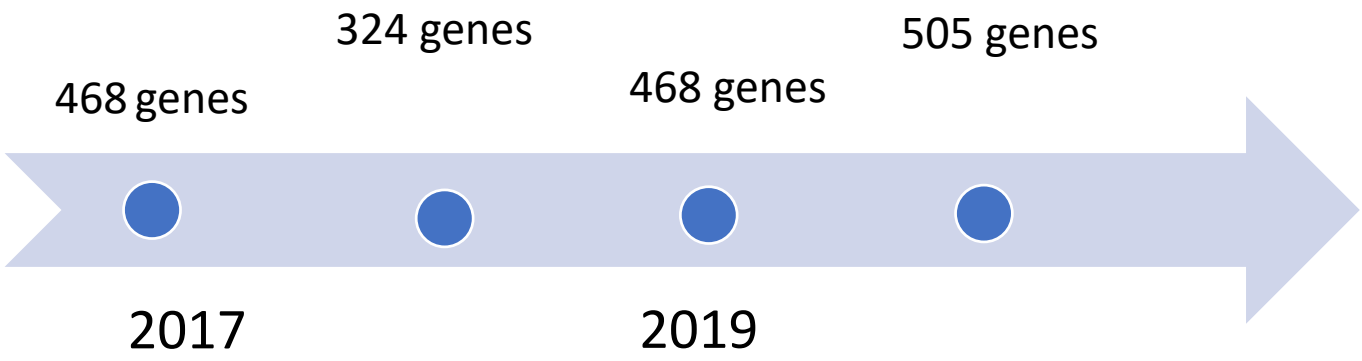
- Introduction
  - Tumor Profiling Assays
- Validation Studies
  - Analytical Accuracy
- Sampling Method
  - Representative Approach

Cancer Clinical Trials

Tumor Profiling

What is tumor profiling assay?

"an in vitro diagnostic test that can identify a higher number of genetic mutations (biomarkers) that may be found in various cancers…" *



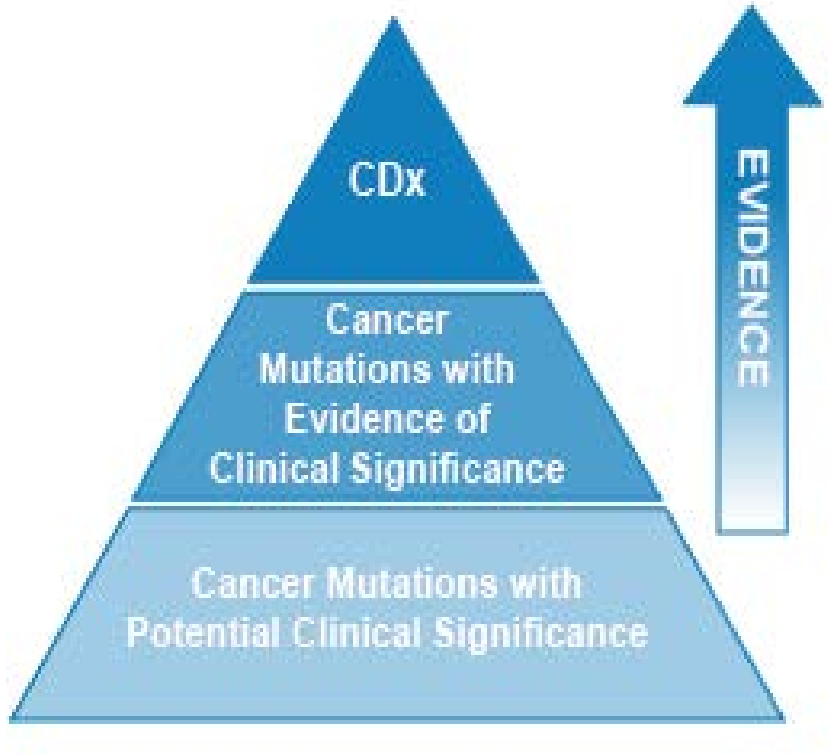
* https://www.fda.gov/news-events/press-announcements/fda-unveils-streamlined-path-authorization-tumor-profiling-tests-alongside-its-latest-product-action

https://www.fda.gov/medical-devices/vitro-diagnostics/nucleic-acid-based-tests

FDA Fact Sheet

CDRH's Approach to Tumor Profiling NGS Tests

https://www.fda.gov/media/109050/download



Three-Tiered Approach for Reporting Biomarkers in Tumor Profiling NGS Tests

Validation Studies

- Clinical Validation
  - CDx
- Analytical Validation
  - LoD
  - Precision
  - Interference
  - Accuracy
  - ….

