White Paper

NeoGenomics minimal residual disease (MRD) testing

A diagnostic/prognostic clinical indicator as well as a biomarker/ endpoint in novel drug development

RED Consulting

Nicholas Jones and Dr. Josette William,
NeoGenomics

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Introduction

MRD refers to the presence of cancer cells that are below the threshold of detection when using conventional morphologic or radiologic methods. After treatment, patients who achieve complete remission (CR) according to morphologic/radiologic assessment alone may still have residual cancer cells in the bone marrow or peripheral blood.[1] MRD can be detected in a simple blood sample (liquid biopsy) by various methods with sensitivity thresholds of < 1 × 10−4 (< 0.01%) to < 1 x 10−6 (< 0.0001%). While there is no consensus on a precise definition of MRD positivity, a sensitivity threshold of at least 10−4 has been shown to accurately predict patient outcomes.[2,3]

Three decades ago, leukemia was almost universally fatal. Patients were treated for weeks rather than months or years (as they are in present-day therapy) that resulted in disease remission. However, nearly all patients relapsed in a short period of time after treatment had stopped, indicating that "minimal residual disease" can cause re-emergence of the cancer. Genetically identified leukemic cells at the time of relapse indicated they originated from those cells present in the primary disease.[4]

Acute lymphoblastic leukemia (ALL) was the first neoplasm where the assessment of early response to therapy by MRD monitoring has proven to be a fundamental tool to guide therapeutic choices. The most standardized methods to study MRD in ALL are multi-parametric flow cytometry (MFC) and polymerase chain reaction (PCR) amplification-based methods. Emerging technologies hold the promise to improve MRD detection in ALL patients. Moreover, novel therapies, such as monoclonal antibodies, bispecific T-cell engagers, and chimeric antigen receptor T cells (CAR-T) represent exciting advancements in the management of B-cell precursor (BCP)-ALL.[5]

The primary objective for the assessment of MRD is to detect the presence of "new" circulating tumor cells, or ctDNA that could potentially indicate recurrence of disease before it happens. Recent advancements in testing methods have led to an improved understanding of the impact of MRD negativity/positivity on patient prognosis and outcomes. Sustained MRD negativity in patients is indicative of complete treatment response and is reflected in overall patient survival. Patients that never achieve MRD negativity or patients that have re-emergence of MRD (loss of MRD negativity) have an incomplete response to therapy or are likely to relapse, respectively. Continuous treatment(s) of MRD-positive patients to achieve initial MRD negativity is warranted.[6] However, a major clinical question remains on when to start "relapse treatment" in patients that convert from negative to positive MRD status. There are indicators/biomarkers that can be used to predict patient relapse. In liquid tumors, such as CLL, MM, CML, or ALL, this can be done by detecting specific cell phenotypes in peripheral blood by flow cytometry. MRD biomarker detection[7] In solid tumors such as non-small cell lung cancer[8] and colorectal cancer[9], liquid biopsy (LBx) can be used to detect circulating cancer cells and/or ctDNA in the periphery.

Although MRD tests are highly quantitative, results are often reported as positive or negative. This quantitative measurement can be converted to a binary measurement (positive or negative) by identifying people as positive who have any residual cancer cells detected by the test or by setting a minimum threshold of residual disease to be detected, for example, >0.1% of cells with an abnormal immune phenotype or residual cells with a mutation variant allele frequency >0.001. Many statistical methods are proposed to identify the 'best' threshold for creating a binary but using thresholds instead of the quantitative measurement is often associated with reduced (at times, substantially reduced) predictive performance.[10]

In addition to its clinical relevance as a prognostic/diagnostic indicator, the incorporation of MRD testing in the development of novel cancer therapeutics is now being driven by relatively new guidance by the FDA.

"The US Food and Drug Administration (FDA) finalized guidance to help sponsors planning to use minimal residual disease (MRD) as a biomarker in clinical trials for treating specific hematologic malignancies."

