

White Paper

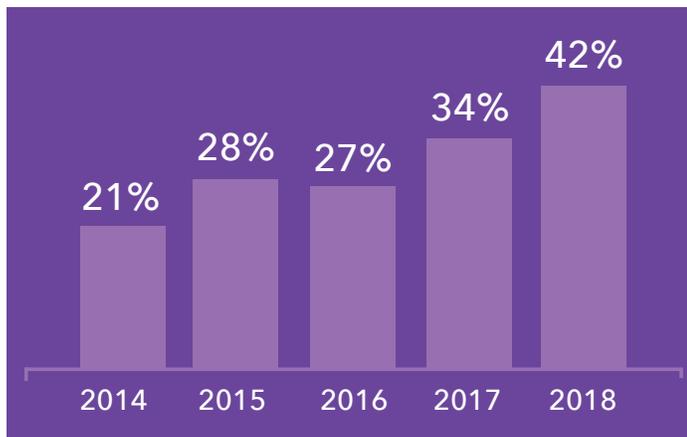
Commercial Considerations for a Successful CDx

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Emphasis on personalized and precision medicines is driving partnerships between pharmaceutical and diagnostic organizations to develop companion diagnostics, with the goal of accelerating clinical trials and regulatory approval.

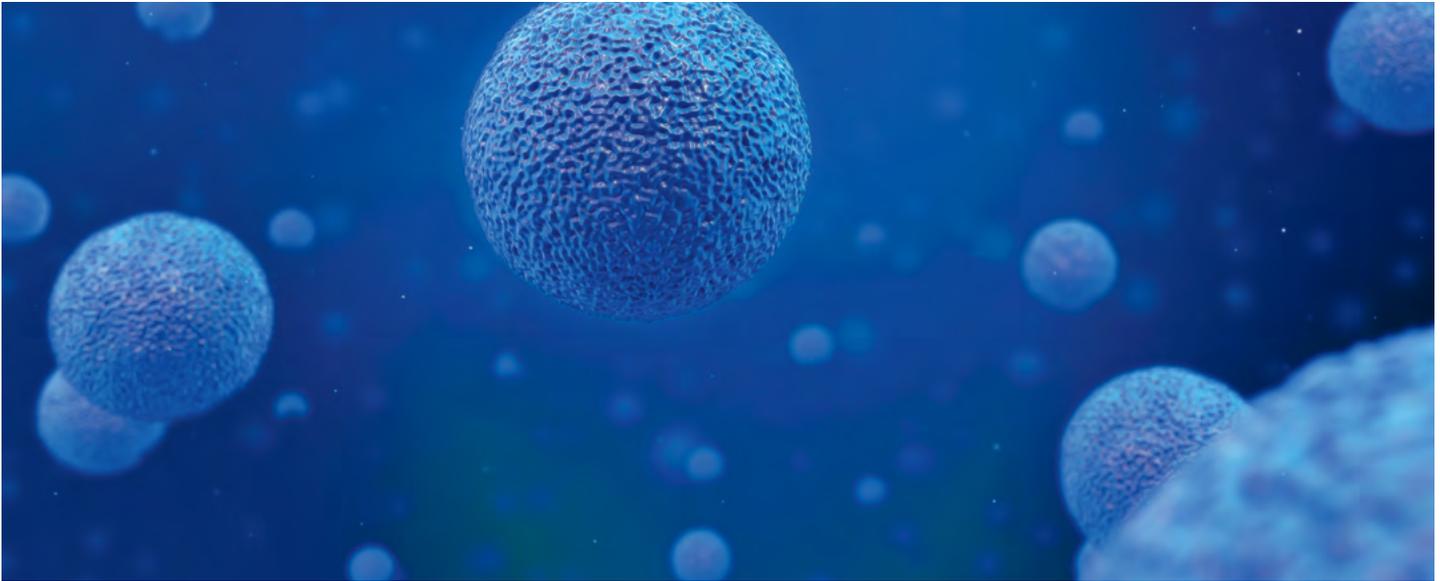


The Personalized Medicine Coalition reports that personalized medicines topped 42% of approvals in 2018, doubling from 21% in 2014.