Analytical Accuracy Study

New Assay **Vs.** Orthogonal Method

Do they agree?

Analytical Accuracy

- Protocol
- SAP
- Sample Size

Study Design

- Clinical Specimens
- Contrived

Samples

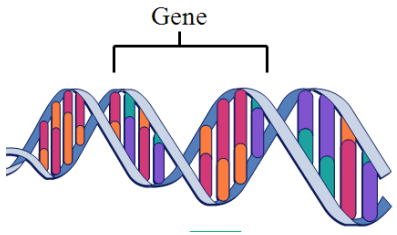
- Primary Analysis (PPA/NPA)
- Sensitivity Analysis

Data Analysis

Sample Size

When compared to orthogonal method, how many specimens are needed?

N=?



Genes
- Multi-genes

Exons
- Targeted gene panel

Variants
- SNV, Indels, CNV, Fusion

Tumor types
- Solid tumor

A hypothetical example

<u># mutations:</u>

500 genes x 10 exons/gene x 300 base pairs per exon

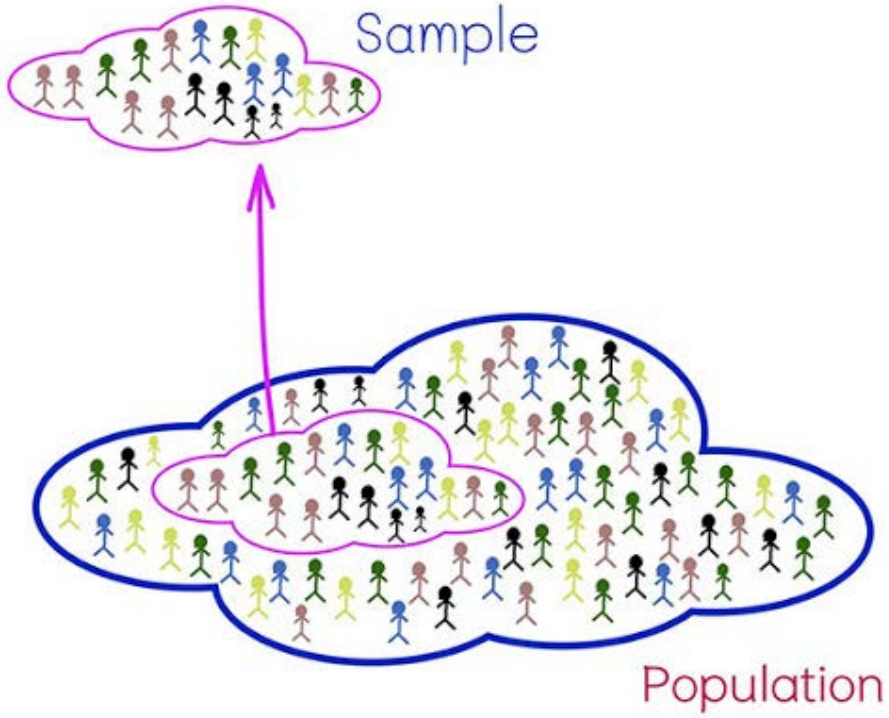
= 1,500,000

That's a lot!

Statistical Challenge

How many clinical specimens are needed to validate so many mutations?

Survey sampling Techniques



- Simple Random Sampling
- Stratified Sampling
- Cluster Sampling
- Multi-stage Sampling

Simple Random Sampling

1% Rule

1% x 1,500,000 = 15,000

Still a lot!

The Least Burdensome Provisions: Concept and Principles

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 5, 2019.

The draft of this document was issued on December 15, 2017.