"The guidance discusses technology that can detect the persistence of malignancy at, what FDA says are, "orders of magnitude below the limit of conventional morphologic detection," which has a threshold limit of one tumor cell in 100 cells. This level of disease burden is known as MRD, the guidance says.

"These technologies measure cell characteristics such as genetic mutations, cell surface markers, or specific DNA gene rearrangements. MRD as a general measure of tumor burden has multiple potential regulatory and clinical uses as a biomarker. Depending upon the clinical setting, MRD may be used to reflect a patient's response to treatment or as a prognostic tool to assess a patient's risk of future relapse. As such, MRD can be used to enrich clinical trial populations or guide allocation into specific treatment arms in clinical trials." [11]

With this guidance, it is almost certain that MRD will become a regulatory endpoint for drug approval. The important positive result from this is that potential life-saving drugs can progress through evaluation and to market more quickly. This will give patients greater access to additional and improved therapeutic treatments. The relevance of monitoring MRD "sequentially" in patients under treatment can provide insights into the dynamics with which patients can achieve MRD negativity regarding the number and intensity of treatments. The kinetics of MRD assessments may provide information that can be used in future therapeutic decision-making and address specific clinical questions as patients respond over time to the drug.[12] In addition, MRD status can be assessed prior to patient selection for a specific treatment protocol in a clinical trial, where it serves as a biomarker predictive of response.

NeoGenomics' experience and capabilities in MRD assessment

NeoGenomics has extensive experience and deep expertise in flow cytometry for assessing MRD status in patients with hematologic malignancies. In addition, in support of efforts in solid tumors, NeoGenomics has acquired Inivata for the wider utilization of its NGS-based, InVisionFirst®-Lung liquid biopsy test in the United States.[13] Inivata are in the advanced stages of completing analytical validation and in the process of meeting the requirements to satisfy clinical validation for their new tumor-informed RaDaR™ Assay for recurrence and minimal residual disease testing in solid tumors. RaDaR is anticipated to deliver an unparalleled level of sensitivity to this field through its 48-variant, tumor-informed personalized MRD detection capabilities.

Flow cytometry (FCM), polymerase chain reaction (PCR) and next-generation sequencing (NGS), are the three most common methods clinicians use to diagnose MRD in patients who have undergone chemotherapy, radiotherapy, or immunotherapy, by using phenotypic markers or differential gene patterns. MRD can be detected in bone marrow aspirates and/or in the circulation with a peripheral blood sample.

MRD serves as an important prognostic marker for clinicians to evaluate response to treatment, predict the likelihood of relapse, and identify if a patient is in a steady state of remission, or progressing toward diseases relapse. The appropriate MRD assessment depends on the type of cancer and the sensitivity required to make the most accurate determination.

The sensitivity of a test dictates its effectiveness at detecting MRD, and the primary outcome is the MRD cellular level. The cutoff level is 0.001% MRD cells (10—5), or 1 MRD cell per 100,000 cells. Measurements above this indicate a higher risk of relapse compared with results below 0.01%, and as the numbers rise above 1%, the risk of disease relapse increases and the chances of survival become less.

Three most common methods of MRD diagnosis

1

Flow cytometry (FCM)

A rapid and quantitative method of identifying cancer cells, with a peak sensitivity of 0.01%—0.001%, 1 cancer cell in 10,000 or 100,000 normal cells, respectively. Multi-parametric (8-color or more) flow cytometry assays are the most used to detect abnormal MRD immunophenotypes. Adequate sensitivity for MRD quantification requires special calibration and assessment of a large number of cells and may not be available from some labs. A fresh sample must be used for flow cytometry; however, a baseline sample is not necessary.

2

Polymerase chain reaction (PCR)

PCR is a well-established method in which a specific section of DNA from cancer cells is replicated and amplified. It has a peak sensitivity of 0.001%, or 1 cancer cell in 100,000 normal cells. Real-time quantitative polymerase chain reaction (real-time qPCR) assays detect fusion genes (e.g. BCR-ABL1).[1] A baseline sample or prior sample obtained at diagnosis with a detectable level of the disease is required to characterize leukemic clones for MRD analysis. NPM1 MRD is another example of MRD detection in AML patients.