NeoGenomics to date has participated in more than 60 companion diagnostic (CDx) projects, developing and deploying a diagnostic test to select and enroll patients in a clinical trial. These cover a broad range of technologies and platforms, including immunohistochemistry (IHC) (48), RNA in situ Hybridization (ISH) (3), Fluorescent in situ hybridization (FISH) (5), PCR (11), Next Generation Sequencing (NGS) (3), and Sanger sequencing (1). Of these projects, NeoGenomics has approximately 30 active programs, most of which are early stage projects using laboratory developed tests (LDTs) or repurposed in vitro diagnostic (IVD) kits for patient selection. NeoGenomics-supported pivotal studies to bring CDx to market include the Agilent PDL1 test for NSCLC, Thermo Fisher's Oncomine Dx Target Test, and Abbott's Vysis CLL FISH Probe Kit. Our position as the leading oncology reference laboratory in the United States, and our ability to support assay development from inception through commercialization, makes NeoGenomics an ideal partner for co-development of a CDx.

NeoGenomics is the largest oncology-focused laboratory in the United States, covering more than 650,000 patients and providing more than one million diagnostic tests in 2019. With more than 15 years of experience providing oncology testing, and the scientific and clinical expertise from more than 120 PhDs and MDs, our team has developed hundreds of diagnostic tests. Expertise includes not only the technologies described above, but also multiplex immunofluorescence, flow cytometry, and immunoassays. In addition to our commercial footprint within the USA, NeoGenomics has wholly-owned laboratories in Geneva (Switzerland), Singapore and China (opening 2020) to support global studies. Our breadth and depth of experience across geographic locations and technologies ensures that we can provide guidance and support from assay inception to companion diagnostic commercialization.

In this white paper we share our collective experiences, combined with opinions towards best practices, to give better insight into our approach to CDx development.



Choosing a Partner

The clinical trial market today is driven by Pharma/Biotech partnerships with contract research organizations (CRO) and specialized laboratories to provide R&D activities. Clinical laboratory testing with the exception of exploratory biomarker testing that can be done in-house, is generally outsourced to CROs with CLIA-certified (or global equivalent) laboratories. Companion diagnostic testing for patient selection and enrollment into a clinical trial must be performed in a licensed laboratory under the supervision of a medical director. In addition to the certified lab, partnership with an IVD manufacturer may be required, especially in the later phases of clinical development, in order to gain regulatory approval and commercial distribution of the CDx test. It is an advantage for Pharma/Biotech companies to partner with a laboratory organization that can support CDx development throughout the diagnostic life cycle in order to avoid delays associated with switching providers or bridging across technologies. NeoGenomics is uniquely positioned for CDx programs through our ability to support all phases of R&D development, clinical sample testing, IVD partnerships and finally US commercial launch.

Criteria for Partner Selection

- CLIA and CAP accredited
- Harmonized global laboratories with CDx-capable platforms
- Dedicated quality system with GCP and 21 CFR part 11 compliance
- Dedicated scientific and medical team for assay development and validation
- Regulatory support
- Project management and data management support
- Ability to support commercial launch after regulatory approval

Types of Partnership Required for CDx Development

- Global, CLIA contract laboratory to provide testing
- IVD manufacturers to provide commercialization and global distribution
- Commercial laboratory to provide test after FDA approval



Choosing a Platform

In our experience, most projects start when NeoGenomics is approached by clients with a biomarker that has been identified as a potential CDx. In these instances, a preliminary assay has been developed on a specific platform in an R&D laboratory or academic institution; alternatively, an assay on our clinical menu can be utilized. From there, NeoGenomics must optimize and analytically validate the assay sufficient for use in patient selection and enrollment in early phase clinical trials, often called a clinical trial assay (CTA).

Unfortunately there can be challenges with biomarker assays that are developed in early phase R&D or preclinical studies, as the assay may not be suited for use in clinical trials or eventual commercialization. This may be driven by the complexity of the assay (making global scalability and reproducibility difficult), and/or sample input requirements and/or the IVD platform (which may not be widely utilized in CLIA laboratories). The latter point is important since regulatory agencies have a strong preference for utilizing established platforms and technologies. A client developing a CDx with a new technology is likely to experience significant delays in the progress of the program and also assume the cost of establishing the platform in the partner labs supporting their clinical trials. In terms of established technologies, IHC, FISH, PCR, and NGS are well accepted. Flow cytometry is now gaining in popularity while multiplex immunofluorescence and mass spectrometry are not pervasive as CDx platform options. NeoGenomics' team of experienced scientific liaisons work with you to provide guidance on testing procedures and platform selection.

Using established IVD platforms permits easier access to manufacturers with extensive experience developing and deploying new diagnostics globally. NeoGenomics is platform agnostic and can support most CDx-capable technologies currently used in modern oncology practice. Our network of established relationships with large IVD manufacturers ensures successful commercial partnerships and long-term commercial support for your project.

