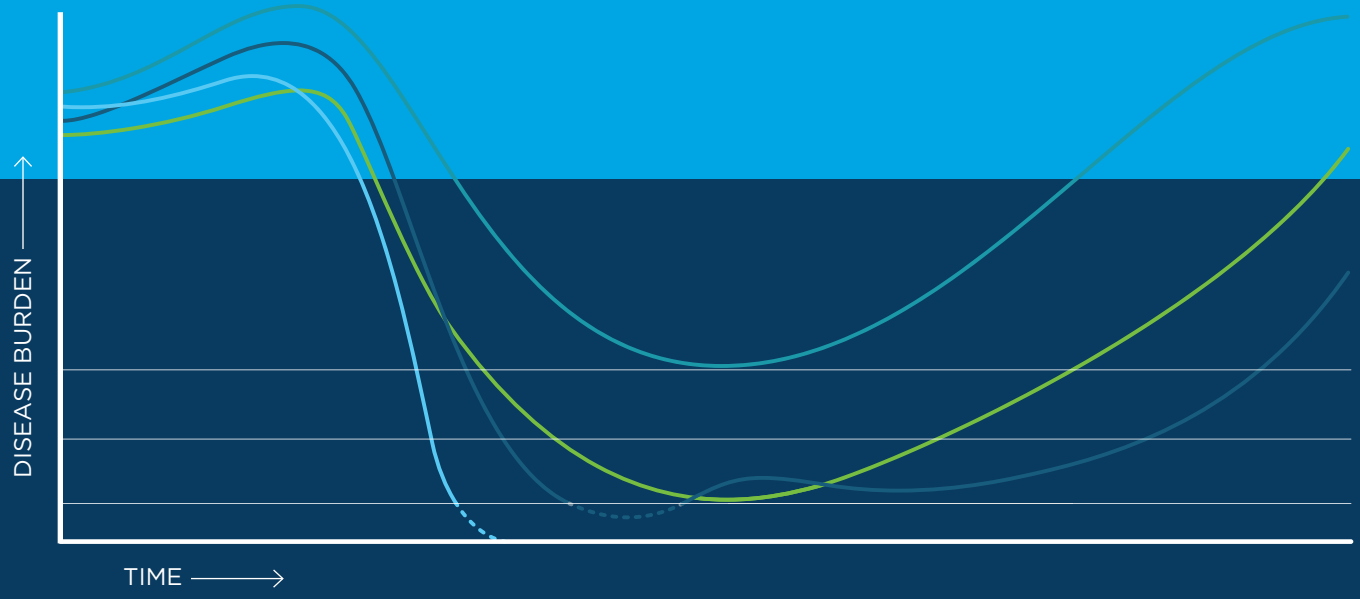
FOR HEALTHCARE PROVIDERS

clonoSEQ®

UNDERSTANDING THE CLONOSEQ ASSAY

Clonality (ID) and Tracking (MRD) Reports



clonoSEQ is available as an FDA-cleared *in vitro* diagnostic (IVD) test service provided by Adaptive Biotechnologies to detect measurable residual disease (MRD) in bone marrow from patients with multiple myeloma or B-cell acute lymphoblastic leukemia (B-ALL) and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL). clonoSEQ is also available for use in other lymphoid cancers as a CLIA-validated laboratory developed test (LDT) service.

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CLONALITY (ID) REPORT:

The Clonality (ID) Test is used to identify dominant DNA sequence(s) in a high disease load diagnostic sample. Identification of at least one dominant DNA sequence is a prerequisite to future monitoring of MRD.

After the dominant DNA sequence(s) has been identified utilizing the Clonality (ID) Test, subsequent monitoring of the associated clone(s) can be completed by ordering Tracking (MRD) Tests.

clonoSEQ is only available by prescription from a licensed healthcare professional. clonoSEQ results should always be used in combination with clinical examination, patient medical history, and other findings. Results may vary based on sample type, body site/location sampled, and other factors. False positive or false negative results may occur for reasons including, but not limited to: contamination, technical, and/or biological factors.

B-CELL CLONALITY (ID) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	03/14/2019	03/16/2019	SP-597516

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

ASSAY DESCRIPTION

The clonoSEQ® Assay is an *in vitro* diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL).

CLONALITY RESULT

1 Dominant Sequence Identified
Suitable for clone tracking (e.g. MRD determination)

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- There was 1 sequence that met the criteria for a "dominant" sequence.
- This dominant sequence has been tagged for tracking in other samples from this patient.
- Based on the dominant sequences identified for this patient, the assay's analytical limit for subsequent MRD detection is 1.903 clonal cells per sample, subject to sample quality and quantity.
- ► **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

CRITERIA FOR DEFINING "DOMINANT" SEQUENCES

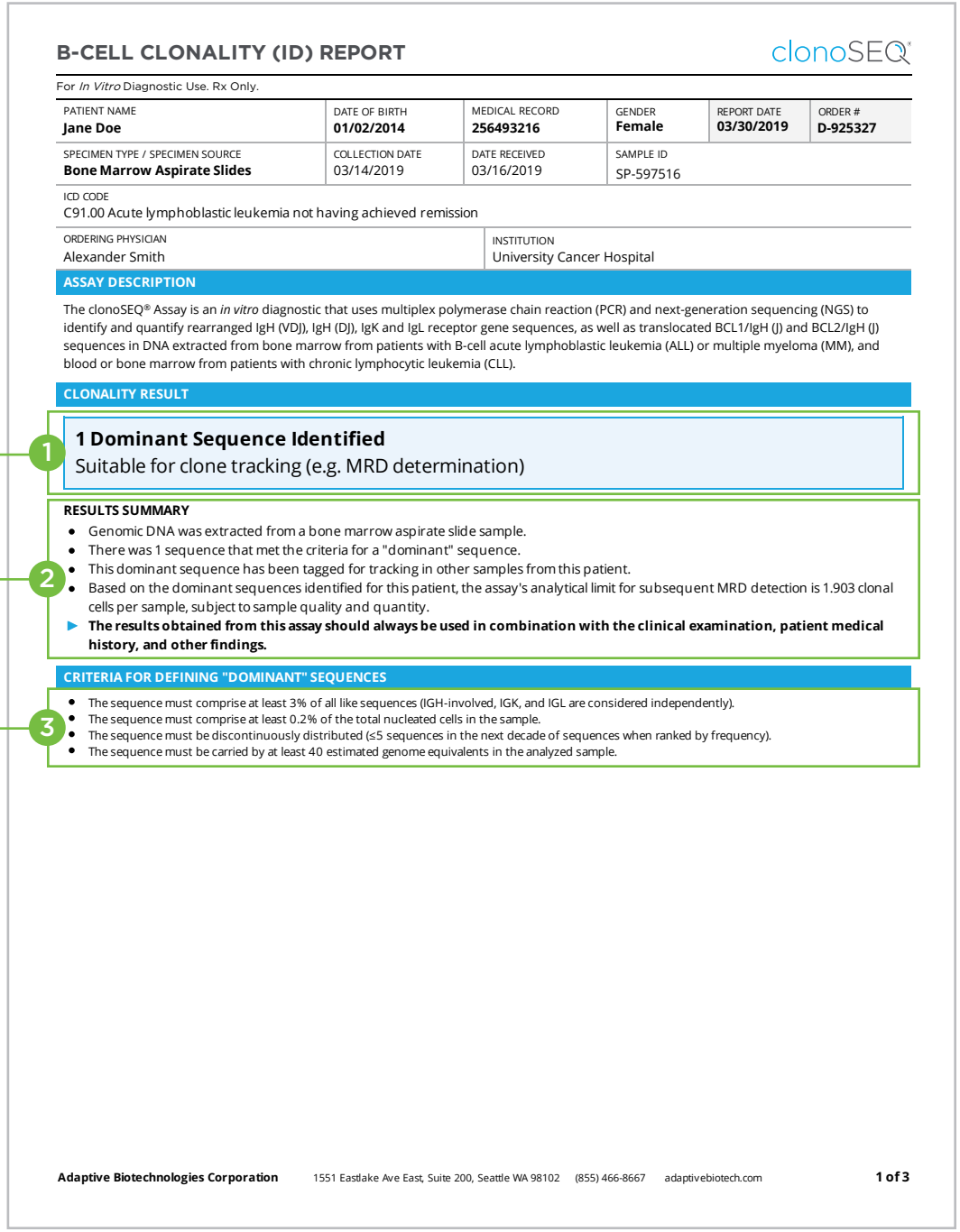
- The sequence must comprise at least 3% of all like sequences (IGH-involved, IGK, and IGL are considered independently).
- The sequence must comprise at least 0.2% of the total nucleated cells in the sample.
- The sequence must be discontinuously distributed (≤5 sequences in the next decade of sequences when ranked by frequency).
- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

Clonality (ID) Report with Dominant Sequences Identified

This is an example B-cell Clonality (ID) Report. The clonoSEQ B-cell Clonality (ID) Report provides results based on analysis of the IgH, IgK and IgL loci as well as Bcl1 and Bcl2 translocations.

