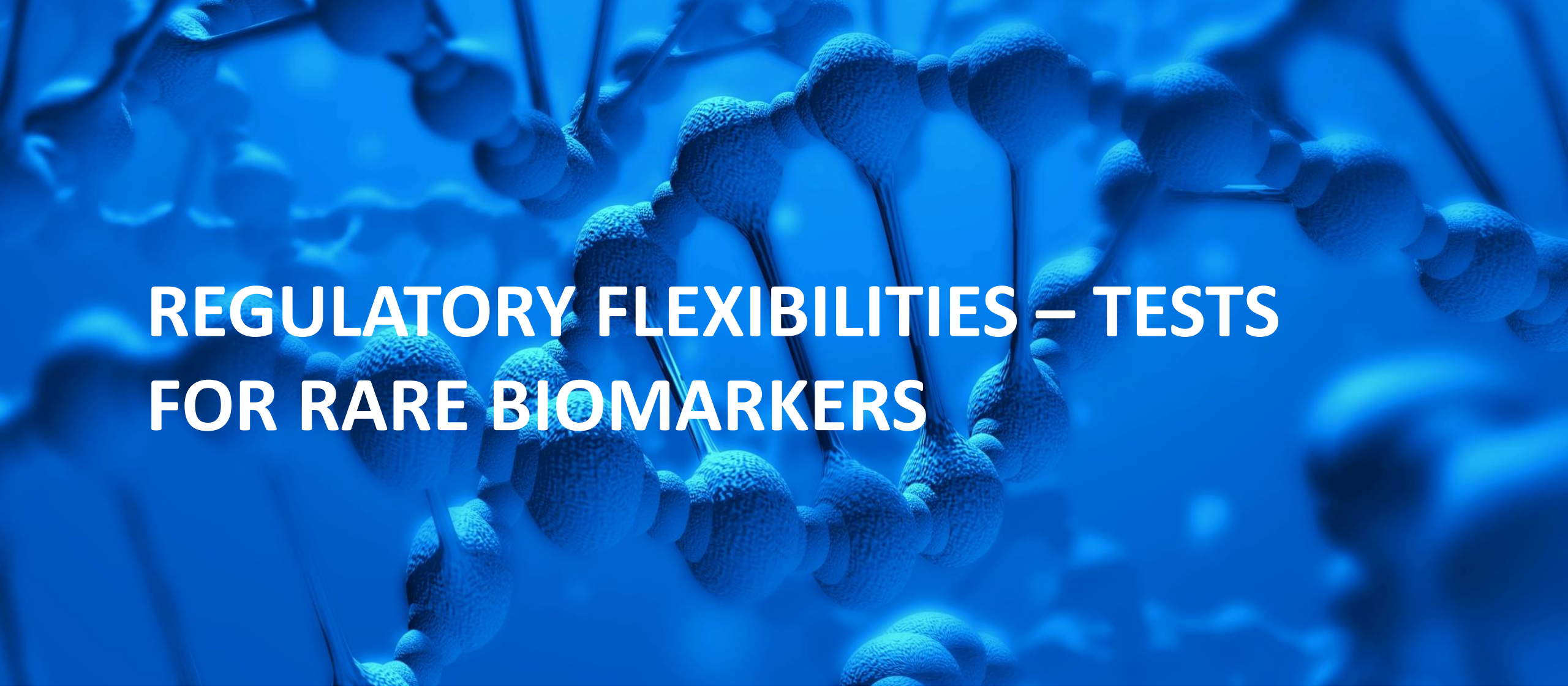

# REGULATORY FLEXIBILITIES – TESTS FOR RARE BIOMARKERS

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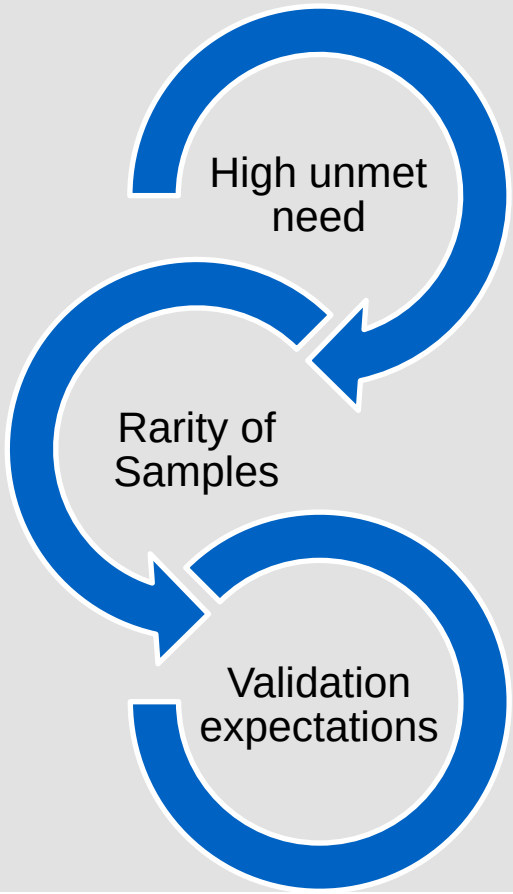
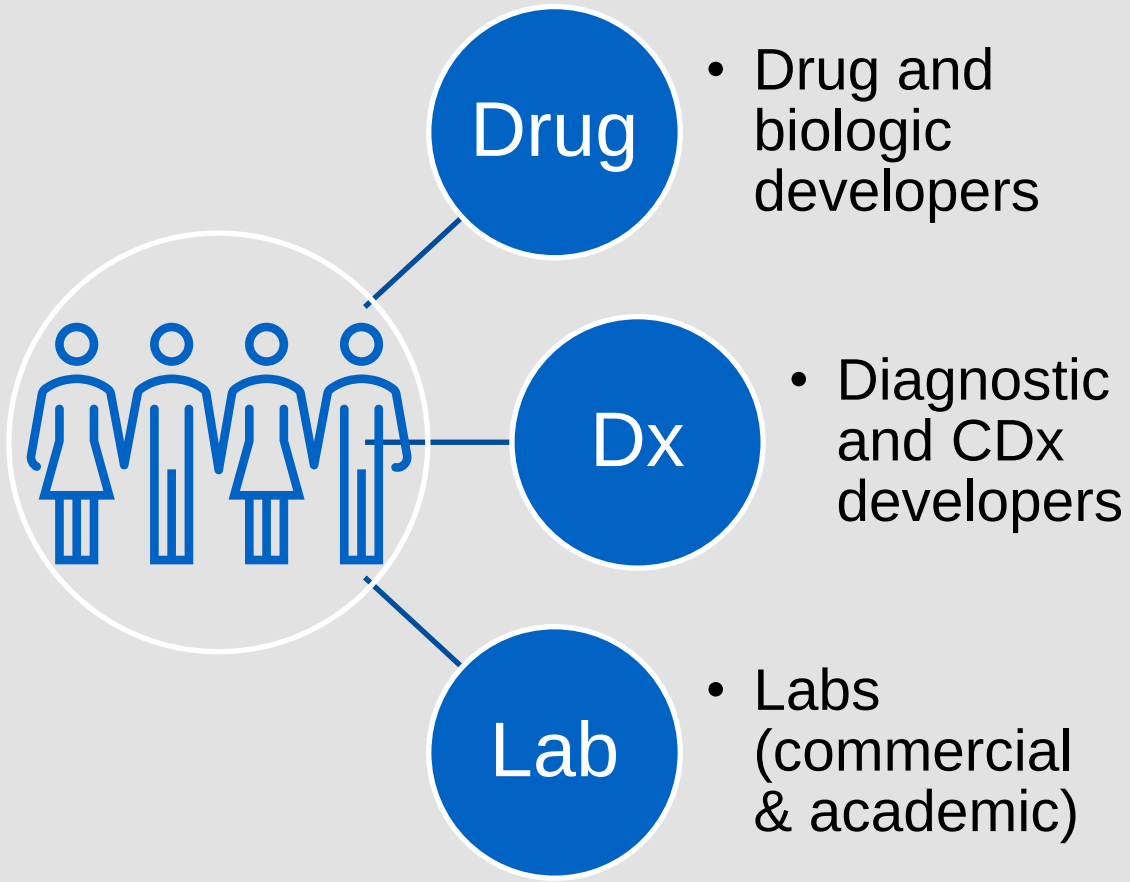
# CHALLENGES IN DEVELOPING CDX FOR RARE BIOMARKERS




- **Rarity of biomarker or condition often means high unmet need**
- **Rarity makes it difficult to find patients for the trial and samples**
- **FDA expectations have not varied based on rarity of biomarker**

