

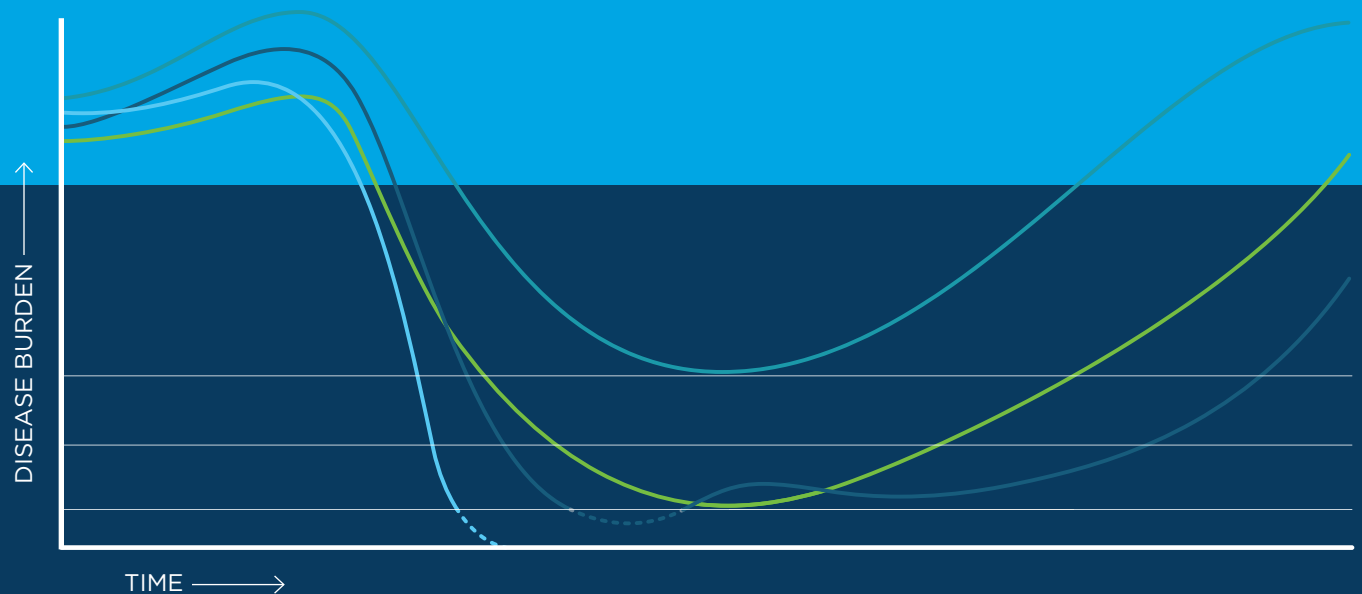
FOR HEALTHCARE PROVIDERS

clonoSEQ®

UNDERSTANDING THE CLONOSEQ ASSAY

Clonality (ID) and Tracking (MRD) Reports

clonoSEQ is an FDA-cleared in vitro diagnostic (IVD) test service provided by Adaptive Biotechnologies for use in B-cell acute lymphoblastic leukemia and multiple myeloma patients to detect and monitor measurable residual disease (MRD) in bone marrow samples. clonoSEQ is also available for use in other lymphoid cancers as a CLIA-regulated laboratory developed test (LDT) service provided by Adaptive Biotechnologies.





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 available by prescription only. clonoSEQ results should always be used in combination with clinical examination, patient medical history, and other findings. Results may vary according to sample time within the course of disease or by sampling site location. 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

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-597516		
ICD CODE C91.00 Acute lymphoblastic leukemia not having achieved remission					
ORDERING PHYSICIAN Alexander Smith			INSTITUTION 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).

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 Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-597516		

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- The sequence must be carried by at least 40 estimated genome equivalents in the analyzed sample.

Result

1

Additional result information

2

Criteria for defining a dominant sequence

3

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.