Page 1 of the report shows that dominant DNA sequences were identified from the submitted sample (1). A more detailed description of the results for this sample can be found in the "Results Summary" section (2). Additional observations provided by a licensed medical professional relating to the report result may be included in an "Additional Comments" section (not pictured). A summary of the criteria used to determine which DNA sequences are dominant and thus can be followed as markers of malignancy is provided at the bottom of the page for reference (3).

Page 1



B-CELL CLONALITY (ID) REPORT

clonoSEQ®

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PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
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ICD CODE
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ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

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CLONALITY RESULT

Result → 1

1 Dominant Sequence Identified
Suitable for clone tracking (e.g. MRD determination)

RESULTS SUMMARY

Additional result information → 2

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- There was 1 sequence that met the criteria for a "dominant" sequence.
- This dominant sequence has been tagged for tracking in other samples from this patient.
- Based on the dominant sequences identified for this patient, the assay's analytical limit for subsequent MRD detection is 1.903 clonal cells per sample, subject to sample quality and quantity.
- ► **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

CRITERIA FOR DEFINING "DOMINANT" SEQUENCES

Criteria for defining a dominant sequence → 3

- The sequence must comprise at least 3% of all like sequences (IGH-involved, IGK, and IGL are considered independently).
- The sequence must comprise at least 0.2% of the total nucleated cells in the sample.
- The sequence must be discontinuously distributed (≤5 sequences in the next decade of sequences when ranked by frequency).
- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

Clonality (ID) Report with Dominant Sequences Identified (continued)

Page 2 of the report shows detailed information relating to the sample (4) including the actual rearranged DNA nucleotide sequence or sequences identified, the sample collection date, the receptor locus in which each dominant sequence was found, the specimen type analyzed, the frequency of the dominant sequence as a fraction of the total nucleated cells assessed, and the total number of cells carrying the rearranged DNA sequence.

Page 2

B-CELL CLONALITY (ID) REPORT

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Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	03/14/2019	03/16/2019	SP-597516

IDENTIFIED DOMINANT SEQUENCE(S)

IGK - Sequence A

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGCGGCCTTCGACAGTTCCTACGTCGTACTACTCCCACATGGACGTCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	FREQUENCY PER TOTAL NUCLEATED CELLS	TOTAL CELLS CONTAINING SEQUENCE
● 03/14/2019	SP-597516	Bone Marrow Aspirate Slides	**84.594%**	**75,810**

● Results for report sample

Specific DNA sequences identified

4

ASSAY METHODS AND LIMITATIONS

METHOD

The clonoSEQ Assay utilizes NGS to determine the level of remaining presumptive disease-associated cells in patients with previously diagnosed lymphoid malignancies: The patient-specific sequence(s) carried by the presumed transformed clone is first identified in a diagnostic sample using a set of multiplexed, locus-specific primer sets for the immunoglobulin heavy-chain locus (IGH), including both complete (IGH-VDJ) and incomplete (IGH-DJ) rearrangements, the immunoglobulin κ locus (IGK), the immunoglobulin λ locus (IGL) and IGH-BCL1/2 translocations. The assay is then applied in one or more follow-up samples to detect the level of the patient-specific sequence(s) corresponding to the prevalence of the sequence carrying clone.

ASSAY LIMITATIONS

False positive or false negative results may occur for reasons including, but not limited to: sample mix up, misidentification, and/or contamination; technical and/or biological factors. Results may vary by sample type or body site/location sampled. The assay may overestimate MRD frequencies near the limit of detection.

Clonality (ID) Report with Dominant Sequences Identified (continued)

Page 3 of the report provides more details on the immune repertoire of the analyzed sample, including the sample clonality, the number of sequences assessed for each locus, and the number of unique sequences assessed (5).

Details on immune repertoire of analyzed sample

Page 3

B-CELL CLONALITY (ID) REPORT

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For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	03/14/2019	03/16/2019	SP-597516

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

SAMPLE CLONALITY [1]	TOTAL NUCLEATED CELLS [2]
0.85	89,617

LOCI	TOTAL SEQUENCES [3]	TOTAL UNIQUE SEQUENCES [4]
IGH	76,872	1,007
IGK	5,856	5,362
IGL	>=2,610	2,610

[1] Sample Clonality	A measure of the lymphocyte population diversity (distinct lymphocyte clonal sub-populations or "clones") comprising the immune repertoire in a given biological sample. Values for clonality vary from 0 to 1. Values close to 1 represent samples with one or a few predominant clones. Values near zero represent a more polyclonal sample.
[2] Total Nucleated Cells	The total number of nucleated cells calculated within the sample, based on quantitation of non-immune receptor loci contained in the reaction and the assumption that the DNA content per cell is diploid.
[3] Total Sequences	A measure of the number of nucleotide sequences detected in the sample for each defined immune receptor locus.
[4] Total Unique Sequences	A measure of the number of unique nucleotide sequences detected in the sample for each defined immune receptor locus.
Limit of Detection (LOD)	The lowest level of residual tracked sequence(s) that can be reliably detected by the clonoSEQ Assay in ≥95% of samples tested. LOD is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.

REFERENCES

- Carlson CS, et al. Nat Commun. 2013;4:2680.
- Faham M, et al. Blood. 2012;120(26):5173-80.
- Logan AC, et al. Leukemia. 2013;27(8):1659-65.
- Martinez-Lopez J, et al. Blood. 2014;123(20):3073-9.
- Paietta E. Bone Marrow Transplantation. 2002;29(6):459-465.
- Pulsipher M, et al. Blood. 2015;125(22):3501-8.
- Rawstron AC, et al. Leukemia. 2016;30(4):929-36.
- Wu D, et al. Clin Cancer Res. 2014;20(17):4540-8.

REPORT APPROVAL

REVIEWED AND RELEASED BY	SIGNATURE	DATE & TIME
Maria C Santos, MD	Maria C Santos	03/30/2019 12:22 PM

This report has been approved by the Clinical Laboratory Director, Stephanie Hallam, PhD, DABMGG. The clonoSEQ Assay is a laboratory service performed at Adaptive Biotechnologies' single site located at 1551 Eastlake Ave E, Seattle, WA 98102. This test was developed and its performance characteristics determined by Adaptive Biotechnologies Corporation. The laboratory is regulated under CLIA (WA-MTS CLIA# 50D2046518) as qualified to perform high complexity clinical testing.

Clonality (ID) Report with No Dominant Sequence Identified

This is an example B-cell Clonality (ID) Report. The clonoSEQ B-cell Clonality (ID) Report provides results based on analysis of the IgH, IgK and IgL loci as well as Bcl1 and Bcl2 translocations.

In this sample report, no dominant DNA sequences were identified from the submitted sample so the result is described as "Polyclonality" (1). This result is often encountered when a sample of insufficient disease load is supplied for testing, so it is important to ensure that samples sent for Clonality (ID) testing are high disease load diagnostic samples. For reference, information about the criteria for defining a sequence as dominant is also provided at the bottom of the page (2).

A 'Polyclonality' result is reported when no dominant sequences are identified in the supplied sample

Criteria for defining a dominant sequence

Page 1

B-CELL CLONALITY (ID) REPORT

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For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	03/14/2019	03/16/2019	SP-6337492

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

ASSAY DESCRIPTION

The clonoSEQ® Assay is an *in vitro* diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL).

CLONALITY RESULT

1

No Dominant Sequence Identified (Polyclonality)
Clone tracking (e.g. MRD determination) is not enabled by this sample

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- There were no sequences that met the criteria for a "dominant" sequence.
- **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

CRITERIA FOR DEFINING "DOMINANT" SEQUENCES

2

- The sequence must comprise at least 3% of all like sequences (IGH-involved, IGK, and IGL are considered independently).
- The sequence must comprise at least 0.2% of the total nucleated cells in the sample.
- The sequence must be discontinuously distributed (≤5 sequences in the next decade of sequences when ranked by frequency).
- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

ASSAY METHODS AND LIMITATIONS

METHOD

The clonoSEQ Assay utilizes NGS to determine the level of remaining presumptive disease-associated cells in patients with previously diagnosed lymphoid malignancies: The patient-specific sequence(s) carried by the presumed transformed clone is first identified in a diagnostic sample using a set of multiplexed, locus-specific primer sets for the immunoglobulin heavy-chain locus (IGH), including both complete (IGH-VDJ) and incomplete (IGH-DJ) rearrangements, the immunoglobulin κ locus (IGK), the immunoglobulin λ locus (IGL) and IGH-BCL1/2 translocations. The assay is then applied in one or more follow-up samples to detect the level of the patient-specific sequence(s) corresponding to the prevalence of the sequence carrying clone.