# FRIENDS OF CANCER RESEARCH EFFORT



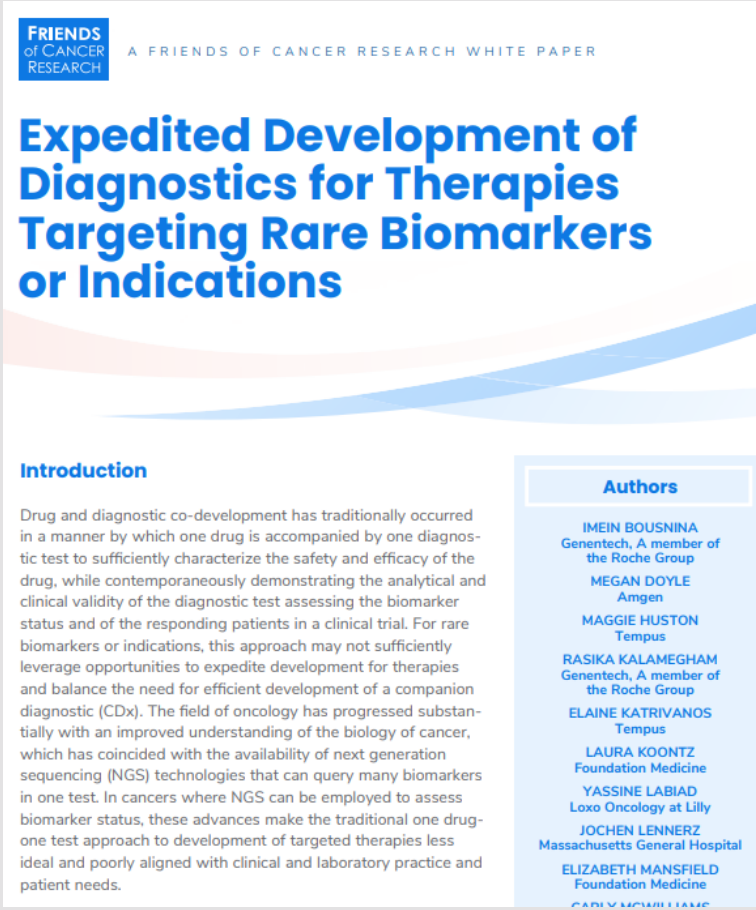

Source: Friends of Cancer Research, Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications, https://friendsofcancerresearch.org/wp-content/uploads/Dx_For_Rare_Biomarkers_White_Paper.pdf

# WHITE PAPER & KEY THEMES

## Propose a framework that would facilitate:

(1) **Enrollment of patients in an efficient manner while maintaining clinical trial integrity**

(2) **Approval of a CDx based on requirements that consider the benefit-risk profile and feasibility of obtaining samples**



FRIENDS of CANCER RESEARCH A FRIENDS OF CANCER RESEARCH WHITE PAPER

**Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications**

**Introduction**

Drug and diagnostic co-development has traditionally occurred in a manner by which one drug is accompanied by one diagnostic test to sufficiently characterize the safety and efficacy of the drug, while contemporaneously demonstrating the analytical and clinical validity of the diagnostic test assessing the biomarker status and of the responding patients in a clinical trial. For rare biomarkers or indications, this approach may not sufficiently leverage opportunities to expedite development for therapies and balance the need for efficient development of a companion diagnostic (CDx). The field of oncology has progressed substantially with an improved understanding of the biology of cancer, which has coincided with the availability of next generation sequencing (NGS) technologies that can query many biomarkers in one test. In cancers where NGS can be employed to assess biomarker status, these advances make the traditional one drug-one test approach to development of targeted therapies less ideal and poorly aligned with clinical and laboratory practice and patient needs.

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# PROPOSED MINIMUM REQUIREMENTS MAY IMPROVE PATIENT ACCESS TO TRIALS FOR RARE INDICATIONS OR BIOMARKERS

| Performance Characteristic | Minimum Requirement* |
|---|---|
| **Concordance (Sensitivity, specificity, accuracy)** | 30 biomarker negative samples<br>A range up to 30 biomarker positive# samples<br>If possible 6 known positives (confirmed using an orthogonal method) |
| **Limit of Detection** | 1 known positive* sample in a serial dilution series with at least 3 replicates at each dilution step |
| **Precision** | Repeatability across operators, reagent lots, days, instruments using 2 positive samples per variant type, with one at 1.5x LOD and one at 2x LOD |
| **Limit of Blank** | 5-10 replicates across 2-3 healthy donor samples using the same sample type |