Specific DNA sequences identified

B-CELL CLONALITY (ID) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-597516		

IDENTIFIED DOMINANT SEQUENCE(S)

IGK - Sequence A

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGCGCCCTTCGACAGTTCCTACGTCTACTCCCACATGGACGCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	FREQUENCY PER TOTAL NUCLEATED CELLS	TOTAL CELLS CONTAINING SEQUENCE
03/14/2018	SP-597516	Bone Marrow Aspirate Slides	84.594%	75,810

● Results for report 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 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

5

B-CELL CLONALITY (ID) REPORT

clonoSEQ[®]

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-597516		

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

SAMPLE CLONALITY ¹	TOTAL NUCLEATED CELLS ²	LOCI	TOTAL SEQUENCES ³	TOTAL UNIQUE SEQUENCES ⁴
0.85	89,617	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 Maria C Santos, MD	SIGNATURE <i>Maria C Santos</i>	DATE & TIME 03/30/2018 12:22 PM
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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

B-CELL CLONALITY (ID) REPORT

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For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-6337492		

ICD CODE

C91.00 Acute lymphoblastic leukemia not having achieved remission

ORDERING PHYSICIAN

Alexander Smith

INSTITUTION

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).

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

- 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).

Details on immune repertoire of analyzed sample

B-CELL CLONALITY (ID) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 03/30/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 03/14/2018	DATE RECEIVED 03/16/2018	SAMPLE ID SP-6337492		

APPENDIX

SUPPLEMENTAL SAMPLE INFORMATION

SAMPLE CLONALITY ¹	TOTAL NUCLEATED CELLS ²	LOCI	TOTAL SEQUENCES ³	TOTAL UNIQUE SEQUENCES ⁴
0.13	82,497	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.
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- Paietta E. *Bone Marrow Transplantation.* 2002;29(6):459-465.
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- Wu D, et al. *Clin Cancer Res.* 2014;20(17):4540-8.

REPORT APPROVAL

REVIEWED AND RELEASED BY Maria C Santos, MD	SIGNATURE <i>Maria C Santos</i>	DATE & TIME 03/30/2018 12:22 PM
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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 Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-657843		
ICD CODE C91.00 Acute lymphoblastic leukemia not having achieved remission					
ORDERING PHYSICIAN Alexander Smith			INSTITUTION 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).

SAMPLE-LEVEL MRD RESULT

+

Residual Sequences Detected

ESTIMATED MRD VALUE:

8

residual clonal cells per million nucleated cells (Range: 6 - 27)

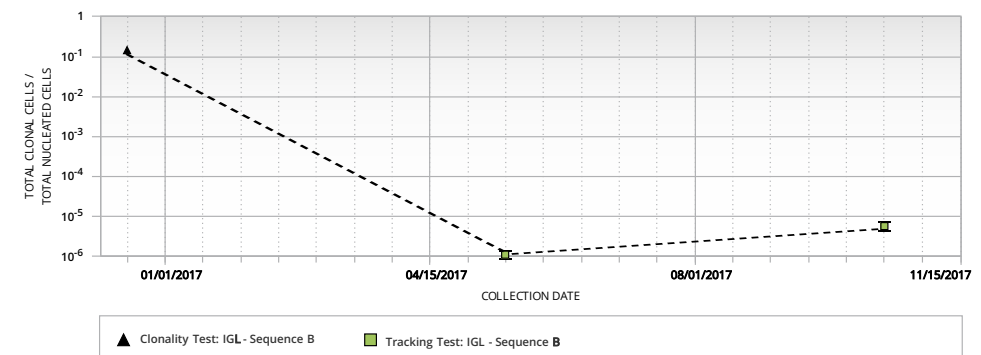
Sequence determining MRD result: IGL Sequence B

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).