ASSAY LIMITATIONS

False positive or false negative results may occur for reasons including, but not limited to: sample mix up, misidentification, and/or contamination; technical and/or biological factors. Results may vary by sample type or body site/location sampled. The assay may overestimate MRD frequencies near the limit of detection.

Clonality (ID) Report with No Dominant Sequence Identified (continued)

Since no dominant sequences were identified in the Clonality (ID) test, a sequences table is not shown on Page 2 of the report. Instead, Page 2 provides more details on the immune repertoire of the analyzed sample, including sample clonality, the number of sequences assessed for each locus, and the number of unique sequences assessed (3).

Page 2

B-CELL CLONALITY (ID) REPORT

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For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**03/30/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	03/14/2019	03/16/2019	SP-6337492

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

Details on immune repertoire of analyzed sample (3)

SAMPLE CLONALITY [1]	TOTAL NUCLEATED CELLS [2]
0.13	82,497

LOCI	TOTAL SEQUENCES [3]	TOTAL UNIQUE SEQUENCES [4]
IGH	158	114
IGK	>=43	43
IGL	>=13	13

[1] Sample Clonality	A measure of the lymphocyte population diversity (distinct lymphocyte clonal sub-populations or "clones") comprising the immune repertoire in a given biological sample. Values for clonality vary from 0 to 1. Values close to 1 represent samples with one or a few predominant clones. Values near zero represent a more polyclonal sample.
[2] Total Nucleated Cells	The total number of nucleated cells calculated within the sample, based on quantitation of non-immune receptor loci contained in the reaction and the assumption that the DNA content per cell is diploid.
[3] Total Sequences	A measure of the number of nucleotide sequences detected in the sample for each defined immune receptor locus.
[4] Total Unique Sequences	A measure of the number of unique nucleotide sequences detected in the sample for each defined immune receptor locus.
Limit of Detection (LOD)	The lowest level of residual tracked sequence(s) that can be reliably detected by the clonoSEQ Assay in ≥95% of samples tested. LOD is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.

REFERENCES

- Carlson CS, et al. Nat Commun. 2013;4:2680.
- Faham M, et al. Blood. 2012;120(26):5173-80.
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- Paietta E. Bone Marrow Transplantation. 2002;29(6):459-465.
- Pulsipher M, et al. Blood. 2015;125(22):3501-8.
- Rawstron AC, et al. Leukemia. 2016;30(4):929-36.
- Wu D, et al. Clin Cancer Res. 2014;20(17):4540-8.

REPORT APPROVAL

REVIEWED AND RELEASED BY	SIGNATURE	DATE & TIME
Maria C Santos, MD	Maria C Santos	03/30/2018 12:22 PM

This report has been approved by the Clinical Laboratory Director, Stephanie Hallam, PhD, DABMGG. The clonoSEQ Assay is a laboratory service performed at Adaptive Biotechnologies' single site located at 1551 Eastlake Ave E, Seattle, WA 98102. This test was developed and its performance characteristics determined by Adaptive Biotechnologies Corporation. The laboratory is regulated under CLIA (WA-MTS CLIA# 50D2046518) as qualified to perform high complexity clinical testing.

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TRACKING (MRD) REPORT:

MRD Detection and Monitoring

After the dominant DNA sequence(s) has been identified utilizing the Clonality (ID) Test, subsequent monitoring of the associated clone(s) can be completed by ordering Tracking (MRD) Tests throughout treatment.

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	10/15/2019	10/16/2019	SP-657843

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

ASSAY DESCRIPTION

The clonoSEQ® Assay is an *in vitro* diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL).

SAMPLE-LEVEL MRD RESULT

\+

Residual Sequences Detected

ESTIMATED MRD VALUE:

8 residual clonal cells per million nucleated cells (Range: 3 - 14)

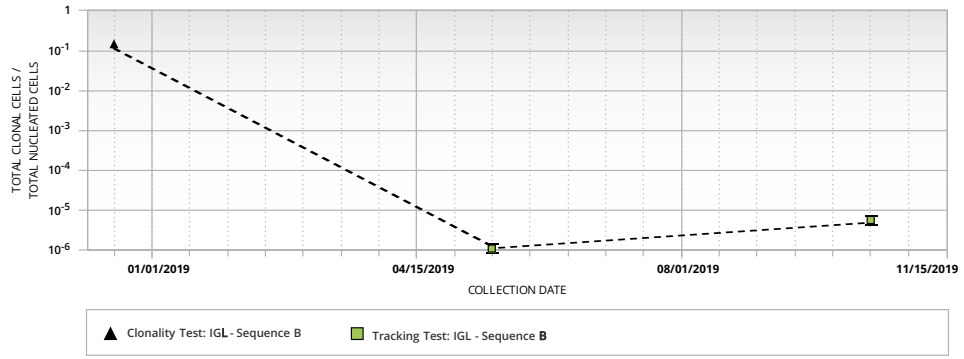
Sequence determining MRD result: IGL Sequence B

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- 2 of the 2 dominant sequences identified in a diagnostic sample from this patient were still present in this current sample.
- 15 copies of the dominant sequence determining the MRD result were observed out of 1,933,098 total nucleated cells evaluated from this sample.
- **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD results for each time point)*



MRD DETECTION AND MONITORING

Tracking (MRD) Report With Residual Sequences Detected

This is an example B-cell Tracking (MRD) Report. The clonoSEQ B-cell Tracking (MRD) Report provides results based on analysis of the IgH, IgK and IgL loci as well as Bcl1 and Bcl2 translocations.

In this sample, residual disease (MRD) was detected by the clonoSEQ Assay. This is indicated by the "plus" sign as well as the language stating "Residual Sequence(s) Detected" in the blue box on page 1 of the report (1). Also in the blue box, the report provides a quantitative assessment of the number of detected residual cells containing that sequence, displayed as a number per 1 million cells in the sample.

Note that a range is also included to the right of the quantitative MRD value. This range represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. The size of the range varies depending on the total number of input cells assessed and the limit of detection of the sequence determining the MRD result.

Further down the page, the Results Summary states the actual number of sequences observed by the assay and the total number of nucleated cells assessed in the sample (2).

Result indicating whether residual sequences were detected and quantifying MRD level as a fraction per 1 million cells

Number of residual sequences observed out of total nucleated cells assessed

Page 1

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	10/15/2019	10/16/2019	SP-657843

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

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SAMPLE-LEVEL MRD RESULT

1

\+

Residual Sequences Detected

ESTIMATED MRD VALUE:

8 residual clonal cells per million nucleated cells (Range: 3 - 14)

Sequence determining MRD result: IGL Sequence B

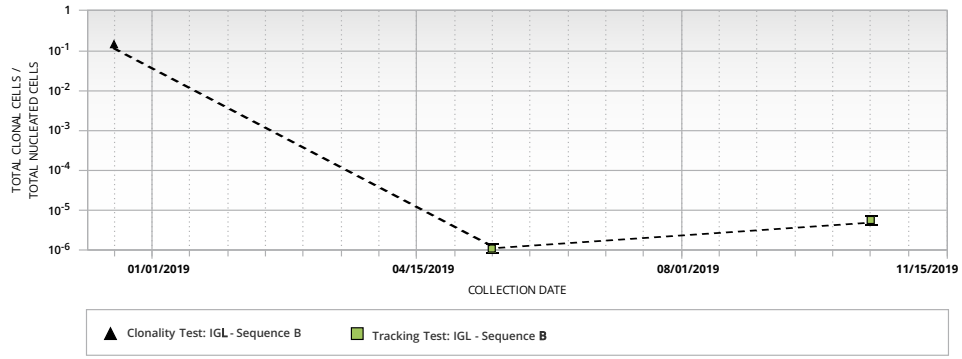
The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- 2 of the 2 dominant sequences identified in a diagnostic sample from this patient were still present in this current sample.
- 2 15 copies of the dominant sequence determining the MRD result were observed out of 1,933,098 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD results for each time point)*



MRD DETECTION AND MONITORING

Tracking (MRD) Report With Residual Sequences Detected (continued)

In the bottom third of the page, a chart (3) provides a longitudinal view of the sample-level MRD result for the current sample as well as for past samples sent for clonoSEQ testing for this patient. Each result is shown as a point on the chart with a corresponding test date; each MRD time point also has an associated confidence interval displayed. Note that the results shown in this chart are "sample level" results, meaning that they reflect the MRD result for the highest frequency dominant sequence in each tested sample. For sequence-level MRD results, see the table on page 2 and/or the chart on page 3 of the report.