3

Next-generation sequencing (NGS)

NGS is an extremely sensitive DNA sequencing method, with a peak sensitivity of 0.0001%, or 1 cancer cell in 1,000,000 normal cells. NGS assays detect clonal rearrangements in immunoglobulin and/or T cell receptor genes. There is an FDA-approved NGS assay to quantify immunoreceptor genes in patients with ALL. A baseline sample or prior sample obtained at diagnosis with disease detectable is required to characterize leukemic clones for MRD analysis. Examples of MRD assessments by NGS currently offered by NeoGenomics include:

- mIgH clonality in CLL, ALL, and lymphoma patients.
- NGS lymphoid Panel for lymphoma patients.
- NGS Myeloid Panel for AML patients (in validation).

The availability of all three MRD testing modalities is important because, in many cases, they are used in combination to provide a complete interpretation of patient status. In this communication, the focus will be on MRD assessments by flow cytometry and how they can be used as a prognostic/diagnostic indicator as well as a biomarker endpoint. Since there are no FDA-approved flow cytometric MRD tests, they are all considered laboratory-developed tests (LDTs). Numerous labs in the US labs perform MRD by flow cytometry, and agencies such as the International Myeloma Working Group have encouraged researchers and clinicians to use an identical methodology to lend way for cross-laboratory consistency in interpretation. All flow cytometry MRD assessments do not have the same analytical performance, which is reflected in the CAP-accreditation of the laboratories. There is no proficiency testing for MRD by flow cytometry in the U.S., and guidance on recommended approaches and interpretation tools are needed for data comparison among laboratories.[14]

Flow cytometry MRD testing offers comparable sensitivity to PCR and is nearly universally accepted for MRD detection requiring the presence of deviation from a normal pattern of lymphoid maturation or specific leukemia phenotypes. The laboratories that offer MRD assessments by flow cytometry require significant technical expertise from both the laboratory staff and interpreting pathologist in order to avoid erroneous results and provide consistency in the data. To achieve the sensitivity level of at least 1 leukemic blast in 10,000 cells, acquiring at least 500,000 cells is necessary. Acquisition of this many cells allows for confident identification of clusters of at least fifty events at the lowest sensitivity threshold. It should be noted that a cluster containing as few as ten events with a clearly aberrant immunophenotype may be sufficient for confident identification. Identification of such small cell clusters requires a validated assay with low background, and high clinical expertise in hematopathology. Various factors, including non-specific antibody binding, improperly titered antibodies, inclusion of irrelevant events in blast analysis, and instrument maintenance and integrity can compromise the assay performance, and impact specificity and sensitivity.

NeoGenomics has an established reputation in clinical oncology with extensive experience and expertise in hematopathology that supports flow cytometry MRD testing in both the clinical services and Pharma services divisions for diagnostic/prognostic evaluation and novel therapeutic development in hematologic malignancies, respectively. Dr. Josette William Ragheb, MD PhD, Global Medical Director Pharma Division, Hematopathologist, with >30 years of experience, is a member of the Medical and Scientific team and provides expertise for Diagnostics services as well as support for Pharma services requiring clinical interpretation of flow cytometry assessments. Nicholas Jones, Director of Global Flow Cytometry, Pharma Services has 20 years of experience developing/validating, and implementing cytometry assays into clinical trials, with major emphasis in novel oncology therapeutics. To maintain consistency across clinical and Pharma services, results from these MRD flow tests are analyzed, with interpretation, by the same clinical hematopathologist that performs diagnostic/prognostic evaluations.

Clinical value of flow cytometry MRD testing

The objectives of treating cancer patients are to reduce/minimize the tumor burden and then hopefully go further and obtain a complete therapeutic response, resulting in total eradication or remission of the disease. However, post-treatment, if there are remaining (residual) cancer cells in the body, they can become active, proliferate and relapse the disease in patients. MRD detection is an indication that the treatment was not completely effective or that the treatment was incomplete and needs to continue longer. MRD may also be an indication that all cancer cells did not respond to the given therapy or that malignant cells became resistant to the anti-cancer therapies used. When a treated patient tests MRD negative (absence of residual cancer cells), this outcome is predictive of long remission periods and prolonged survival rates. MRD testing provides great clinical value by acting as a gauge to direct cancer treatments and to provide better patient care.