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

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

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-657843		
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SAMPLE-LEVEL MRD RESULT

1

+

Residual Sequences Detected

ESTIMATED MRD VALUE:

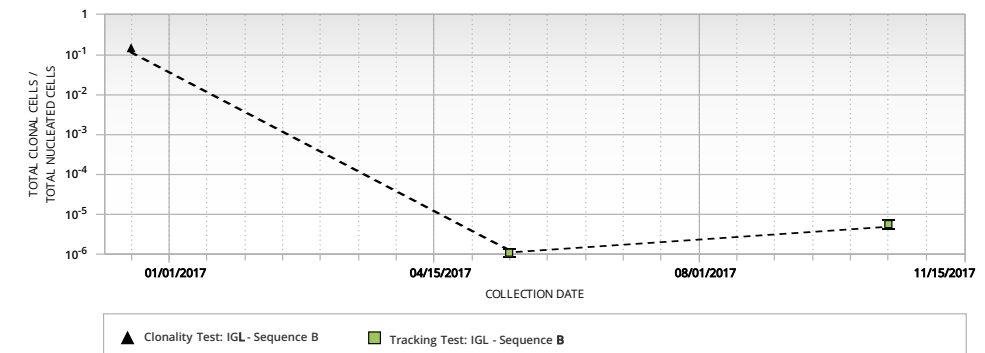
8 residual clonal cells per million nucleated cells (Range: 6 - 27)

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.

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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.

B-CELL TRACKING (MRD) REPORT



For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-657843		

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ORDERING PHYSICIAN Alexander Smith	INSTITUTION University Cancer Hospital
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SAMPLE-LEVEL MRD RESULT

+

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ESTIMATED MRD VALUE:

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residual clonal cells per million nucleated cells (Range: 6 - 27)

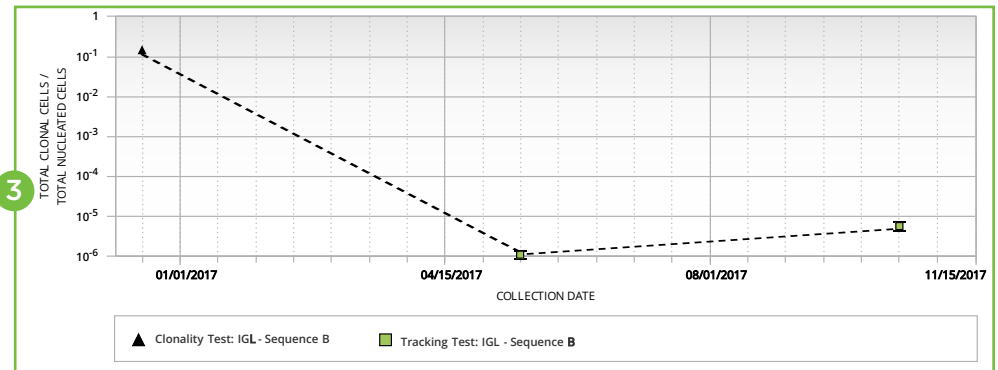
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- ▶ **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

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).

DNA sequences being tracked

4

Indicates the sequence determining the MRD result for the current sample

5

B-CELL TRACKING (MRD) REPORT



For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID 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

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCCGGCCCTCGACAGTTCTACTACTCCACATGGACGTCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2017	SP-657843	Fresh Bone Marrow	7	3 - 13
05/15/2017	SP-563745	Fresh Bone Marrow	0	0 - 1
12/15/2016	SP-758362	Bone Marrow Aspirate Slides	119,534	-

IGL - Sequence B SEQUENCE DETERMINING CURRENT MRD RESULT

TCAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTACTGTGCCCTGGGGGATATTAGTAGTAGTACCAGCTGCTATCCTGAGGCCAGACACCAAC
TGGTTCGACCCCTGGGGCCAGGGAAAC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2017	SP-657843	Fresh Bone Marrow	8	3 - 14
✓ 05/15/2017	SP-563745	Fresh Bone Marrow	0	0 - 1
✓ 12/15/2016	SP-758362	Bone Marrow Aspirate Slides	120,256	-

● Results for report sample ✓ Sequence determining previous MRD result

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).

7 Chart showing sequence-level MRD results over time

8 Summary of assay method and limitations

9 Details on immune repertoire of analyzed sample

B-CELL TRACKING (MRD) REPORT

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-657843		

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

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

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

SAMPLE CLONALITY ¹	TOTAL NUCLEATED CELLS ²	LOCI	TOTAL SEQUENCES ³	TOTAL UNIQUE SEQUENCES ⁴
0.04	1,933,098	IGH	≥78,588	78,588
		IGK	20,064	12,181
		IGL	859	785

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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

B-CELL TRACKING (MRD) REPORT

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PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2017	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Fresh Bone Marrow	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-657843		

SUPPLEMENTAL SEQUENCE INFORMATION

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

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.
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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.
- Palletta 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 Maria C Santos, MD	SIGNATURE <i>Maria C Santos</i>	DATE & TIME 03/30/2018 12:22 PM
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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).