Page 1

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

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Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

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SAMPLE-LEVEL MRD RESULT

+ Residual Sequences Detected

ESTIMATED MRD VALUE:

8 residual clonal cells per million nucleated cells (Range: 3 - 14)

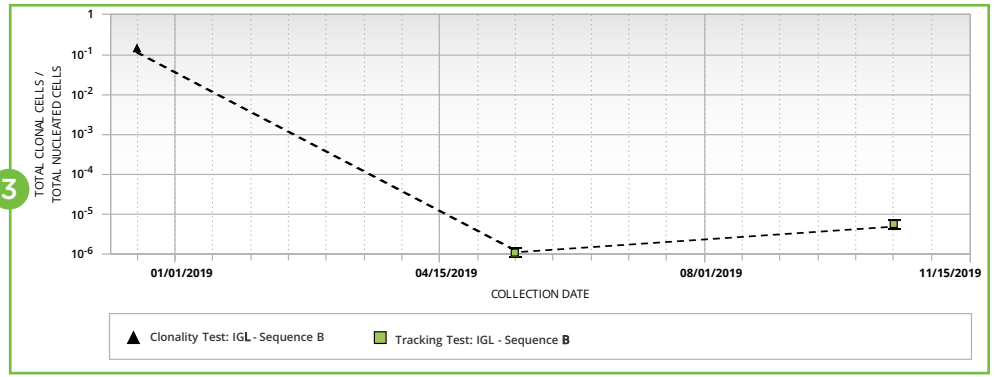
Sequence determining MRD result: IGL Sequence B

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- 2 of the 2 dominant sequences identified in a diagnostic sample from this patient were still present in this current sample.
- 15 copies of the dominant sequence determining the MRD result were observed out of 1,933,098 total nucleated cells evaluated from this sample.
- **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD results for each time point)*



3 Chart showing sample-level MRD results over time

MRD DETECTION AND MONITORING

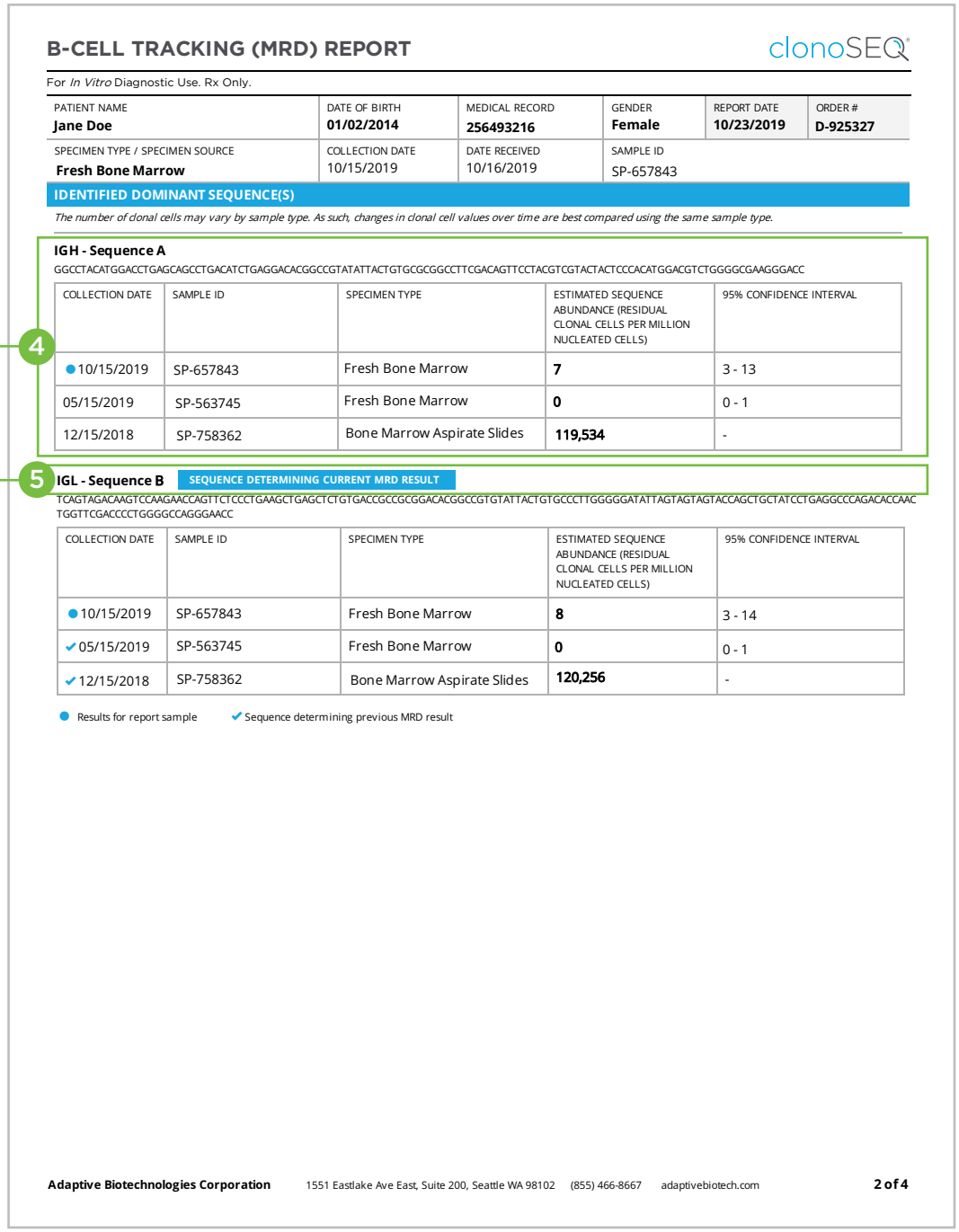
Tracking (MRD) Report With Residual Sequences Detected (continued)

Page 2 of the report shows detailed information relating to the current and previous samples (4) including the actual rearranged DNA nucleotide sequence or sequences identified, sample collection dates the receptor locus which each dominant DNA sequence was found, the specimen type analyzed, the estimated sequence abundance (i.e., the number of residual clonal cells per million nucleated cells), and the 95% confidence interval for each MRD result.

A blue bar (5) will be placed next to one of the sequences listed on this page to indicate that it is the sequence determining the MRD result for the current sample. The sequence(s) that determined the MRD result for previous samples are noted with a blue check mark.

Any MRD result which falls below the limit of detection (LOD) for a particular sequence is indicated with a double-cross which will be displayed in the estimated sequence abundance column next to the relevant result(s).

Page 2



B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	10/15/2019	10/16/2019	SP-657843

IDENTIFIED DOMINANT SEQUENCE(S)

The number of clonal cells may vary by sample type. As such, changes in clonal cell values over time are best compared using the same sample type.

IGH - Sequence A

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGCGGCCTTCGACAGTTCCTACGTCGTACTACTCCCACATGGACGTCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2019	SP-657843	Fresh Bone Marrow	**7**	3 - 13
05/15/2019	SP-563745	Fresh Bone Marrow	**0**	0 - 1
12/15/2018	SP-758362	Bone Marrow Aspirate Slides	**119,534**	-

IGL - Sequence B SEQUENCE DETERMINING CURRENT MRD RESULT

TCAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCCCTTGGGGGATATTAGTAGTAGTACCAGCTGCTATCCTGAGGCCCAGACACCAAC
TGGTTCGACCCCTGGGGCCAGGGAACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2019	SP-657843	Fresh Bone Marrow	**8**	3 - 14
✔ 05/15/2019	SP-563745	Fresh Bone Marrow	**0**	0 - 1
✔ 12/15/2018	SP-758362	Bone Marrow Aspirate Slides	**120,256**	-

● Results for report sample ✔ Sequence determining previous MRD result

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4 DNA sequences being tracked

5 Indicates the sequence determining the MRD result for the current sample

MRD DETECTION AND MONITORING

Tracking (MRD) Report With Residual Sequences Detected (continued)

Page 3 of the report displays the sequence-level information from Page 2 in a chart format (7). This "sequence-level MRD" chart provides a longitudinal view of results for each individual tracked sequence, for the current sample as well as for past samples sent for clonoSEQ testing for this patient. Similar to the "sample-level" chart on Page 1, the sequence-level chart includes a point on the chart for each test with a corresponding test date, but on this chart, each individual sequence is displayed separately.