Unlike solid tumors, blood cancers such as multiple myeloma (MM), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) can be monitored by measuring the presence and frequency of cancerous cells in the peripheral blood or bone marrow. Well established MRD flow cytometry panels have been used universally and extensively to detect and measure the presence of malignant cells at low frequency. The expression of several cell surface markers can easily be used as criteria to discriminate neoplastic cells from normal cells. In addition, the expression level of "neoplastic" markers could be used to identify phenotypes associated with certain patient outcomes. Because of advantages such as high applicability, rapid turn-around time, intrinsic quality control, no need for baseline sample and cost-effectiveness, flow MRD data has been used prognostically for guiding treatment decisions in pediatric and adult leukemia patients as well as assigning patients into different MRD-based risk groups.[15] For our clinical service, there are several well-established MRD flow panels that have been used extensively by NeoGenomics to assist physicians and hospitals in diagnosis and treatment of cancer patients with hematologic malignancies. We are on track to perform over 19,000 MRD assessments from liquid biopsies in 2021. NeoGenomics' experienced hematopathology team analyzes all data and provides patient-specific interpretations. The following are descriptions and requirements for the MM and CLL panels, which are used to determine patient MRD status.

MM and CLL panels used to determine patient MRD status

Multiple Myeloma (MM) MRD panel

- **Panel composition:**
  - CD45
  - CD19
  - CD20
  - CD27
  - CD38
  - CD45
  - CD56
  - CD81
  - CD117
  - CD138
  - cKappa
  - cLambda
- This MM MRD panel has been shown to detect MRD in patients with previously diagnosed and treated multiple myeloma. The limit of detection is 0.001%.
- A 3–4 mL EDTA bone marrow aspirate specimen is required for this assessment. Sodium heparin is acceptable but not Lithium heparin or ACD.

Chronic Lymphocytic Leukemia (CLL) MRD Panel)

- **Panel composition:**
  - CD45
  - CD3
  - CD5
  - CD19
  - CD20
  - CD22 (or ROR1)
  - CD43
  - CD79b
  - CD81
- This CLL MRD panel follows the strategy developed by the European Research Initiative in CLL (ERIC) and can detect MRD at the 0.01% level. This evaluation has become increasingly important as specific CLL treatments improve. Detection of MRD above 0.01% is reported to be an independent predictor of progression-free survival and overall survival in CLL patients treated with chemoimmunotherapy. This panel may also be used to determine ROR1 expression on leukemic cells for treatment purposes if the ROR1 marker is included. The prognostic value of achieving MRD-negative status with other CLL therapies is under investigation in clinical trials.
- A 2–3 mL EDTA bone marrow, or 5–6 mL EDTA peripheral blood sample are required for this assessment. Sodium heparin is acceptable for both sample types, whilst Lithium heparin or ACD are not acceptable.

B-Cell/B-precursor Acute Lymphoblastic Leukemia (B-ALL) MRD Panel

- **Panel composition:**
  - CD45
  - CD3
  - CD9
  - CD10
  - CD19
  - CD20
  - CD34
  - CD38
  - CD58
  - CD13/CD33
  - CD71
  - Syto16
- This B-ALL MRD panel follows the strategy developed by the Children's Oncology Group (COG) and can detect MRD at the 0.01% level. The B-ALL MRD is highly predictive of relapse in patients treated for acute lymphoblastic leukemia
- A 2–3 mL EDTA bone marrow, or 5–6 mL EDTA peripheral blood sample are required for this assessment. Sodium heparin is acceptable for both sample types, while Lithium heparin or ACD are not acceptable.