1
Result indicating whether residual sequences were detected

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

B-CELL TRACKING (MRD) REPORT

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PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-237584		
ICD CODE C91.00 Acute lymphoblastic leukemia not having achieved remission					
ORDERING PHYSICIAN Alexander Smith			INSTITUTION 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).

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

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

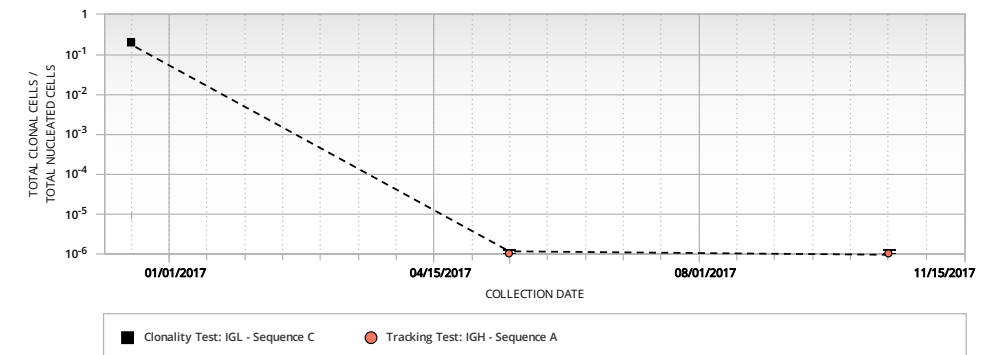
Sequence determining MRD result: IGH Sequence A

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.

Chart showing sample-level MRD results over time

B-CELL TRACKING (MRD) REPORT

clonoSEQ®

For *In Vitro* Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-237584		

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

ORDERING PHYSICIAN
Alexander Smith

INSTITUTION
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).

SAMPLE-LEVEL MRD RESULT

No Residual Sequences Detected

ESTIMATED MRD VALUE:

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

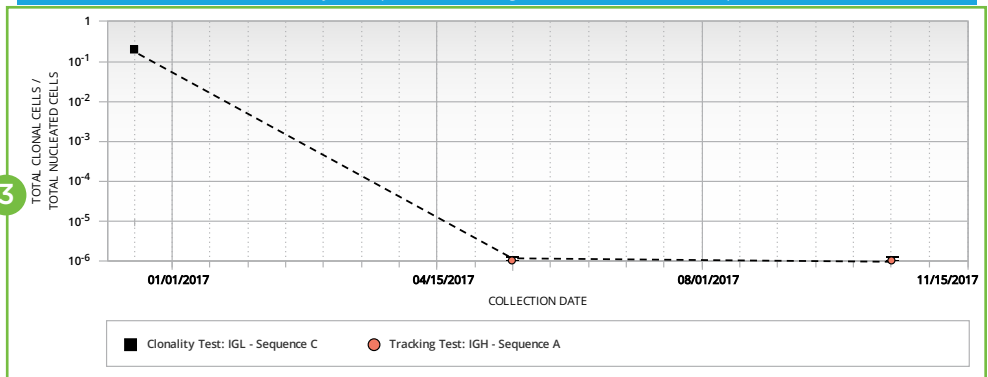
Sequence determining MRD result: IGH Sequence A

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)

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.

