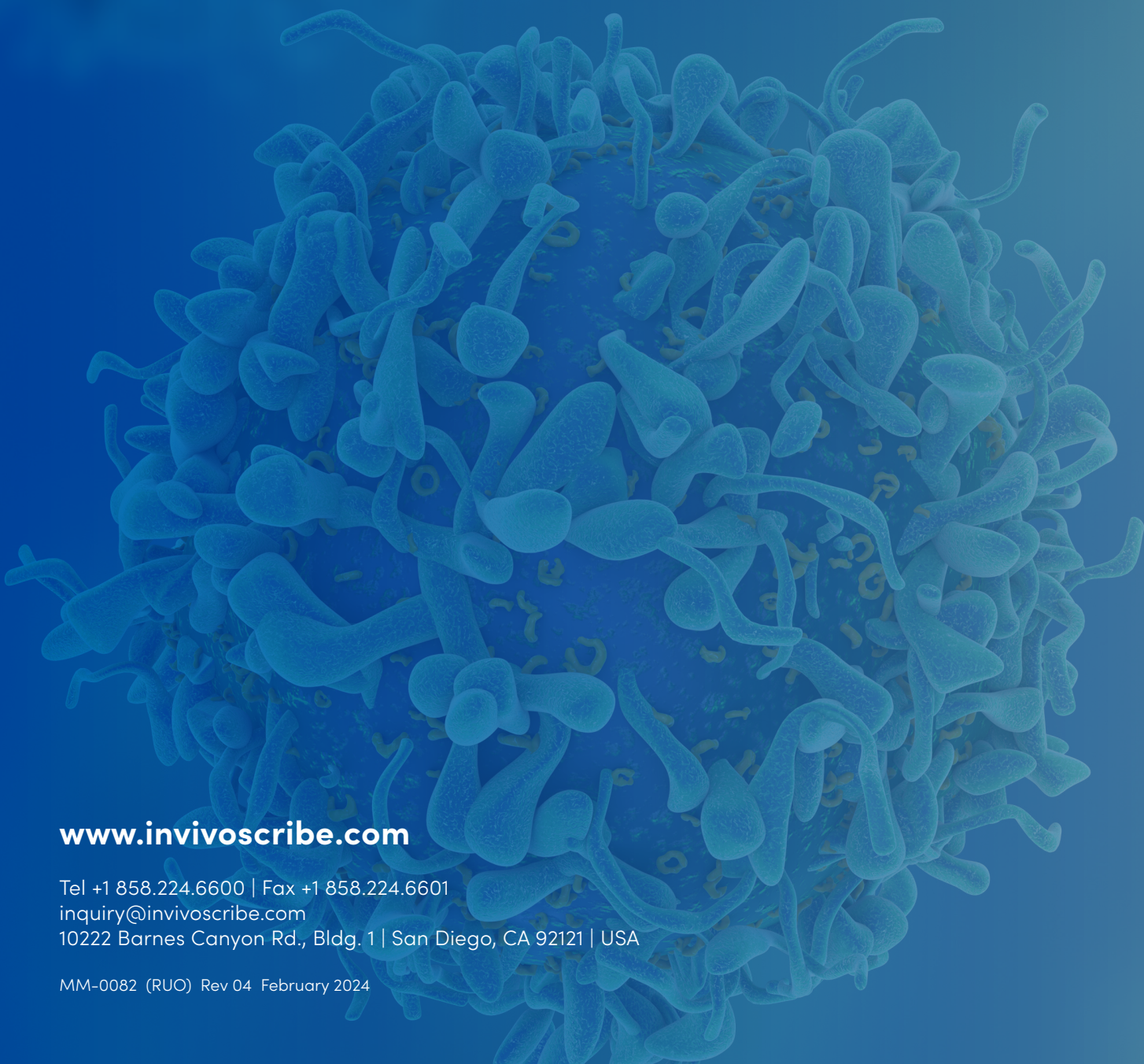




T-Cell Receptor Gamma Capillary Electrophoresis Assays

Research Use Only (RUO)



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1. Overview of Assays

Both Invivoscribe's T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 and *TCRG* Gene Clonality Assay were designed to identify T-cell clonality in suspect lymphoproliferations and are to be used in conjunction with other laboratory tests and results interpreted in the context of all available information. Despite this similarity, there are some noteworthy differences.