Our Development Strategy (Early phase)

When initiating new programs, NeoGenomics presents three options for development, validation and deployment of a CDx, or a CDx-ready assay:

In all cases, the assays must be analytically validated to CTA grade before they can be used for patient selection in early-phase clinical trials. A brief overview for each of these three approaches is described below:

1. LDT: A laboratory developed test is developed and validated fit-for-purpose within NeoGenomics. This is the most popular option for most companies because of low cost and shorter development timelines relative to an IVD kit. NeoGenomics will select a platform and appropriate reagents that are required for CDx development, manufacturing, and eventual regulatory approval. Development timelines range from 4-8 months, depending on complexity and the availability of validation tissues, before an assay is validated and ready for use in clinical trials. Development time can be shorter for CLIA developed assays already on NeoGenomics' clinical menu, but rigorous validation with intended use samples is required in most instances before the LDT is CTA level.

2. Existing IVD Kit: An existing IVD kit is an ideal solution, if it exists, as it presents an optimized assay and an established pathway to regulatory approval and commercialization. IVD kits can be re-purposed for early phase clinical trials without permission from the manufacturer. However, re-purposing these assays for a new drug is considered off-label use by the FDA and will require a separate approval for each additional indication. Similar to the LDT, an existing IVD kit will require analytical validation with intended use samples with a development time of 4-6 months before it is considered CTA grade. Finally, the use of an existing IVD kit provides an added benefit of reducing market complexity (for example, multiple competing CDx tests for similar therapeutic classes of drugs such as BRAF or EGFR inhibitors). In recent FDA guidance, the Agency has signaled support for broader claims for CDx across specific groups of oncology therapeutics, rather than the one-drug-one-diagnostic approach first promulgated in their 2014 Guidance, recognizing that this approach increases complexity for ordering physicians.¹

CDx Options

1. Use of a laboratory developed test (LDT) — either an assay transfer, de novo assay development, or use of an existing LDT on NeoGenomics' menu
2. Repurpose an existing FDA-approved IVD kit
3. Partner with a medical device manufacturer to develop an IVD kit

3. Custom Manufactured IVD Kit: A collaboration with an IVD partner to develop and manufacture an IVD kit is not an often-pursued option for early phase development due to high costs and long lead times of 12-18 months or more. These types of partnerships are typically pursued later in development, when chances of approval are higher, and the costs of commercializing a CDx are de-risked. In cases where a new IVD kit is the only option, and the issues of cost and time are not limitations, the development and commercialization strategy will be greatly simplified in the later phase studies (2-3) when most pharma clients look to identify an IVD partner to cover final development and approval of their CDx test.

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-oncology-therapeutic>

Our Development Strategy (Late Stage)

Once a CTA-grade assay reaches Phase 2 or Phase 3 development, a crucial decision point regarding regulatory approval and commercialization must be addressed. If a pharma partner wishes to co-develop a companion diagnostic with their drug, an IVD partner must be chosen to manufacture the device and gain regulatory approval of the assay. Currently there are two options for the US market for regulatory approval.

1. The FDA-approved LDT

- Shorter development timelines
- Lower cost
- Limited to USA only; international test offerings need to be developed separately
- Well suited for:
 - Rare indications where one testing laboratory is appropriate
 - Requirement of a sample type or technology that is not widely distributed in the US clinical labs market
 - Time limitations, especially where the requirement for a CDx is discovered in Phase 3 development

2. The FDA-approved IVD kit

- IVD manufacturer can generally support global regulatory approval, distribution, and commercialization
- Longer development timelines
- Higher cost
- Well suited for large indications where multiple testing sites in the USA are required

Current Options for US Market Regulatory Approval

1. FDA-approved LDT (single-site PMA, 510(k) or HDE). This is an FDA-cleared or approved test that may only be offered at the laboratory where the assay was developed and validated
2. FDA-approved IVD Kit. This is an FDA-approved test developed and manufactured for distribution. It may be used by any licensed laboratory in the USA

The FDA-approved LDT option, in our experience, is growing in popularity and this is reflected by the growing number of such tests that have been approved (five through the end of 2019). The use of an FDA-approved LDT does not necessarily preclude support from a major IVD manufacturer. Supply agreements with manufacturers to provide GMP-grade reagents ensure that these types of tests are high quality and that long-term supply is guaranteed. Indeed, many IVD manufacturers may pass on commercialization of a test due to low market demand, but can provide long-term support in terms of platforms and reagent manufacture for an FDA-approved LDT.