Specific DNA sequences identified

4

Prior assay version MRD results information

5

B-CELL TRACKING (MRD) REPORT



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PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID 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

GGCCTACATGGACCTGAGCAGCCTGACATCTGAGGACACGGCCGTATATTACTGTGCGCGCCCTCGACAGTTCCTACGTCGTACTCTCCACATGGACGTCTGGGGCGAAGGGACC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2018	SP-237584	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
✓ 05/15/2017	SP-546732	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
12/15/2016	SP-974563	Fresh Bone Marrow	62,222	-

IGK - Sequence B

CGATGT CAGACTGTGGTGGATATAGTGGCTACGATTAGGGTCTTTGACTACTGGGCCAGGGAAAC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2017	SP-237584	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
05/15/2017	SP-546732	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
12/15/2016	SP-974563	Fresh Bone Marrow	106,978	-

IGL - Sequence C

TCAGTAGACAAGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTGACCCCGCGGACACGGCCGTGATTACTGTGCCCTGGGGGATATTAGTAGTAGTACCAGCTGCTACTCTGGGCCAGACACCAAC
TGGTTGACCCCTGGGGCCAGGGAAAC

COLLECTION DATE	SAMPLE ID	SPECIMEN TYPE	ESTIMATED SEQUENCE ABUNDANCE (RESIDUAL CLONAL CELLS PER MILLION NUCLEATED CELLS)	95% CONFIDENCE INTERVAL
● 10/15/2017	SP-237584	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
05/15/2017	SP-546732	Bone Marrow Aspirate Slides	<i>not detected</i>	0 - 2
✓ 12/15/2016	SP-974563	Fresh Bone Marrow	133,763	-

● Results for report sample ✓ Sequence determining previous MRD result

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).

6 Chart showing sequence-level MRD results over time

7 Summary of assay method and limitations

8 Details on immune repertoire of analyzed sample

B-CELL TRACKING (MRD) REPORT

For In Vitro Diagnostic Use. Rx Only.

PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2018	ORDER # D-925327
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides	COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID SP-237584		

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

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

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

SAMPLE CLONALITY ¹	TOTAL NUCLEATED CELLS ²	LOCI	TOTAL SEQUENCES ³	TOTAL UNIQUE SEQUENCES ⁴
0.09	1,331,826	IGH	$\geq 120,400$	120,400
		IGK	160,834	68,357
		IGL	48,683	21,795

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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.

9 Limit of detection and limit of quantitation for each tracked sequence

10 Glossary of terms and references

11 Limit of blank

B-CELL TRACKING (MRD) REPORT						clonoSEQ®
For In Vitro Diagnostic Use. Rx Only.						
PATIENT NAME Jane Doe	DATE OF BIRTH 01/02/2014	MEDICAL RECORD 256493216	GENDER Female	REPORT DATE 10/23/2018	ORDER # D-925327	
SPECIMEN TYPE / SPECIMEN SOURCE Bone Marrow Aspirate Slides		COLLECTION DATE 10/15/2017	DATE RECEIVED 10/16/2017	SAMPLE ID 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.					
¹¹ 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						
<ul style="list-style-type: none"> 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 Maria C Santos, MD	SIGNATURE <i>Maria C Santos</i>	DATE & TIME 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.						
Adaptive Biotechnologies Corporation	1551 Eastlake Ave East, Suite 200, Seattle WA 98102	(855) 466-8667	adaptivebiotech.com	4 of 4		

Intended Use:

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 or multiple myeloma.

clonoSEQ measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological features.

The clonoSEQ Assay is a single-site assay performed at Adaptive Biotechnologies Corporation.

Special Conditions for Use:

- For *in vitro* diagnostic use.
- For prescription use only (Rx only).

Limitations:

- clonoSEQ is for use with bone marrow specimens collected in EDTA tubes.
- Results should always be used in combination with clinical examination, patient medical history, and other findings.
- Results may vary according to sample time within the course of disease or by sampling site location.
- clonoSEQ may overestimate MRD frequencies near the limit of detection (LoD).
- MRD frequency LoD varies based on the amount of DNA tested; using less DNA input may prevent MRD detection at low frequencies.
- The volume and cellularity of sampled input material may affect the ability to detect low levels of disease.
- Sample processing and cell enrichment strategies may affect the measured MRD frequency.
- False positive or false negative results may occur for reasons including, but not limited to: contamination, technical, and/or biological factors.
- MRD values obtained with different assay methods may not be interchangeable due to differences in assay methods and reagent specificity.

For important information about the FDA-cleared uses of clonoSEQ, including test limitations, visit clonoseq.com/technical-summary.

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