The *TCRG* Gene Clonality Assay includes two master mixes: *TCRG* Tube A and *TCRG* Tube B. *TCRG* Tube A contains primers that target the V γ 1-8 + V γ 10 genes and J γ 1.1, J γ 1.3, J γ 2.1, and J γ 2.3 genes (also known as J γ P1, J γ 1, J γ P2, and J γ 2, respectively), generating 4 polyclonal distribution size ranges. *TCRG* Tube B contains primers that target the V γ 9 + V γ 11 genes and J γ 1.1, J γ 1.3, J γ 2.1, and J γ 2.3 genes, generating 4 polyclonal distribution size ranges (see figure).

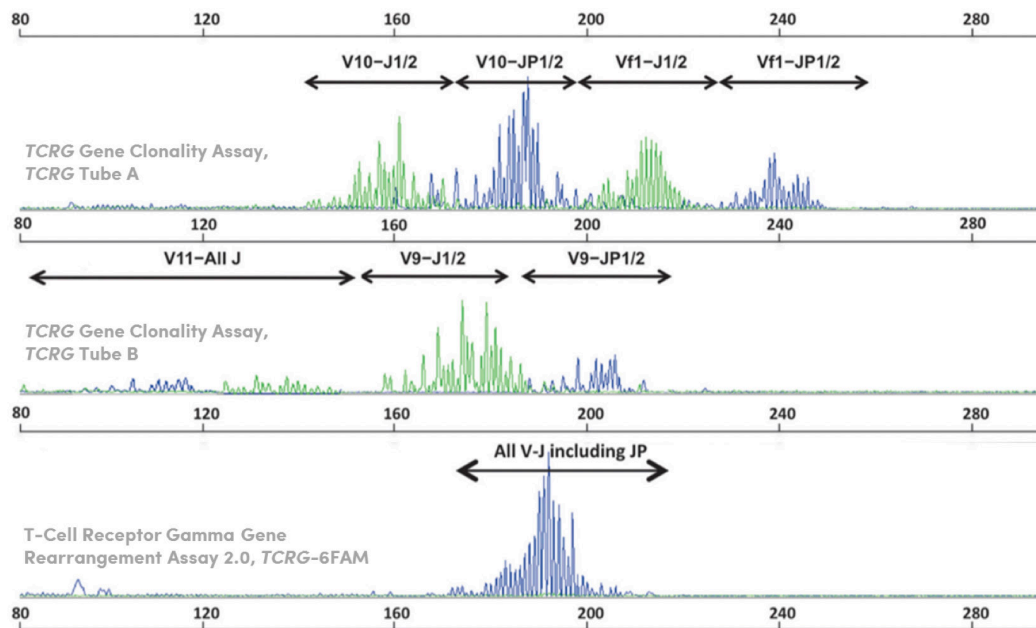
Conversely, the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 includes a single master mix, *TCRG* – 6FAM, which targets genes described in lymphoid malignancies, including the V γ 2, 3, 4, 5, 8, 9, 10, & 11 and J γ 1/J γ 2, J γ P, and J γ P1/J γ P2 regions. The resulting polyclonal background lies within a single valid size range, generating a more robust and easily interpreted signal in comparison to other *TCRG* clonality assays which have multiple valid size ranges. Moreover, this design is better suited to detect *TCRG* gene rearrangements in FFPE samples, due to its smaller valid size range of 159 bp to 207 bp (see figure).

Some of the benefits of the T-Cell Receptor Gamma Gene Rearrangement 2.0 Assay include:

- Allows a higher sample throughput with the single master mix assay
- Offers easy setup and simpler interpretation than the two-tube approach
- Generates smaller amplicon sizes, meaning better success when testing FFPE samples
- Reduces the DNA required for testing by half by reducing PCR reactions from two to one

Figure 1: GeneScan analysis indicating rearrangement valid size ranges generated from the same polyclonal sample with the assays listed below. Figure adapted from: Marine, A., *et al.*, (2019) *HemaSphere* 3(3):e255.