Validation

A biomarker assay must be sufficiently validated before it can be used for patient selection and enrollment — an assay must be transitioned from research-grade to CTA-grade. There is no single approach to validating a CTA-grade assay or CDx grade assay, and the elements generally depend on the platform being used and whether the assay is qualitative or quantitative in nature. Validation methodologies, approaches and best practices can be found in FDA Guidance, CAP or CLIA guidelines, or industry groups such as the Clinical Laboratory Standards Institute. In our experience, a FDA summary of approval documents for approved CDx are useful for guidance on predicate devices. Allowance of sufficient time for pre-submission meetings with the Center for Devices and Radiological Health (CDRH) is the recommended approach.

While industry guidance is readily available, obtaining the required intended use specimens is often more challenging. Fit for purpose assay validation requires the use of samples separate from those obtained in the clinical trial (that is, test and validation data sets must be separate). Samples used for validation must be the same sample type and matrix (intended use) that will be tested in the clinical study. Contrived samples are generally not acceptable unless working with an ultra-rare indication. Since relevant clinical samples are critical for a successful validation and CDx submission, careful forethought and planning is recommended to collect and bank clinical samples from prospective trials in the event any bridging studies are required.

The validation of a CTA-grade assay should meet certain criteria established for CDx assessments, which will ultimately depend on the platform and use of the test. For instance, IHC pathology is generally not amenable to linearity or limit of detection measurements. Finally, in instances where an assay is already on a clinical test menu of a CRO laboratory provider, it is important to review the validation to ensure that all appropriate criteria were met. In our experience, a CLIA-validated LDT available at a diagnostic reference lab is rarely validated sufficiently for use to select and enroll patients in a clinical trial. If a biomarker is hypothesized to be predictive of patient response or safety, and the Phase 1a study will be used to verify this hypothesis, we strongly advise clients that the assay be well-validated for all appropriate criteria prior to the start of that initial study.

Validation Criteria (Early Phase Development)

- Accuracy — confirm the performance of the assay using an orthogonal methodology
- Sensitivity and Limit of Detection — Lower limit of detection, lower limit of quantitation and limit of blank
- Specificity
- Linearity
- Precision — repeatability of the assay across instrument runs, days, operators, and pathologist
- Stability

As clinical trial evaluation progresses favorably towards Phase III, further validation will be required to prepare the assay for potential submission to regulatory authorities. If a CDx is being developed with an IVD partner, the manufacturer will assume the responsibility for leading the validation activities. If NeoGenomics was partnered for the CDx development with an FDA-approved LDT test, our scientific team will perform all additional validation work.

Expanded Validation Requirements

- Expanded precision — repeatability of the assay including the above factors plus reagent lots, different laboratories, different pathologists, and other variables
- Interfering substances
- Pre-analytical variations
- Tumor heterogeneity
- Guard-banding
- Extended sample stability and reagent stability

Regulatory Management

In early phase development in the United States, for any assay that will be used for patient selection, or enrollment, a Risk Assessment must be performed by the CDRH or an Institutional Review Board (IRB). Those assays deemed to be Significant Risk (SR) require filing as an Investigational Device Exemption (IDE) with the FDA before the test can be used in clinical trials. Assays determined to be Non-Significant Risk (NSR) may be utilized under abbreviated IDE requirements, which allows testing to be performed without an IDE filing. In our experience, most CTAs are designated NSR in early phase development. We still encourage pharma clients to obtain guidance from the agency during the IND pre-submission process well before the IND submission is planned, as an unexpected NSR determination can add several months to development timelines.

Market approval or clearance of a CDx is one of the final stages for commercialization and should follow the appropriate regulatory path for the device that has been determined through development and validation. Within the United States:

- **Filing a Pre-Market Approval (PMA) or 510(k) with CDRH which applies to both IVD kits and single site PMAs. Beyond the analytical validation, the manufacturer must implement all Good Manufacturing Practices consistent with 21 CFR 820. The IVD manufacturer, or partner laboratory, assumes the responsibility for all of these activities.**
- **An alternative approval pathway is the Humanitarian Device Exemption (HDE) pathway. This regulatory pathway applies to diseases or conditions that affect not more than 8,000 patients on an annual basis in the United States. These devices are generally limited to rare diseases. Although providing a faster route for approval than a typical PMA, requiring only demonstration of safety and not efficacy, there are strict limitations placed on how the device may be used by clinicians.**

In general, we recommend frequent interactions with the Agency to obtain guidance and best practices for analytical and clinical validation of any assay intended for use as a CDx.