In addition to the sequence-level chart, this page lists the criteria used by the clonoSEQ Assay to define dominant sequences, as well as a summary of the assay method and limitations (8).

The appendix provides more details on the immune repertoire of the analyzed sample, including the sample clonality, the number of sequences assessed for each locus, and the number of unique sequences assessed (9).

Page 3

B-CELL TRACKING (MRD) REPORT

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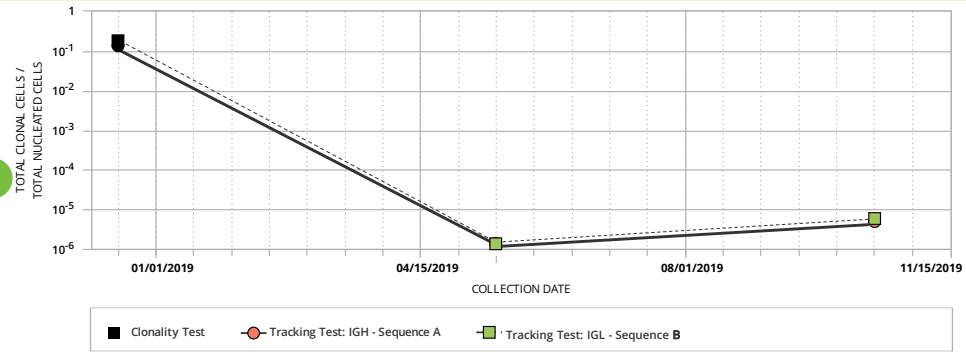
PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	10/15/2019	10/16/2019	SP-657843

SEQUENCE-LEVEL MRD TRACKING *(inclusive of all identified dominant sequences)*

Chart showing sequence-level MRD results over time

7



CRITERIA FOR DEFINING "DOMINANT" SEQUENCES

- The sequence must comprise at least 3% of all like sequences (IGH-involved, IGK, and IGL are considered independently).
- The sequence must comprise at least 0.2% of the total nucleated cells in the sample.
- The sequence must be discontinuously distributed (≤5 sequences in the next decade of sequences when ranked by frequency).
- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

Note: These criteria are applied when defining the trackable dominant sequence(s) in a high disease load (ID) sample or when identifying new dominant sequences in a follow-up (MRD) sample.

ASSAY METHODS AND LIMITATIONS

Summary of assay method and limitations

8

METHOD

The clonoSEQ Assay utilizes NGS to determine the level of remaining presumptive disease-associated cells in patients with previously diagnosed lymphoid malignancies: The patient-specific sequence(s) carried by the presumed transformed clone is first identified in a diagnostic sample using a set of multiplexed, locus-specific primer sets for the immunoglobulin heavy-chain locus (IGH), including both complete (IGH-VDJ) and incomplete (IGH-DJ) rearrangements, the immunoglobulin κ locus (IGK), the immunoglobulin λ locus (IGL) and IGH-BCL1/2 translocations. The assay is then applied in one or more follow-up samples to detect the level of the patient-specific sequence(s) corresponding to the prevalence of the sequence carrying clone.

ASSAY LIMITATIONS

False positive or false negative results may occur for reasons including, but not limited to: sample mix up, misidentification, and/or contamination; technical and/or biological factors. Results may vary by sample type or body site/location sampled. The assay may overestimate MRD frequencies near the limit of detection.

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

Details on immune repertoire of analyzed sample

9

SAMPLE CLONALITY [1]	TOTAL NUCLEATED CELLS [2]
0.04	1,933,098

LOCI	TOTAL SEQUENCES [3]	TOTAL UNIQUE SEQUENCES [4]
IGH	≥78,588	78,588
IGK	20,064	12,181
IGL	859	785

MRD DETECTION AND MONITORING

Tracking (MRD) Report With Residual Sequences Detected (continued)

Page 4 of the report continues details on the immune repertoire of the analyzed sample, noting the limit of detection and limit of quantitation for each sequence tracked (10). The limit of detection (LOD) and limit of quantitation (LOQ) are independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.

A glossary of terms and references relevant to the report is also provided on this page (11).

Within the glossary, the assay's limit of blank, which is zero, is stated and defined (12). A limit of blank equal to zero indicates that in tests of assay performance on samples that were known to have zero residual disease, the clonoSEQ Assay did not generate any false-positive results.

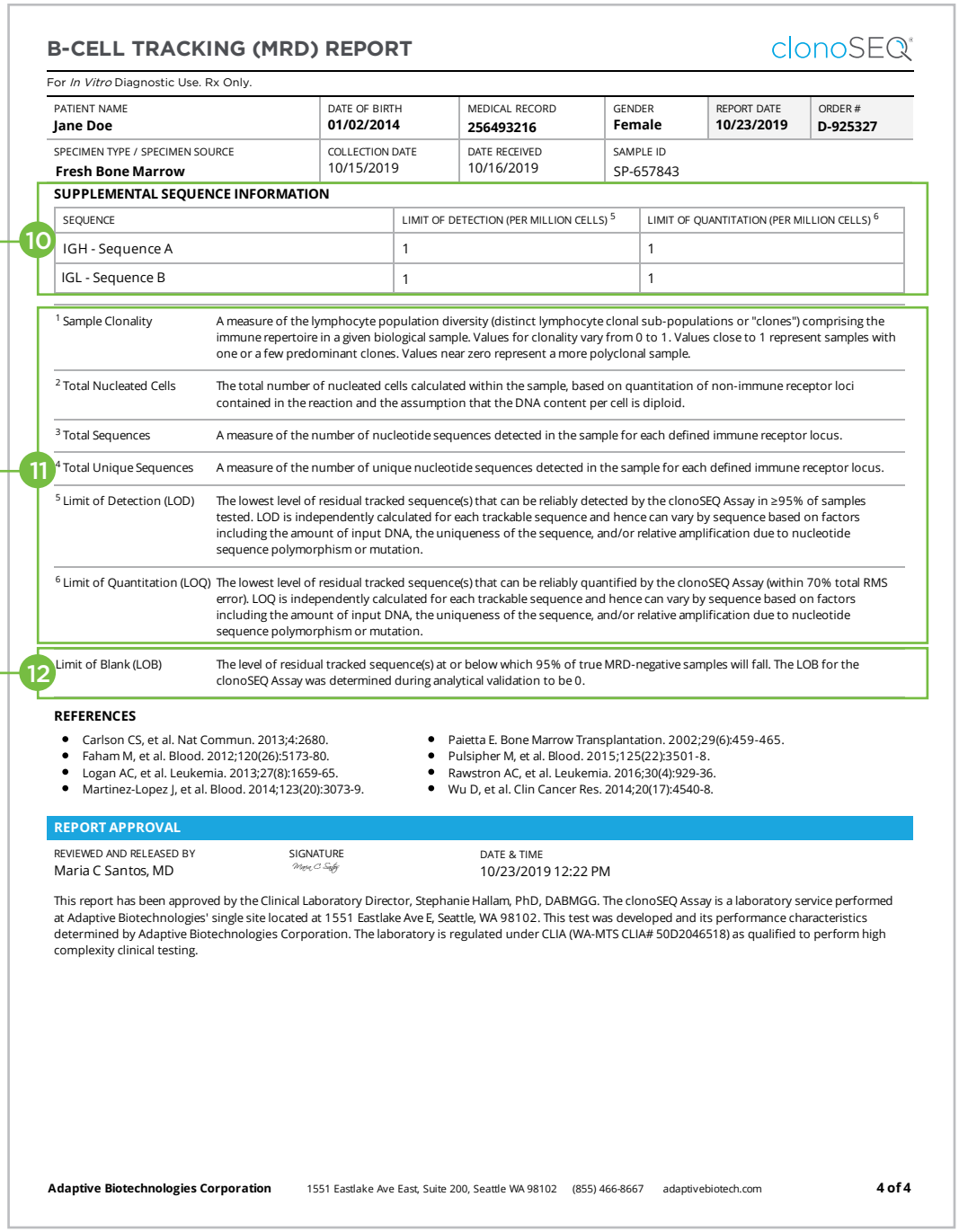
Note: False positive or false negative results may still occur, for reasons including contamination, technical and/or biological factors.