- (A) *TCRG* Gene Clonality Assay, *TCRG* Tube A master mix;
- (B) *TCRG* Gene Clonality Assay, *TCRG* Tube B master mix;
- (C) T-Cell Receptor Gamma Gene Rearrangement Assay 2.0, *TCRG*-6FAM master mix



2. Assay Performance Characteristics

These two assays were designed differently, thus the results generated with each assay are interpreted differently. The primary improvements of the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 over the *TCRG* Gene Clonality Assay are the addition of JyP target and consolidation of multiple polyclonal distributions into a single distribution. When PCR products are grouped into a single distribution, it generates an increased signal, improving sensitivity and reducing the likelihood of false positive from minor peaks in dispersed repertoires. For example, minor peaks in the V γ 11 valid size range can be mistakenly reported as significant due to lack of other polyclonal peaks within that distribution.

Because the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 targets more regions compared to the *TCRG* Gene Clonality Assay, it detects more types of rearrangements. Furthermore, the different primer designs used by these assays could exhibit variability when comparing results generated by the two assays. If a primer binding site utilized by the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 is mutated, the intended primer may not bind efficiently and result in low amplification of the target in question; *TCRG* Gene Clonality Assay primers may bind at a different location and amplify the same target. The opposite may be true as well.

Overall, we do expect a high degree of concordance between the two assays, but it is not expected to be 100%, as these are different assays with unique primer designs. The following references compare the and describe the characteristics and workflow parameters of the one-tube and/or two-tube assays:

1. **Assay Design Affects the Interpretation of T-Cell Receptor Gamma Gene Rearrangements¹**
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2963914/>
2. **A Single-Tube, EuroClonality-Inspired, TRG Clonality Multiplex PCR Aids Management of Patients with Enteropathic Diseases, including from Formaldehyde-Fixed, Paraffin-Embedded Tissues²**
[https://jmd.amjpathol.org/article/S1525-1578\(18\)30173-9/pdf](https://jmd.amjpathol.org/article/S1525-1578(18)30173-9/pdf)
3. **A New and Simple TRG Multiplex PCR Assay for Assessment of T-cell Clonality³**
https://journals.lww.com/hemasphere/Fulltext/2019/06000/A_New_and_Simple_TRG_Multiplex_PCR_Assay_for.8.aspx

3. Additional Positive Controls

While both assay kits include positive and negative controls, Invivoscribe offers additional controls that are compatible with these kits. Please see Table 1 for details.

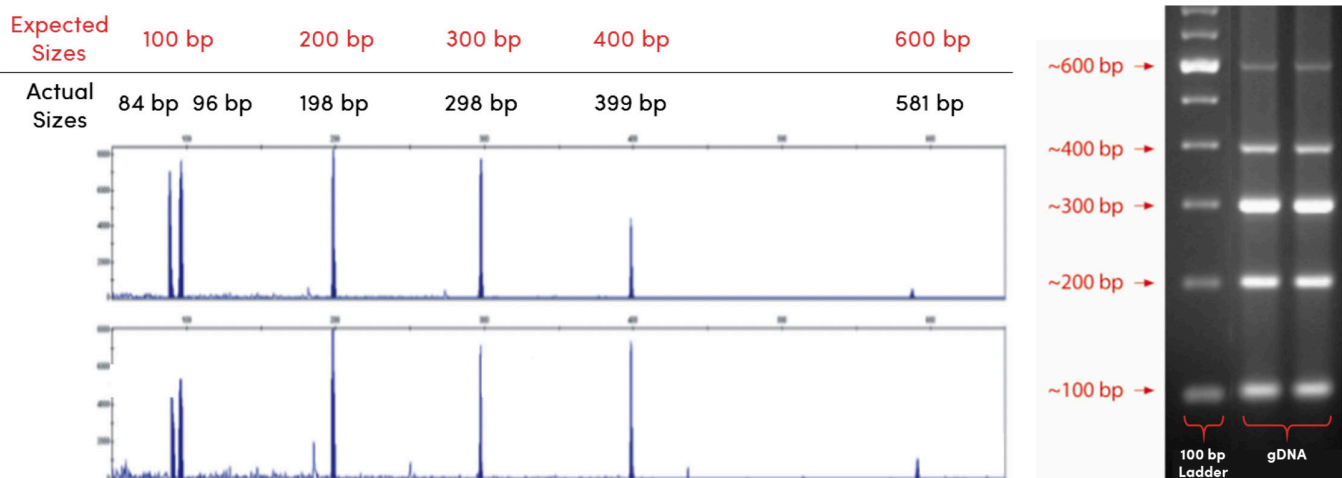
Table 1. Positive Controls Compatible with either or both TCRG assays