Commercial Timing

Ideally, a drug and the corresponding CDx are approved in parallel. However, if a CDx enrichment strategy is enlisted late in clinical development, this may not be possible due to the time required to develop a CDx-grade assay that is ready for regulatory approval, compounded with FDA review times, which can easily be 2 to 3 years in total. Rather than delay drug approval, CDx and drug approval can be decoupled with endorsement from the FDA. Companies may complete pivotal phase 3 trials with a CTA grade validated assay while completing final development of the CDx-grade assay in parallel. In this instance, the FDA grants conditional approval of the drug while the CDx goes through the final phase development. This approach was used for Pembrolizumab approval with MSI-H tumors and larotrectinib approval for NTRK-positive tumors. While the CDx development was progressing, the drug manufacturer relied on clinical laboratories in the USA to offer LDT versions of the assay. NeoGenomics can support this approach by ensuring availability of LDTs on our clinical menu while CDx development is done in parallel.

In our experience, an FDA-approved LDT is an excellent option if the requirement for a CDx is discovered late in development. This allows for a faster and less expensive bridge to get an FDA-approved CDx to market.

Commercial Strategy

Even after a FDA-approved CDx is developed, there is no guarantee of commercial success. If a new drug is to be successful, treating physicians need access to testing that is easy to order and delivers fast and interpretable results. Unfortunately, an assay that works well in clinical trials may not be readily adopted by US physicians or commercial laboratories. If the CDx is a FDA-approved LDT, only one laboratory in the US can offer the test. However, if the CDx is a distributable IVD kit, the pharma partner is relying on multiple commercial laboratories in the US to adopt and offer the assay. Depending on cost considerations as well as the scientific and technical complexities of the CDx assessment widespread adoption by clinical laboratories may be challenging, because the economics of clinical trial laboratory testing and clinical reference testing are very different.

CRO laboratories providing testing for clinical trials have different operational and financial structures from clinical reference laboratories that provide testing for physicians and hospitals. Within the context of clinical trials, contract laboratories price their services according to the cost incurred to provide specific testing as well as estimated value provided to the pharma client. In addition, if specialized services, such as placement of a dedicated instrument, decreased turnaround time, special sample handling procedures are required, the CRO laboratory can charge a premium for these services.

In the United States, reimbursement for clinical reference laboratories is tightly constrained when compared with CRO laboratories. Reimbursement is based on CPT coding, which is set by the Centers for Medicare and Medicaid Services (CMS). For the most part this coding does not provide premium reimbursement for CDx-grade tests, and no provision is made for any specialized services or instrumentation that may be required. Third party payers reference CPT coding when setting their reimbursement structures, and generally provide the same limitations. Some diagnostics may not be covered by payers even if approved by the FDA. For this reason, laboratories may elect to offer a copy of the CDx effectively as a validated fit-for-purpose LDT to capture the performance standard of the FDA-approved IVD kit. Alternatively, if the economics are adverse, commercial labs may decline to offer the test at all.

These considerations may determine the fate of the pharma company's CDx assay for adoption in the US market. The decision for a laboratory to offer an LDT versus a CDx is complex and multifactorial. At NeoGenomics we strive to offer the best possible testing to physicians and patients. However, support of all existing FDA-approved CDx is beyond our capabilities, even as the largest oncology reference laboratory in the USA.

Considerations for offering CDx vs LDT

- Does the test utilize general-purpose instrumentation in oncology reference laboratories? Or is the purchase of specialized equipment required?
- Is the sample type compatible with standard pathology practice? Or will samples require special handling?
- Low sample volumes and tight turnaround time requirements
- Does an existing CPT code cover the test or technology?
- Does CPT coding adequately cover the cost of running the CDx?
- Cost of the IVD kit versus general purpose reagents

NeoGenomics has extensive experience and expertise bringing new CDx and LDTs to the US market. We can provide clinical and scientific consultative services early on and throughout the development process to help ensure that a CDx project is well positioned for commercial success.