*Requirements and number of samples should be guided by the complexity and prevalence of the biomarker being detected
#Can be a contrived sample

**These metrics can also facilitate bridging studies for CDx**

Source: Friends of Cancer Research, Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications, https://friendsofcancerresearch.org/wp-content/uploads/Dx_For_Rare_Biomarkers_White_Paper.pdf



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# REGULATORY FLEXIBILITIES – HOW AND WHEN TO APPLY

## Recommendations

- Consider a threshold of 10,000 patients likely to have the disease/condition to define rare biomarkers
- Publish benefit-risk assessment in SSED. Rarity may alter benefit/risk.

**Table 2.** Example Considerations for Benefit-Risk Analysis

| Rare Disease/ Variant/ Required Tissue for Validation | Characteristic Qualifying as Rare |
|---|---|
| **NTRK** | • Prevalence of Variant (0.32% across solid cancers) |
| **ROS-1** | • Prevalence of Variant (1.0% of lung non-small cell lung cancer) |
| **TNBC after progression on primary therapy that metastasizes to the bone** | • Tissue type and availability |
| **Fine Needle Aspirate (FNA) in NSCLC** | • Paired biopsy and FNAs from the same patient needed for validation |

Source: Friends of Cancer Research, Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications, https://friendsofcancerresearch.org/wp-content/uploads/Dx_For_Rare_Biomarkers_White_Paper.pdf

# REGULATORY FLEXIBILITIES PROPOSED IN THE PAPER

## Analytical Validation

- For approved NGS panels, FDA should leverage pre-existing platform-level validation
- FDA should not require revalidation of variants in the same location or base pair
- FDA should not require validating a variant across all different types of cancers

## Clinical Validation

- FDA should rely on the proposed CDx's clinical performance (based on clinical outcome data) rather than on concordance studies to LDTs used for enrollment, which may have unknown/varying performance.
- FDA should consider whether bridging studies could be part of post-market commitments

## Other Regulatory Flexibilities

- Allow use of a prespecified modification plan for new indications
- Waive or shift into post-market certain studies (e.g., interfering substances, reproducibility, bridging studies).
- Allow for post-market collection of real-world evidence

**FDA should allow sponsors to provide some combination of the following to supplement clinical samples:**

- Contrived samples
- Similar tumor types/sample types
- Representative variant validation
- Prior data that demonstrate adequate analytical validity for their assay

Source: Friends of Cancer Research, Expedited Development of Diagnostics for Therapies Targeting Rare Biomarkers or Indications, https://friendsofcancerresearch.org/wp-content/uploads/Dx_For_Rare_Biomarkers_White_Paper.pdf

# OTHER SIMILAR ACTIVITIES

## Current Challenges in CDx Co-Development:

1. Evolution of Drug Development – rare mutations, biomarkers, speed
2. Use of Multiple CDx & Approved CDx
3. Biomarker-Driven Therapies Outside of Oncology

**Proposals Being Developed to Evolve the CDx Paradigm To Address These Challenges**

# EXAMPLE: REAL-TIME CDX REVIEW PILOT

**Apply for designation**

- Early data show drug promise
- High unmet need

**Designation granted**

- Based on established criteria, e.g.
- CDx needed
- Expedited drug

**Features**

- Earlier engagement
- Risk-based development
- Rolling review

# EX: LIMITED CLINICAL TRIAL ASSAY APPROVAL WITH CONTROLS

***Drug approval with PMC - limited testing available with controls in place***


- Complete AV required for assay type and based on risk/tiered approach

- Drug clinical study in which CTA is used
- In parallel, provide locked down CTA to lab(s) that will be identified in BLA/NDA filing
- Lab(s) conduct AV and generate data

- Dx sponsor submits M1, can add the AV data from the lab(s)
- CDRH can review AV data prior to drug launch

- Drug approved with post-market CDx commitment

- Identified labs can run the locked down CTA
- Periodic reporting from these sites could generate RWE
- Collect data on biomarker negative patients

- Conduct and include bridging studies
- Include RWE gathered by CTA use



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# SUMMARY

- **Co-development has evolved – rare biomarkers + accelerated programs are more frequent**
- **New CDx technologies available today may allow for regulatory flexibilities to more readily be applied**
- **Stakeholders should continue to work together and explore ideas for addressing challenges**

# QUESTIONS?