Part Number	Description	Product Size(s)	
		TCRG Gene Clonality Assay	T-Cell Receptor Gamma Gene Rearrangement Assay 2.0
40880190	100% IVS-0004 Clonal Control DNA	TCRG Tube A: 211 bp TCRG Tube B: n/a	TCRG – 6FAM: 179 bp and 188 bp
40880430	100% IVS-0008 Clonal Control DNA	TCRG Tube A: 218 bp and 229 bp TCRG Tube B: n/a	TCRG – 6FAM: 195 bp and 207 bp
40880490	100% IVS-0009 Clonal Control DNA	TCRG Tube A: 212 bp TCRG Tube B: 115 bp	TCRG – 6FAM: 188 bp and 191 bp
40881210	100% IVS-0021 Clonal Control DNA	TCRG Tube A: 211 bp TCRG Tube B: 143 bp and 167 bp	TCRG – 6FAM: 183 bp and 188 bp

4. Sample Integrity

Invivoscribe capillary fluorescence assays generate robust results using genomic DNA (gDNA) extracted from a wide array of specimen types. If the integrity of the sample is in question, the Specimen Control Size Ladder master mix can be used to verify the quality and quantity of the extracted gDNA is suitable to generate results with Invivoscribe assays. Specimen Control Size Ladder master mixes are included with most Invivoscribe kits, including the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0. Examples of the expected results for Gel and ABI Fluorescence detection with this master mix are shown in Figure 2, respectively:

Figure 2: Expected results amplifying gDNA with: (Right) the Specimen Control Size Ladder – Unlabeled for Gel Detection (Catalog #20960020). Expected product size are indicated in red; a 100 bp ladder is also shown for size reference. (Below) the Specimen Control Size Ladder – 6FAM for ABI Fluorescence Detection (Catalog #20960021). Expected product sizes are indicated in red and actual product sizes are indicated in black.



5. Sample Interpretation

Many publications have indicated T-cell receptor gamma gene rearrangement analysis is useful as an ancillary test in the diagnosis of T-cell neoplasms.¹⁻⁶ However, the design of the assay can have a large impact on assay interpretation, correlating increasing assay complexity with more complicated and difficult interpretation.^{1,3}

The T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 was designed with this consideration in mind, simplifying interpretation by using an individual, yet comprehensive, master mix labeled with one fluorochrome that generates a single, robust valid size range. This is a major improvement in comparison to the *TCRG* Gene Clonality Assay, which uses two master mixes labeled with two fluorochromes that generate a total of eight valid size ranges for interpretation. A comparison of assay interpretation guidelines is provided in Table 2.

The higher complexity of the *TCRG* Gene Clonality Assay can lead to false positive results due to low-amplitude polyclonal distributions with pseudoclonal peaks.¹ Because of the limited repertoire generated by *TRG* rearrangements, amplification of a sample with a high tumor load and limited number of T-cells can generate products that appear to be (oligo)clonal or pseudoclonal.⁶