Limit of detection and limit of quantitation for each tracked sequence

Glossary of terms and references

Limit of blank

Page 4



B-CELL TRACKING (MRD) REPORT

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PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Fresh Bone Marrow	10/15/2019	10/16/2019	SP-657843

SUPPLEMENTAL SEQUENCE INFORMATION

10

SEQUENCE	LIMIT OF DETECTION (PER MILLION CELLS) [5]	LIMIT OF QUANTITATION (PER MILLION CELLS) [6]
IGH - Sequence A	1	1
IGL - Sequence B	1	1

11

[1] Sample Clonality	A measure of the lymphocyte population diversity (distinct lymphocyte clonal sub-populations or "clones") comprising the immune repertoire in a given biological sample. Values for clonality vary from 0 to 1. Values close to 1 represent samples with one or a few predominant clones. Values near zero represent a more polyclonal sample.
[2] Total Nucleated Cells	The total number of nucleated cells calculated within the sample, based on quantitation of non-immune receptor loci contained in the reaction and the assumption that the DNA content per cell is diploid.
[3] Total Sequences	A measure of the number of nucleotide sequences detected in the sample for each defined immune receptor locus.
[4] Total Unique Sequences	A measure of the number of unique nucleotide sequences detected in the sample for each defined immune receptor locus.
[5] Limit of Detection (LOD)	The lowest level of residual tracked sequence(s) that can be reliably detected by the clonoSEQ Assay in ≥95% of samples tested. LOD is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.
[6] Limit of Quantitation (LOQ)	The lowest level of residual tracked sequence(s) that can be reliably quantified by the clonoSEQ Assay (within 70% total RMS error). LOQ is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.

12

Limit of Blank (LOB)	The level of residual tracked sequence(s) at or below which 95% of true MRD-negative samples will fall. The LOB for the clonoSEQ Assay was determined during analytical validation to be 0.

REFERENCES

- Carlson CS, et al. Nat Commun. 2013;4:2680.
- Faham M, et al. Blood. 2012;120(26):5173-80.
- Logan AC, et al. Leukemia. 2013;27(8):1659-65.
- Martinez-Lopez J, et al. Blood. 2014;123(20):3073-9.
- Paietta E. Bone Marrow Transplantation. 2002;29(6):459-465.
- Pulsipher M, et al. Blood. 2015;125(22):3501-8.
- Rawstron AC, et al. Leukemia. 2016;30(4):929-36.
- Wu D, et al. Clin Cancer Res. 2014;20(17):4540-8.

REPORT APPROVAL

REVIEWED AND RELEASED BY	SIGNATURE	DATE & TIME
Maria C Santos, MD	Maria C Santos	10/23/2019 12:22 PM

This report has been approved by the Clinical Laboratory Director, Stephanie Hallam, PhD, DABMGG. The clonoSEQ Assay is a laboratory service performed at Adaptive Biotechnologies' single site located at 1551 Eastlake Ave E, Seattle, WA 98102. This test was developed and its performance characteristics determined by Adaptive Biotechnologies Corporation. The laboratory is regulated under CLIA (WA-MTS CLIA# 50D2046518) as qualified to perform high complexity clinical testing.

MRD DETECTION AND MONITORING

Tracking (MRD) Report With No Residual Sequences Detected

This is an example B-cell Tracking (MRD) Report. The clonoSEQ B-cell Tracking (MRD) Report provides results based on analysis of the IgH, IgK and IgL loci as well as Bcl1 and Bcl2 translocations.

In this sample, residual disease was NOT detected by the clonoSEQ Assay. This is indicated by the language "Residual Sequence(s) Not Detected" in the blue box on page 1 of the report (1). Also in the blue box, the report provides a quantitative assessment of the number of detected residual cells containing that sequence, displayed as a number per 1 million cells in the sample. In this example, the number of detected residual cells is zero.

Note that a range is also included to the right of the quantitative MRD value. This range represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. The size of the range varies depending on the total number of input cells assessed and the limit of detection of the sequence determining the MRD result. For a test in which residual disease was not detected, the range reflects the fact that there was zero disease in the tested sample, but that some disease could still be present in the patient (due to sampling bias).

Further down the page, the Results Summary states the actual number of sequences observed by the assay and the total number of nucleated cells assessed in the sample (2).

Result indicating whether residual sequences were detected (1)

Number of residual sequences observed out of total nucleated cells assessed (2)

Page 1

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

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PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	10/15/2019	10/16/2019	SP-237584

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

ASSAY DESCRIPTION

The clonoSEQ® Assay is an *in vitro* diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL).

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 2) **

Sequence determining MRD result: IGH Sequence A

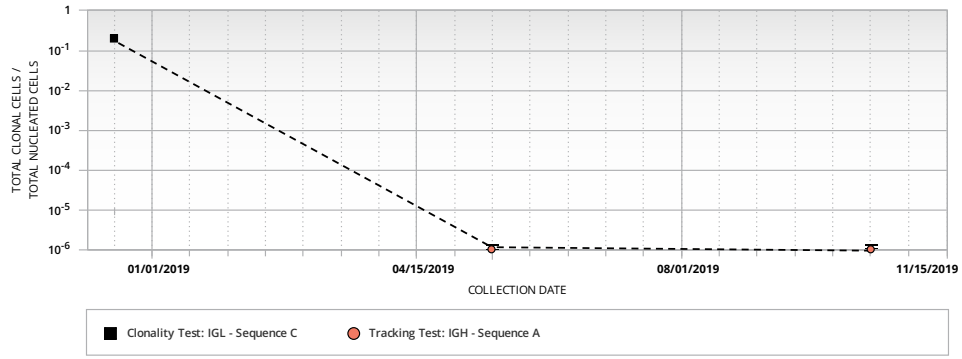
The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- The 3 dominant sequences identified in a diagnostic sample from this patient were not detected in this current sample.
- ** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 1,331,826 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD results for each time point)*



MRD DETECTION AND MONITORING

Tracking (MRD) Report With No Residual Sequences Detected (continued)

In the bottom third of the page, a chart (3) provides a longitudinal view of the sample-level MRD result for the current sample as well as for past samples sent for clonoSEQ testing for this patient. In this example, the patient was MRD-positive in previous tests, but no residual disease was detected in the current sample. Each result is shown as a point on the chart with a corresponding test date; each MRD time point also has an associated confidence interval displayed. Note that the results shown in this chart are "sample level" results, meaning that they reflect the MRD result for the highest frequency dominant sequence in each tested sample. For sequence-level MRD results, see the table on page 2 and/or the chart on page 3 of the report.

Page 1

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	10/15/2019	10/16/2019	SP-237584

ICD CODE
C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN	INSTITUTION
Alexander Smith	University Cancer Hospital

ASSAY DESCRIPTION

The clonoSEQ® Assay is an *in vitro* diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM), and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL).

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

0 residual clonal cells (Range: 0 - 2) **

Sequence determining MRD result: IGH Sequence A

The MRD range presented above represents the 95% confidence interval for the measured number of residual clonal sequences per million nucleated cells. Details for each identified dominant sequence from this sample are provided on subsequent pages of this report.

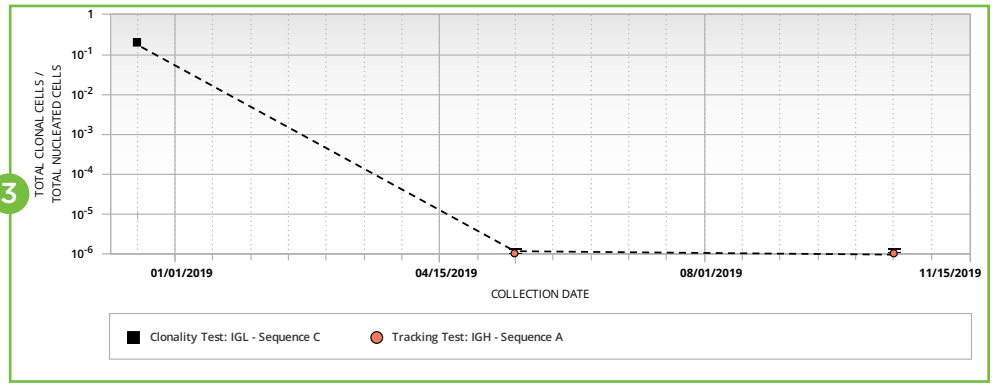
RESULTS SUMMARY

- Genomic DNA was extracted from a bone marrow aspirate slide sample.
- The 3 dominant sequences identified in a diagnostic sample from this patient were not detected in this current sample.

** The sensitivity of this assay is directly related to the total number of cells (or cellular equivalents of genomic DNA) analyzed. There were 1,331,826 total nucleated cells evaluated from this sample.

▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD results for each time point)*



3 Chart showing sample-level MRD results over time

MRD DETECTION AND MONITORING

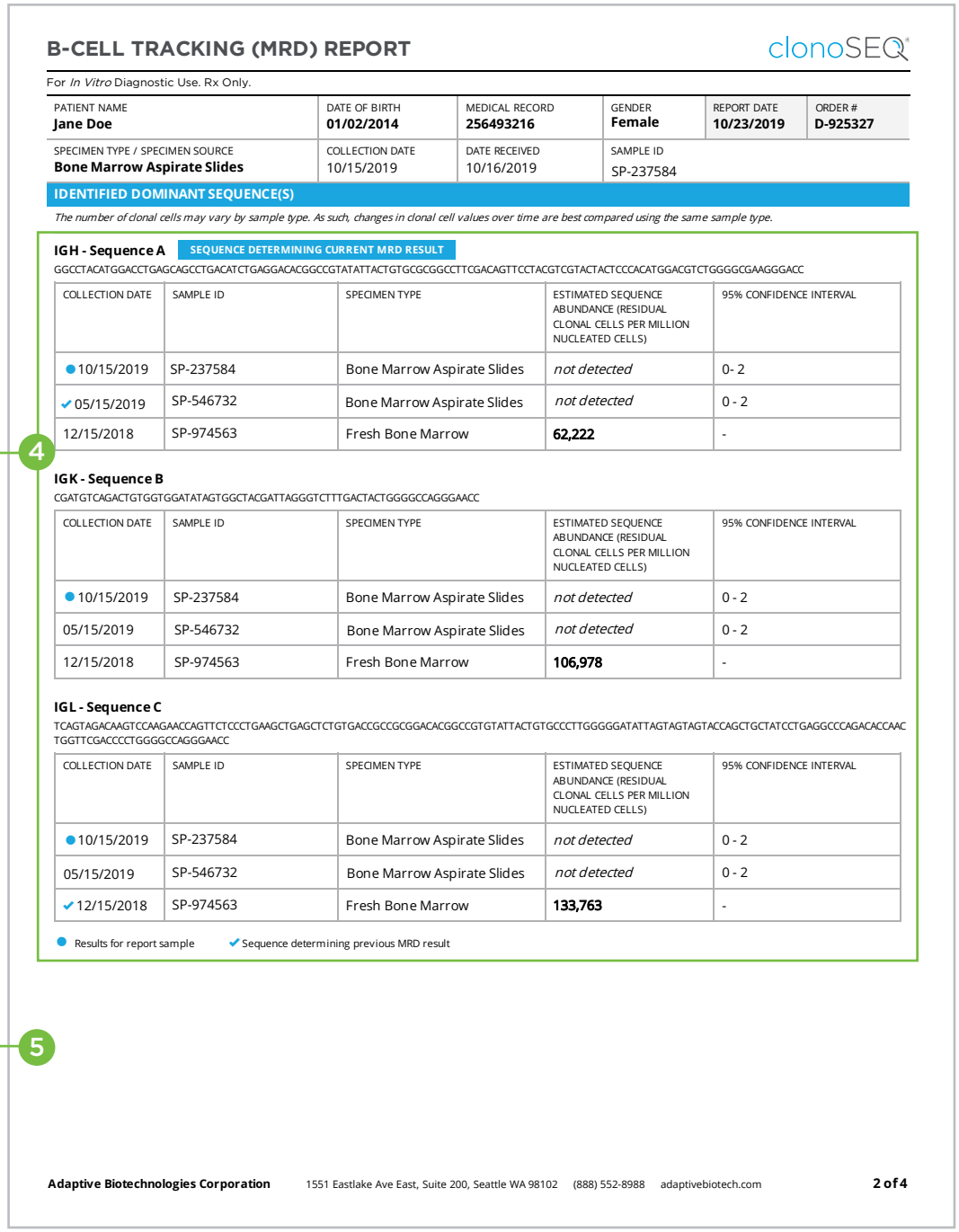
Tracking (MRD) Report With No Residual Sequences Detected (continued)

Page 2 of the report shows detailed information relating to the current and previous samples (4) including the actual rearranged DNA nucleotide sequence or sequences identified, sample collection dates, the receptor locus which each dominant sequence was found, the specimen type analyzed, the estimated sequence abundance (i.e., the number of residual clonal cells per million nucleated cells), and the 95% confidence interval for each MRD result.

Since no residual sequences were detected in the current sample, the estimated sequence abundance is zero.

For some patients, the report may indicate that one or more of the dominant DNA sequences being tracked may have been identified using a prior version of the clonoSEQ Assay (5). Strong concordance data support the use of this/these sequence(s) for continued MRD tracking with clonoSEQ. MRD results from a prior version of the clonoSEQ Assay will not display on this report, but are available via the Diagnostic Portal.[1] Please note that quantitative MRD values may not be directly comparable across assays, particularly for small differences in values.

Page 2



B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	10/15/2019	10/16/2019	SP-237584

IDENTIFIED DOMINANT SEQUENCE(S)

The number of clonal cells may vary by sample type. As such, changes in clonal cell values over time are best compared using the same sample type.

IGH - Sequence A SEQUENCE DETERMINING CURRENT MRD RESULT

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGCGGCCTTCGACAGTTCCTACGTCGTACTACTCCCACATGGACGTCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2019	SP-237584	Bone Marrow Aspirate Slides	*not detected*	0- 2
✔ 05/15/2019	SP-546732	Bone Marrow Aspirate Slides	*not detected*	0 - 2
12/15/2018	SP-974563	Fresh Bone Marrow	**62,222**	-

IGK - Sequence B

CGATGTCAGACTGTGGTGGATATAGTGGCTACGATTAGGGTCTTTGACTACTGGGGCCAGGGAACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2019	SP-237584	Bone Marrow Aspirate Slides	*not detected*	0 - 2
05/15/2019	SP-546732	Bone Marrow Aspirate Slides	*not detected*	0 - 2
12/15/2018	SP-974563	Fresh Bone Marrow	**106,978**	-

IGL - Sequence C

TCAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCCCTTGGGGGATATTAGTAGTAGTACCAGCTGCTATCCTGAGGCCCAGACACCAAC
TGGTTCGACCCCTGGGGCCAGGGAACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2019	SP-237584	Bone Marrow Aspirate Slides	*not detected*	0 - 2
05/15/2019	SP-546732	Bone Marrow Aspirate Slides	*not detected*	0 - 2
✔ 12/15/2018	SP-974563	Fresh Bone Marrow	**133,763**	-

● Results for report sample ✔ Sequence determining previous MRD result

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4 Specific DNA sequences identified

5 Prior assay version MRD results information

1. Data on file. Adaptive Biotechnologies. 2017.

MRD DETECTION AND MONITORING

Tracking (MRD) Report With No Residual Sequences Detected (continued)

Page 3 of the report displays the sequence-level information from Page 2 in a chart format (6). This “sequence-level MRD” chart provides a longitudinal view of results for each individual tracked sequence, for the current sample as well as for past samples sent for clonoSEQ testing for this patient. Similar to the “sample-level” chart on Page 1, the sequence-level chart includes a point on the chart for each test with a corresponding test date, but on this chart, each individual sequence is displayed separately.

In addition to the sequence-level chart, this page lists the criteria used by the clonoSEQ Assay to define dominant sequences, as well as a summary of the assay method and limitations (7).

The appendix provides more details on the immune repertoire of the analyzed sample, including the sample clonality, the number of sequences assessed for each locus, and the number of unique sequences assessed (8).

Page 3

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

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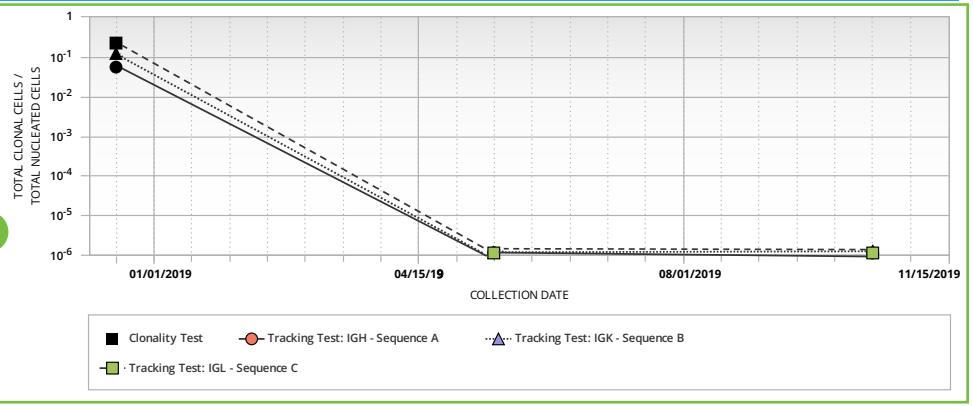
PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	**D-925327**

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	10/15/2019	10/16/2019	SP-237584

SEQUENCE-LEVEL MRD TRACKING *(inclusive of all identified dominant sequences)*



6 Chart showing sequence-level MRD results over time

CRITERIA FOR DEFINING "DOMINANT" SEQUENCES

- The sequence must comprise at least 3% of all like sequences (IGH-involved, IGK, and IGL are considered independently).
- The sequence must comprise at least 0.2% of the total nucleated cells in the sample.
- The sequence must be discontinuously distributed (≤5 sequences in the next decade of sequences when ranked by frequency).
- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

Note: These criteria are applied when defining the trackable dominant sequence(s) in a high disease load (ID) sample or when identifying new dominant sequences in a follow-up (MRD) sample.