These MRD flow panels are useful clinically for screening patients as well as longitudinal assessments for MRD, iCR (incomplete response), and CR (complete response) to therapy in conjunction with other test modalities, including morphological assessment and molecular tests. Flow MRD assessments are used similarly in clinical trials to monitor sequentially disease status in patients receiving experimental therapy. Representative flow data exhibiting patient MRD level at screening, as well as from subsequent flow testing showing MRD levels at >0.01%–5% (iCR) and <0.01% (near CR), are illustrated in the following section.

Value of flow cytometry MRD assessment as a surrogate biomarker or endpoint in clinical trials

Minimal residual disease testing is a way of testing how much disease is left after therapy. MRD testing is now being used more often in the clinic to gauge how well a treatment worked, and researchers are hopeful that MRD testing will help clinical trials move along faster. If MRD testing can be used as a new clinical trials "endpoint," then clinical trials can be performed to gain new insights. As MRD testing becomes more popular, the data could show when a patient may want to stop or continue treatment. It is difficult to say that it can predict how a patient will do after therapy is stopped. Being MRD negative is better than being MRD positive, as MRD negative patients typically live longer. There is some doubt if there will be a relationship between MRD negative and overall survival. Clinical trials will be key to understanding how to use MRD testing in a predictive way.[16]

MRD can potentially be used as a clinical and regulatory endpoint to evaluate a drug's effect both on a patient's future relapse risk and subsequent treatment survival outcomes. There has been a pressing need to update regulatory science to include the use of MRD as a surrogate endpoint for early drug approvals. The issuance of the draft guidance by FDA and EMA further highlights the importance of the potential use of MRD as a surrogate endpoint for early licensure/approval, especially in the frontline of hematologic malignancies. This would not only stimulate new drug development in this therapeutic area but would also bring potentially efficacious drugs quicker to patients with debilitating diseases.

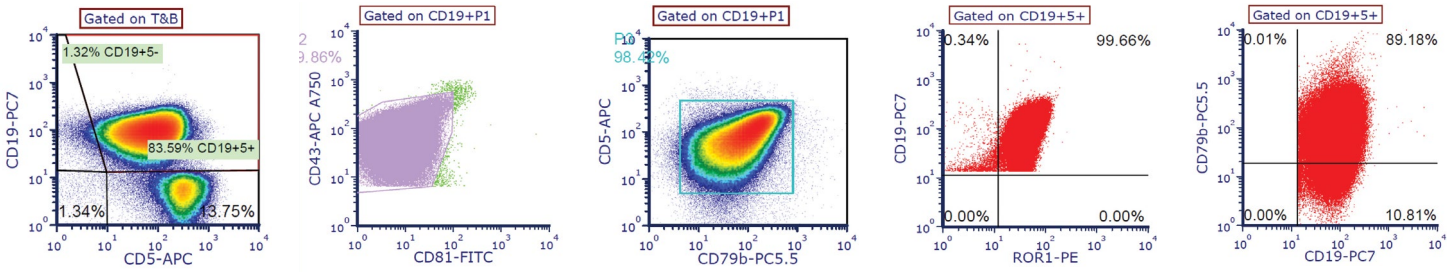
Many clinical risk classifications may not be able to accurately predict relapse in patients with hematologic malignancies, which may result in inappropriate use or timing of treatments. To improve risk classification, MRD has been regarded as an important prognostic factor for predicting disease recurrence. The sponsor can use MRD level to serve as a stratification factor, select patients at high risk, or enrich the trial population.

The term biomarker is commonly understood as referring to a characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Within this definition, MRD can be used and regarded as a potential biomarker. The terminology listed below is derived from the BEST Resource definitions and the guidance for industry and FDA staff Qualification Process for Drug Development Tools, but slightly modified to reflect applicability to MRD. Sponsors can potentially use MRD status as any of the following types of biomarkers:[17]

- **Diagnostic biomarker:** a biomarker used to detect or confirm the presence of a disease or conditions of interest or to identify individuals with a subtype of the disease.
- **Prognostic biomarker:** a biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. A prognostic biomarker informs about the natural history of the disease in that particular patient in the absence of a therapeutic intervention.
- **Predictive biomarker:** a biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a drug product.
- **Efficacy-response biomarker:** a biomarker that is used to show that a response has occurred in an individual who has been exposed to a drug product.
- **Monitoring biomarker:** a biomarker measured serially and used to detect a change in the degree or extent of the disease.