Table 2. Comparison of Invivoscribe *TCRG* Assay Interpretation Guidelines

Interpretation by Assay		Final Call (Sample Report)
<i>TCRG</i> Gene Clonality Assay Valid Size Range <i>TCRG</i> Tube A: 145 bp – 255 bp <i>TCRG</i> Tube B: 80 bp – 220 bp*	T-Cell Receptor Gamma Gene Rearrangement Assay 2.0 Valid Size Range <i>TCRG</i> – 6FAM: 159 bp – 207 bp	
1 or 2 significant peaks within the valid size range(s). Significant Peak: 3X amplitude of 3rd highest peak within the same polyclonal distribution	1 or 2 significant peaks within the valid size range Significant Peak: 3X amplitude of lower neighboring peak	Detection of <i>TCRG</i> Gene Rearrangements, consistent with the presence of a clonal cell population.
N/A	3 or more significant peaks within the valid size range Significant Peak: 3X amplitude of lower neighboring peak	Detection of <i>TCRG</i> Gene Rearrangements, consistent with the detection of biclonality or oligoclonality.
Absence of significant peaks within the valid size range(s)	Absence of significant peaks within the valid size range	Negative for detection of <i>TCRG</i> Gene Rearrangements.

*Interpret peaks within context of all sample information.

Sample Analysis and Interpretation using the IdentiClone® RUO *TCRG* 2.0 software

The IdentiClone RUO *TCRG* 2.0 software provides an objective interpretation of raw data files (FSA) generated by ABI 3500 and ABI 3500xL instruments to identify clonal gene rearrangements in unknown samples. Software interpretation includes assessment of the raw data files (FSA) generated by the ABI 3500/3500xL instruments while referencing a configured platemap for sample traceability. Each master mix test set, including samples, a positive control, a negative control, and a no template control, is considered as a “run.” These runs can be configured individually using the Software Plate Setup function and loaded onto the same plate along with additional runs. After detection is complete, the data files are uploaded to the Software, which proceeds with analysis, referencing the platemap to complete the analysis for that sample.

6. Protocol Tips: T-Cell Receptor Gamma Gene Rearrangement Assay 2.0

Importing Plate Layout into GeneMapper

1. Open a new project and select **Microsatellite** for the project type.
2. Add raw data files derived from CE analysis to the project using the **Add samples to Project** icon in the toolbar.
3. Once the samples are added, verify that **Analysis Method** selected is **Microsatellite Default** and that the appropriate **Size Standard** is selected.
 - If necessary, select samples and press the **Analyze** green play button in the toolbar.
 - There will be a **green, yellow, or red** symbol in the SQ column for each analyzed sample.
4. If the symbol is **red**, the software will not calculate the peak sizes or display the sample data. In this case, view the size standard chart by selecting samples and clicking the **Size Match Editor** icon in the toolbar to verify the peak sizes were correctly identified.
 - If the SQ peaks were called correctly, click **Override SQ**, and then **Apply**.
 - If some peaks were called incorrectly, re-assign the peaks by right clicking and selecting the correct size values.
 - The GS 400 HD ROX size standard provides 21 labeled fragments of: 50, 60, 90, 100, 120, 150, 160, 180, 190, 200, 220, 240, 260, 280, 290, 300, 320, 340, 360, 380, and 400 nucleotides (nt).
 - The GS 600 LIZ Size Standard provides 36 single-stranded labeled fragments of: 20, 40, 60, 80, 100, 114, 120, 140, 160, 180, 200, 214, 220, 240, 250, 260, 280, 300, 314, 320, 340, 360, 380, 400, 414, 420, 440, 460, 480, 500, 514, 520, 540, 560, 580 and 600 nt.
5. Select any samples that have a green play button in the **Status** column of the GeneMapper table and press the **Analyze** green play button in the toolbar.
 - Please note, it may be necessary to lower the Minimum Peak Height threshold in order to detect all peaks in a Gaussian distribution:
 - Select **GeneMapper Manager** from the **Tools** menu, navigate to the **Analysis Methods** tab, and open the **Microsatellite Default Analysis Method Editor**.
 - Navigate to the **Peak Detector** tab, select **User Specified (rfu)** toggle, and input the desired peak height for 6FAM dye.
 - If changes are made, click the **Analyze** green play button in the toolbar.
6. In the GeneMapper table, highlight the samples of interest and select **Display Plots** in the GeneMapper toolbar.
7. Once the Display Plot is open, verify that **Microsatellite Default** is selected in **Plot Settings** and the appropriate fluorophore is selected (6FAM).
 - Select/Deselect the associated colored boxes in the toolbar, OR navigate to the **View** menu in the **Display Plot**, select **Dyes**, and select the appropriate dyes.
 - As a reminder, 6FAM is **Blue**, HEX is **Green**, NED is **Yellow** or Black and ROX is **Red** in GeneMapper v4.0.
8. In order to view the peak size and height, select the **Sizing Table** icon in the toolbar.