This document supersedes "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles," issued on October 4, 2002.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director at (301) 796-6900. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Law of Large Population (LLP)*

"A simple random draw of 400 subjects can achieve the same effect as a test of 10,000 out of 1 million subjects (f=1%) assuming the positivity rate is 0.5% (ρ=0.005)… "

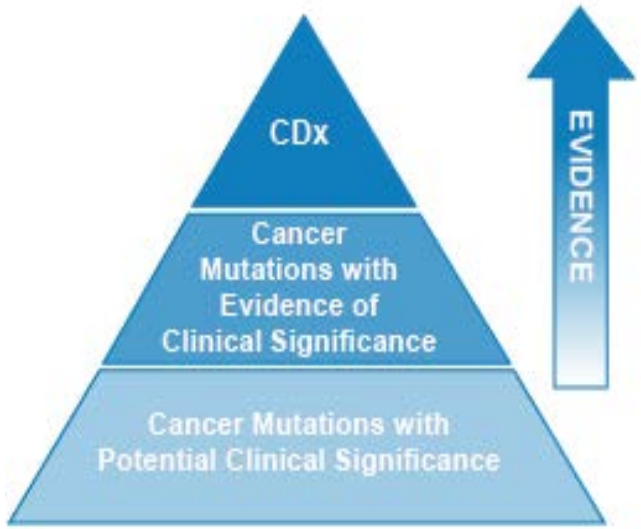
$$\mathrm{n} = \frac{1}{\rho^2} \times \frac{f}{1-f}$$

Mean-squared Error (MSE)

$$\mathrm{MS}E(\bar{G}_n) = E[\bar{G}_n - \bar{G}_N]^2$$

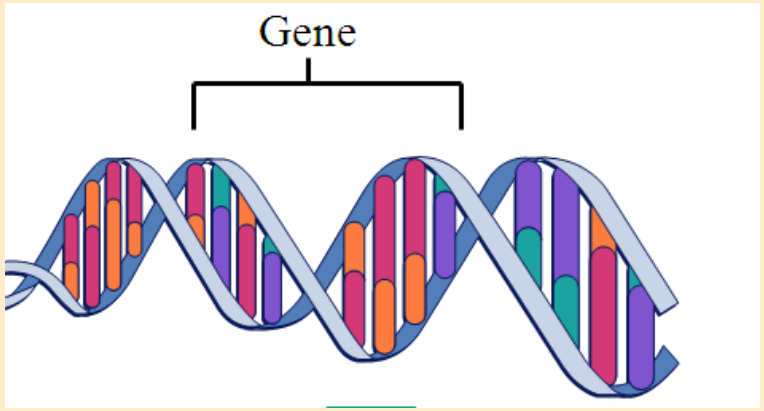
* Xiao-li, Meng. Statistical Paradise and Paradoxes in Big Data. The Annals of Applied Statistics. 2018: 12(2), 685-726.

Will a random sample of 400 specimens be adequate for the accuracy study for tumor profiling assays?



Three-Tiered Approach for Reporting Biomarkers in Tumor Profiling NGS Tests

Representative approach

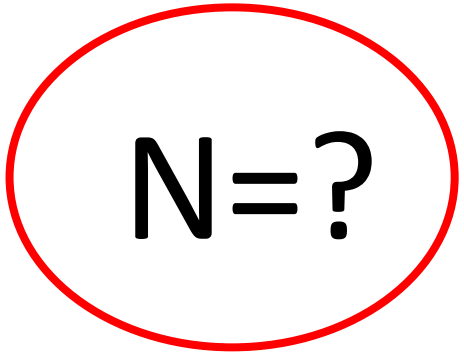


Gene
- Representative
- Level 2 genes

Variant
- SNV and indels
- CNV and fusion

Tumor type
- Major tumors
- Challenging

How many clinical specimens are needed to validate tumor profiling assays?



Genes

Variants

Tumor Types

Conclusion

Representative Approach

- A Least Burdensome Approach
- Good clinical input
- Sound statistical explanation
- Consistent regulatory consideration

Acknowledgement

I would like to thank Drs. Bipasa Biswas, Changhong Song and other colleagues at FDA/CDRH for their feedback.

Thank you!

Questions?