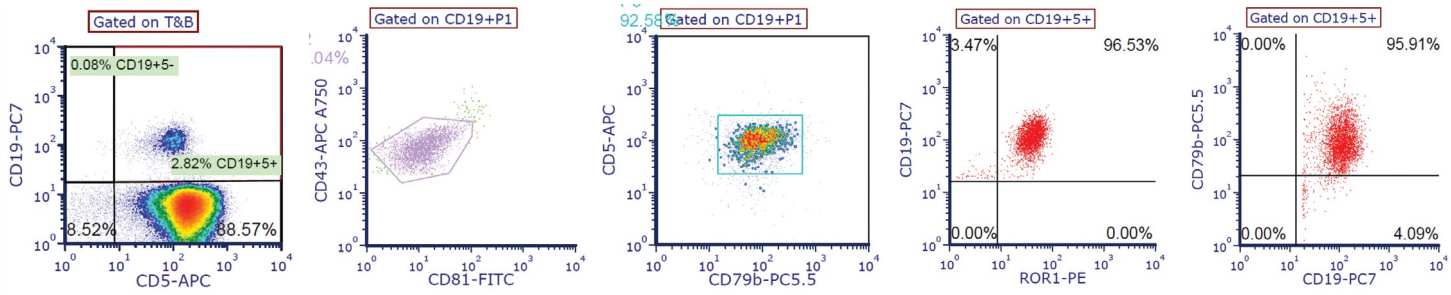
NeoGenomics Pharma Services has provided flow cytometry MRD expertise to multiple sponsors conducting clinical trials to evaluate the effectiveness of novel cancer therapy. The following examples show representative flow cytometric data illustrating sequential patient analysis, using CLL modified ERIC MRD assessment, during experimental therapeutic intervention.

Figure 1: Time point 1 (baseline)



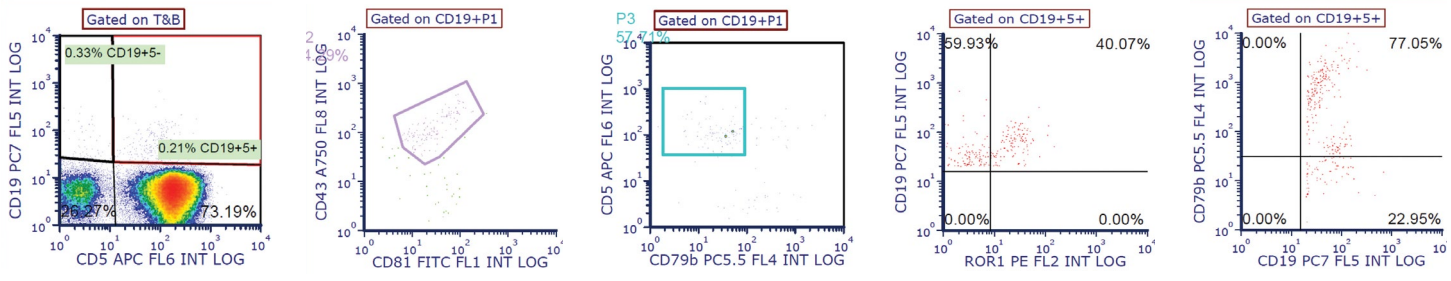
Subpop	count	% of CD45+ lymphs	% of total nucleated cells
CLL-MRD	556931	75.02	56.93

Figure 2: Time point 2 (6 months)



Subpop	count	% of CD45+ lymphs	% of total nucleated cells
CLL-MRD	2605	1.99	0.27

Figure 3: Time point 3 (follow-up, 18 months)



Subpop	count	% of CD45+ lymphs	% of total nucleated cells
CLL-MRD	53	0.04	<0.01

Patient A: Sequential MRD Assessment CLL Modified ERIC	
Time point	**% MRD**
Baseline	56.93
~6 months	0.27
~18 months	<0.01

Table 1: MRD levels detected in sequential monitoring of CLL patients during therapeutic intervention.