Recommended Injection Parameters and Peak Detector Settings for the T-Cell Receptor Gamma Gene Rearrangement Assay 2.0

Injection Parameters*

Parameter	Injection Time	Injection Voltage	Capillary Length	Polymer	Dye Set	Oven Temp	Run Time	Run Voltage	PreRun Time	PreRun Voltage	Data Delay
Value	7 sec.	1.0 kVolts	50 cm	POP7	G5	60°C	1630 sec.	19.5 kVolts	180 sec.	15 kVolts	1 sec.

Peak Detector Settings*

Parameter	Peak Detector Algorithm	Minimum Peak Height	Blue	Orange	Valid Size Range
Value	Basic	User Specified (RFU)	50	50	159 bp – 207 bp

*Please refer to the user manual for further instructions.

Analyzing Samples in GeneMapper

- Examine all assay controls prior to interpretation of sample results. If the controls do not yield the correct results, the assay is not valid and the samples should not be interpreted.
- When analyzing the samples in GeneMapper, only analyze peaks within the valid size range of the master mix.
- To determine whether a peak is clonal or polyclonal, compare the height of the peak to the height of the polyclonal background within the same sample.
 - A validation study is recommended to determine an appropriate peak height ratio.
- Do not use RFU values to determine whether a peak is clonal, as RFU values can be affected by a variety of factors, such as the capillary array and laser life.

Troubleshooting Size Quality (SQ) Error(s)

A SQ Error indicates that GeneMapper did not identify the size standard peaks correctly, causing the generated products to be identified at an incorrect size. Most SQ errors are caused by saturated signal(s), resulting in spectral pullup and mis-identification of peak sizes. If this type of error is observed in undiluted positive controls and the size standard peaks are identified correctly or corrected, the SQ Error is of no significance since control validity relies on the presence or absence of a peak at the expected size. However, if signal saturation is observed in the negative control, sensitivity controls, or unknown samples, the run must be repeated on the ABI instrument to prevent result misinterpretation. Before repeating the ABI run with samples exhibiting saturated signal(s), adjust the injection conditions and/or dilute amplified products. Please note that diluting unknown sample amplicons could dilute a weak clonal product below the assay level of detection. The steps below will correct SQ Errors:

1. Verify the size standard peaks are correctly identified in the GeneMapper software prior to reviewing the data by selecting the samples then clicking the **Size Match Editor** icon in the tool bar.
2. If the peaks labeled with SQ Errors were called correctly, click **Override SQ**, then click **Apply**.
3. If the size standard peaks are identified incorrectly, (in the **Size Match Editor**) manually reassign the ROX size standard peaks to match the expected sizes: Right click on the incorrect size value and select the correct size value, then click the **Override SQ** button.
4. Repeat step(s) 2 or 3, above, for all samples indicating an SQ Error based on the peak size verification result (step 1).
5. Click the **Analyze** green play button to reanalyze the data.
 - The data will update to display the revised product sizes.

If SQ Errors continue to occur, recalibrate the ABI instrument per the manufacturer instructions. Further optimization to reduce the number of SQ Errors includes adjusting the volume of size standard added to each well of the ABI plate.