Commercial Launch

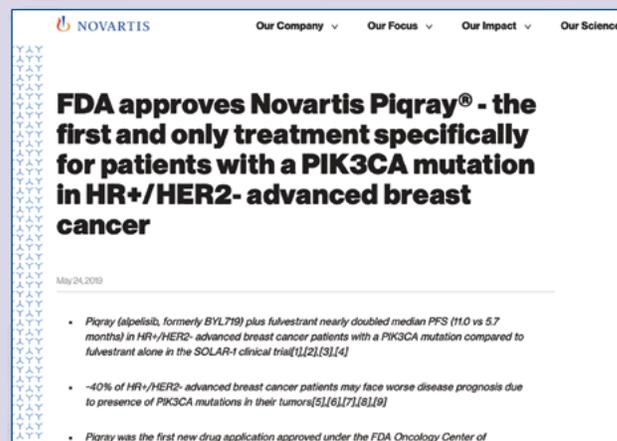
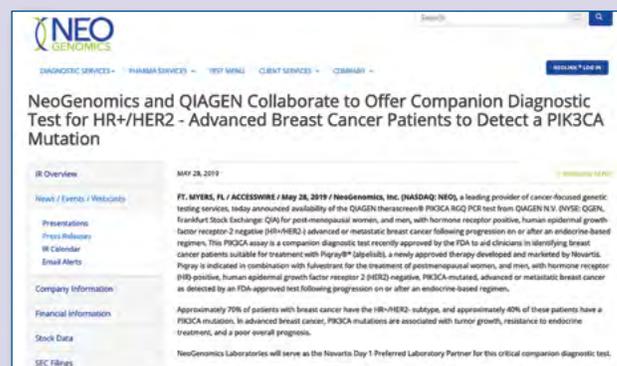
Any delay in the availability of a companion diagnostic assay can negatively affect the launch of a new drug or biologic. Following FDA approval, providers need ready access to the CDx so that the physicians have the information to determine the right therapeutic choice. Coordinating drug and CDx launch (Day One Launch) is difficult due to the fragmented testing market in the US but it is crucial for the commercial launch of any personalized medicine.

NeoGenomics can fully support Day One Launch in the United States. If NeoGenomics participates in the pivotal clinical trials as a central testing site for the associated CDx, we can readily support diagnostic launch following FDA approval. NeoGenomics ability to support and provide Day One Launch was illustrated in the Novartis Piqray® CDx program in which we were first to offer the theascreen PIK3CA RGQ PCR assay for HR+/HER2- breast cancer patients.

NeoGenomics has a broad footprint across the United States and a sales force of more than 100 individuals focusing on pathologists, oncologists, hospitals, and third-party payers. Our large size and established relationships with major IVD manufacturers additionally ensure that assays are properly placed in our laboratories to support CDx testing. In addition, we offer support for all aspects of patient management including diagnostic confirmation as well as molecular diagnostic and prognostic testing required as part of standard cancer care. We work closely with physicians to make companion diagnostic testing easily available.

NOVARTIS CDx Case Study - Piqray

NeoGenomics Becomes First to Launch PIK3CA CDx as Part of 'Day One' Program



Summary / Conclusions

Development of companion diagnostics has simultaneously made drug development faster, by increasing the likelihood that a drug will be approved, while simultaneously making drug development more complicated, by adding a parallel medical device approval. This white paper has covered our general approach to CDx development while illustrating potential pitfalls or limitations that must be considered throughout the course of clinical studies and FDA approval. Complexity necessitates an approach bespoke to the client, drug, and patient population. All of our CDx projects are unique in their own way, and our team of experts is here to provide guidance.

Additional Resources

Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-oncology-therapeutic>

List of Approved Companion Diagnostics

<https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools>

Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product (Draft Guidance)

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-codevelopment-vitro-companion-diagnostic-device-therapeutic-product>

In Vitro Companion Diagnostic Devices

<https://www.fda.gov/media/81309/download>

Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry.

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-vitro-diagnostics-oncology-trials-streamlined-submission-process-study-risk>

Bioanalytical Method Validation

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioanalytical-method-validation-guidance-industry>

FDA Guidance for HDE Programs

<https://www.fda.gov/media/74307/download>

Standards for Validation of CLIA and LDT assays

https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf; see also 42 CFR § 493.1253 - Standard: Establishment and verification of performance specifications.



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About NeoGenomics Pharma Services

NeoGenomics' Pharma Services unifies several innovative companies' scientific and medical leadership under one leading brand, offering one of the most comprehensive laboratory services menu available for biomarker testing supporting oncology clinical trials globally. We provide our clients with an unparalleled level of expertise, service, flexibility, and scalability. Additionally, we offer alternative business models and solutions across the continuum of development from pre-clinical research and development through commercialization.

To learn more about NeoGenomics Pharma Services visit us online at neogenomics.com/pharma-services, call us at 800.720.4363 or email us at pharmaservices@neogenomics.com.

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