ASSAY METHODS AND LIMITATIONS

7 Summary of assay method and limitations

METHOD

The clonoSEQ Assay utilizes NGS to determine the level of remaining presumptive disease-associated cells in patients with previously diagnosed lymphoid malignancies: The patient-specific sequence(s) carried by the presumed transformed clone is first identified in a diagnostic sample using a set of multiplexed, locus-specific primer sets for the immunoglobulin heavy-chain locus (IGH), including both complete (IGH-VDJ) and incomplete (IGH-DJ) rearrangements, the immunoglobulin κ locus (IGK), the immunoglobulin λ locus (IGL) and IGH-BCL1/2 translocations. The assay is then applied in one or more follow-up samples to detect the level of the patient-specific sequence(s) corresponding to the prevalence of the sequence carrying clone.

ASSAY LIMITATIONS

False positive or false negative results may occur for reasons including, but not limited to: sample mix up, misidentification, and/or contamination; technical and/or biological factors. Results may vary by sample type or body site/location sampled. The assay may overestimate MRD frequencies near the limit of detection.

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

8 Details on immune repertoire of analyzed sample

SAMPLE CLONALITY [1]	TOTAL NUCLEATED CELLS [2]
0.09	1,331,826

LOCI	TOTAL SEQUENCES [3]	TOTAL UNIQUE SEQUENCES [4]
IGH	≥120,400	120,400
IGK	160,834	68,357
IGL	48,683	21,795

MRD DETECTION AND MONITORING

Tracking (MRD) Report With No Residual Sequences Detected (continued)

Page 4 of the report continues details on the immune repertoire of the analyzed sample, noting the limit of detection and limit of quantitation for each sequence tracked (9). The limit of detection (LOD) and limit of quantitation (LOQ) are independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.

A glossary of terms and references relevant to the report is also provided on this page (10).

Within the glossary, the assay's limit of blank, which is zero, is stated and defined (11). A limit of blank equal to zero indicates that in tests of assay performance on samples that were known to have zero residual disease, the clonoSEQ Assay did not generate any false-positive results.

Note: False positive or false negative results may still occur, for reasons including contamination, technical and/or biological factors.

Limit of detection and limit of quantitation for each tracked sequence

Glossary of terms and references

Limit of blank

Page 4

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME	DATE OF BIRTH	MEDICAL RECORD	GENDER	REPORT DATE	ORDER #
Jane Doe	**01/02/2014**	**256493216**	**Female**	**10/23/2019**	D-925327

SPECIMEN TYPE / SPECIMEN SOURCE	COLLECTION DATE	DATE RECEIVED	SAMPLE ID
Bone Marrow Aspirate Slides	10/15/2019	10/16/2019	SP-237584

SUPPLEMENTAL SEQUENCE INFORMATION

SEQUENCE	LIMIT OF DETECTION (PER MILLION CELLS) [5]	LIMIT OF QUANTITATION (PER MILLION CELLS) [6]
IGH - Sequence A	1	2
IGK - Sequence B	7	9
IGL - Sequence C	143	179

[1] Sample Clonality	A measure of the lymphocyte population diversity (distinct lymphocyte clonal sub-populations or "clones") comprising the immune repertoire in a given biological sample. Values for clonality vary from 0 to 1. Values close to 1 represent samples with one or a few predominant clones. Values near zero represent a more polyclonal sample.
[2] Total Nucleated Cells	The total number of nucleated cells calculated within the sample, based on quantitation of non-immune receptor loci contained in the reaction and the assumption that the DNA content per cell is diploid.
[3] Total Sequences	A measure of the number of nucleotide sequences detected in the sample for each defined immune receptor locus.
[4] Total Unique Sequences	A measure of the number of unique nucleotide sequences detected in the sample for each defined immune receptor locus.
[5] Limit of Detection (LOD)	The lowest level of residual tracked sequence(s) that can be reliably detected by the clonoSEQ Assay in ≥95% of samples tested. LOD is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.
[6] Limit of Quantitation (LOQ)	The lowest level of residual tracked sequence(s) that can be reliably quantified by the clonoSEQ Assay (within 70% total RMS error). LOQ is independently calculated for each trackable sequence and hence can vary by sequence based on factors including the amount of input DNA, the uniqueness of the sequence, and/or relative amplification due to nucleotide sequence polymorphism or mutation.
Limit of Blank (LOB)	The level of residual tracked sequence(s) at or below which 95% of true MRD-negative samples will fall. The LOB for the clonoSEQ Assay was determined during analytical validation to be 0.

REFERENCES

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REPORT APPROVAL

REVIEWED AND RELEASED BY	SIGNATURE	DATE & TIME
Maria C Santos, MD	Maria C Santos	10/23/2019 12:22 PM

This report has been approved by the Clinical Laboratory Director, Stephanie Hallam, PhD, DABMGG. The clonoSEQ Assay is a laboratory service performed at Adaptive Biotechnologies' single site located at 1551 Eastlake Ave E, Seattle, WA 98102. This test was developed and its performance characteristics determined by Adaptive Biotechnologies Corporation. The laboratory is regulated under CLIA (WA-MTS CLIA# 50D2046518) as qualified to perform high complexity clinical testing.

clonoSEQ® is available as an FDA-cleared *in vitro* diagnostic (IVD) test service provided by Adaptive Biotechnologies to detect measurable residual disease (MRD) in bone marrow from patients with multiple myeloma or B-cell acute lymphoblastic leukemia (B-ALL) and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL). clonoSEQ is also available for use in other lymphoid cancers as a CLIA-validated laboratory developed test (LDT) service. For important information about the FDA-cleared uses of clonoSEQ including test limitations, please visit clonoSEQ.com/technical-summary.

Test Limitations

ALL, MM and CLL: MRD values obtained with different assay methods may not be interchangeable due to differences in assay methods and reagent specificity. The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings. The clonoSEQ Assay is for use with specimens collected in EDTA tubes. Results may vary according to sample time within the course of disease or by sampling site location. The assay may overestimate MRD frequencies near the limit of detection (LoD). The MRD frequency LoD varies based on the amount of gDNA that is tested and using lower gDNA input may prevent MRD detection at low frequencies. Sample processing and cell enrichment strategies may affect the measured MRD frequency. The volume and cellularity of sampled input material may affect the ability to detect low levels of disease. False positive or false negative results may occur for reasons including, but not limited to: contamination; technical and/or biological factors such as the type of rearrangement or the size of the junction region. The assay has been validated with the Illumina NextSeq500 and 550.

For CLL: MRD is based on measurements of tumor cells detected in peripheral blood and/or bone marrow. However, patients may have significant residual disease in unassessed compartments and U-MRD in one compartment cannot fully rule out the presence of disease in the other compartment; for example, U-MRD in blood may not be the same in bone marrow. Therefore assessment of MRD in CLL should employ a multimodal approach including clinical examination, patient medical history, and other findings. Outcome for patients with MRD detectable in bone marrow but not in peripheral blood (PB-/BM+) may differ according to type of therapy. This assay is capable of monitoring specific tumor clonotypes. The association between MRD assessments and patient clinical status for the purpose of monitoring changes in disease (e.g., relapse, remission, stable disease) has not been demonstrated. The value of MRD in CLL for previously untreated or “watch and wait” patients is not established. CLL is a heterogeneous disease. MRD values and expectations for outcome may not be generalizable across treatments. Changes in MRD should be interpreted with caution when used to evaluate disease burden in therapies that have not been validated. Regardless of MRD status, cytogenetics play an independent role in patient risk status and its impact on PFS/OS.

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