Troubleshooting Miscalled/Unidentified Peaks

Another potential issue that may be encountered includes unidentified peaks which are miscalled as belonging to an adjacent peak. This phenomena occurs when the electropherogram indicates two adjacent peaks and the peak table only indicates one peak. Subsequently, when this data is pasted into the Algorithm Worksheet, the calculation does not identify a potentially significant peak because there is no adjacent peak to which it can be compared. This can easily be remedied by changing the Peak Detection settings in GeneMapper, as the software uses the settings **Polynomial Degree** and **Peak Window Size** to determine the start and end of each peak. The default value for Polynomial Degree is 3 and Peak Window Size is 15. Please see Thermo Fisher language regarding these settings below:⁷

- Polynomial Degree and Peak Window Size settings affect the peak detection sensitivity. Adjust these parameters to detect a single base pair difference while minimizing the detection of shoulder effects and/or noise (see Table 3 and Figure 3).

Table 3. Change peak detection sensitivity using Polynomial Degree and Peak Window Size

Function	Polynomial Degree Value	Peak Window SizeValue
Increase Sensitivity	Higher	Lower
Decrease Sensitivity	Lower	Higher

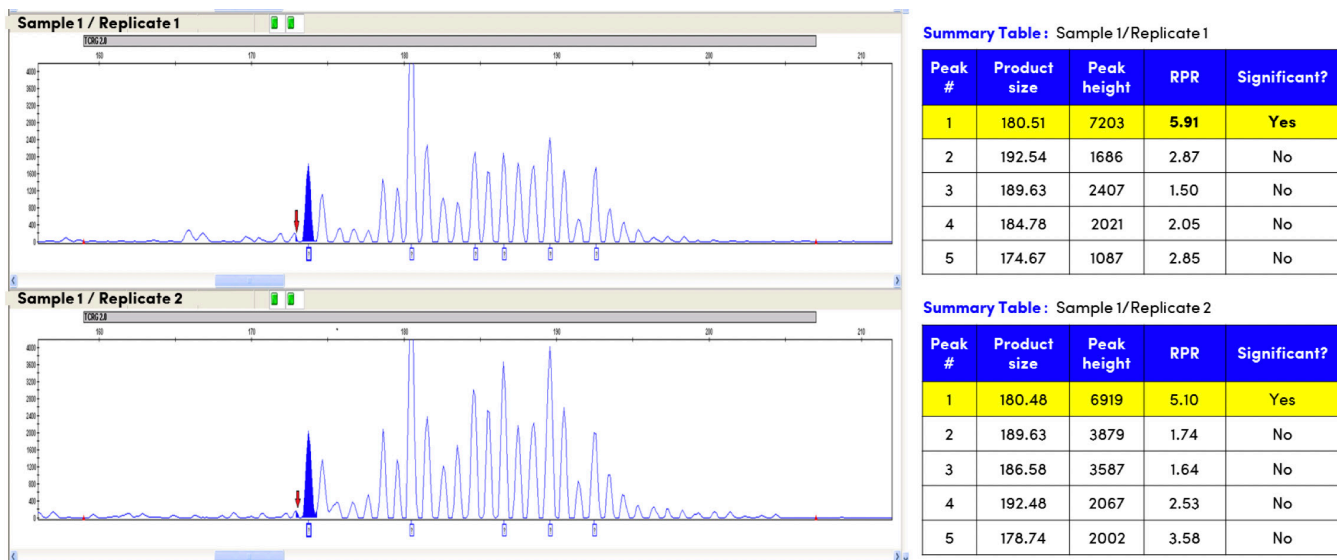
- The peak window size functions with the polynomial degree to set the sensitivity of peak detection. The peak detector calculates the first derivative of a polynomial curve fitted to the data within a window that is centered on each data point in the analysis range.
- Using curves with larger polynomial degree values allows the curve to more closely approximate the signal and, therefore, the peak detector captures more of the peak structure in the electropherogram.
- The peak window size sets the width (in data points) of the window to which the polynomial curve is fitted to data:
 - Higher peak window size values smooth out the polynomial curve, which limits the structure being detected.
 - Smaller window size values capture more of the peak structure.