The flow results shown in **Figures 1**, **2** and **3** illustrate the value of MRD monitoring for CD45/CD5/CD79b positive cells during experimental drug therapy, and the data provides a precise indication of therapeutic efficacy over the course of treatment. Sequential testing of peripheral blood samples over time (**Table 1**) indicates that % MRD levels fell dramatically from baseline (56.93) to iCR at 6 months (0.27), and CR at around 18 months (<0.01). Clearly this is an example of how MRD can serve as the primary "biomarker" to evaluate a patient's response to novel drug therapy in clinical trials. In addition, these data can be used to determine treatment processes, such as timing and dosage, as well as the use of MRD to identify responder and non-responder patient populations.

Conclusion

The evolution of regulatory science to allow innovative approaches, such as MRD, to the development of new therapeutic treatments for hematologic malignancies could expedite approval of drugs that could potentially improve patient outcomes. Incorporation of MRD into clinical trial evaluation protocols in which sequential analysis can be performed may determine the efficacy of novel investigational drugs earlier by acting as a surrogate biomarker of patient outcome and endpoint in clinical trials, compared with current traditional approaches. Since MRD measures tumor burden at levels that are undetectable through conventional lab techniques it can also potentially act as a clinical and regulatory endpoint, which supports its use in future clinical trials as well as for clinical decision making.

Ongoing and future clinical trials will continue to evaluate the definition and the role of MRD in treatment decision-making. On the one hand, the achievement of an MRD-negative status does not necessarily mean that treatment should be stopped, or that a new therapy can cure the disease. With the limitations of all MRD testing, it means that we can't be sure that the disease is eradicated even in MRD-negative cases. On the other hand, an MRD-positive status after treatment brings into question whether it is necessary to change treatment or dosage, improving the depth of response. However, before developing response-adjusted treatment strategies based on MRD status, either intensifying or changing treatment for MRD-positive patients or de-escalating treatment for MRD-negative patients, we need to determine if sustained MRD negativity should be viewed as the goal of any treatment.[18] Continued use of MRD as a biomarker in clinical trials will provide information that will help define the most appropriate time point for its evaluation as a clinical endpoint.

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 menus 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 development continuum, from pre-clinical research and development through commercialization.

To learn more about NeoGenomics Pharma Services, visit us online at neogenomics.com/pharma-services.

NeoGenomics Pharma Services is your premier research partner with NGS and other innovative services. Please contact NeoGenomics Pharma Services at 800.720.4363 or email at pharmaservices@neogenomics.com.

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12701 Commonwealth Dr., Suite 9
Fort Myers, FL 33913
United States
Phone: 866.776.5907
Fax: 239.690.4237

31 Columbia
Aliso Viejo, CA 92656
United States
Phone: 800.720.4363
Fax: 949.425.5865

7256 S. Sam Houston Pkwy W. Suite 300
Houston, TX 77085
United States
Phone: 800.720.4363 / 713.528.4363
Fax: 713.668.3565

NeoGenomics Laboratories, Inc.
4570 Executive Drive, Suite 250
San Diego, CA 92121
Phone: 949.445.7300 5056
Fax: 713.668.3565

A-One Business Center
Bâtiment A5, 2nd Floor
Z.A. La Pièce / Route de l'Etraz 1
1180 Rolle, Switzerland
Phone: +41 (0)21 721 06 00
Fax: +41 (0)21 826 00 73

NeoGenomics Singapore Pte Ltd
61 Science Park Road, #02-11,
Singapore 117525
Phone: +65 6591 5200

Suzhou NeoGenomics Pharmaceutical Research Co., Ltd Building 6, Block 19, Yong'An Road Huguan Industrial Park, Suzhou New District, China

neogenomics.com