To adjust these settings, follow the steps below:

1. Open **GeneMapper** and from the top menu, select **Tools**, then **GeneMapper Manager**.
2. Navigate to the **Analysis Methods** tab to view available analysis methods.
 - An existing **Analysis Method** can be edited, or (the preferred option) an existing **Analysis Method** can be edited then saved with a new name.
3. Select **Save as...** to create a copy of the selected analysis method with a new name.
4. Select the **Analysis Method** created in the previous step and click **Open**.
5. Navigate to the **Peak Detector** tab, and set **Peak Detection Algorithm** to **Advanced**.
 - The **Peak Window Size** and **Polynomial Degree** settings can now be altered.
6. Test a few different conditions with a sample set to identify the optimal settings for this instrument.
 - Use the guidelines in Table 3 to determine how to adjust these settings based on the observed issue and anticipated resolution.

Figure 3. Sample data generated with GeneMapper using the default *Peak Detection Algorithm* settings vs. optimized *Peak Detection Algorithm* settings.

Default *Peak Detection Algorithm* settings: *Polynomial Degree* = 3; *Peak Window Size* = 15. Notice the peak indicated by the red arrow is not identified in the peak table, rendering the 173 bp peak as not significant (since it is compared to the higher peak on the left).



Optimized *Peak Detection Algorithm* settings: *Polynomial Degree* = 3; *Peak Window Size* = 11. Notice the peak indicated by the red arrow is now identified in the peak table, rendering the 173 bp peak as **significant** (since it is now compared to the lower peak on the right).



7. IdentiClone RUO TCRG 2.0 Software Operational Instructions

Plate Setup Function

1. Open the IdentiClone RUO TCRG 2.0 Software.
2. Create a plate map using the Plate Setup function.
3. Enter information into the 4 fields located above the plate map: Plate Name, Results Group, File Name Convention, and Barcode (Optional)
 - These fields are limited to 50 characters or less and may only include letters (A-Z, a-z), numbers (0-9), hyphen (-) and underscore (_). No spaces or special characters (other than specified) will be accepted.
 - File Name Convention and Results Group will be automatically populated with default settings.
4. Configure runs to be included on the plate map.
 - Runs must be configured before annotating the plate.
 - Up to 24 runs can be configured per plate (A run represents a set of controls and corresponding samples).
5. Select each well assigned to a run and enter required information on the right side of the window. Save well following verification of information.
 - Select the appropriate Sample Type from the designated dropdown box: PC, NC, NTC or Sample.
 - Enter Sample Name, a unique identification associated with a patient sample.
 - Confirm that the correct Run is assigned to the sample.
 - (Optional) Enter Notes, if any.

Platemap rules:

- Each run must include a Positive, Negative and No Template Control; these controls will be indicated on the platemap as PC (positive control), NC (negative control), and NTC (no template control)
 - Fields marked with asterisk (*) are required to save a well.
 - The fields Sample Name and Notes may only contain 50 characters or less.
 - Sample Name can only include letters (A-Z, a-z), numbers (0-9), hyphens (-) and underscores (_). No spaces or special characters (other than specified) are allowed.
 - The highlighted well position in the Plate Setup will become bold once all parameters are defined and saved for a particular sample or control.
6. Upon defining and saving all samples and controls for every run in the plate, click Save Plate.
 7. Select the directory filepath for the output files (CSV and LIVS).
 - The CSV file contains platemap information and will be imported to the ABI 3500xL or ABI 3500xL Dx Genetic Analyzer.
 - The LIVS file contains platemap specific data required for analysis and will be used in conjunction with the respective ABI 3500xL or ABI 3500xL Dx result files (i.e., FSA file).

Important: Once generated, do NOT alter CSV and LIVS. If any further modifications are needed, generate a new platemap to obtain a new set of paired CSV and LIVS output files.

8. Save/Print PDF template of plate map (Optional).

Analysis Function

1. Open the IdentiClone RUO TCRG 2.0 Software.
2. Select the Analysis tool from the home user Interface.
 - Verify that both FSA and LIVS files for the associated run(s) and plate(s) are located in the same directory filepath.
3. Click Analyze FSA and LIVS files (Figure 18).
 - Navigate to the directory filepath containing the FSA and LIVS files, select the folder, and confirm the selection. Multiple plates can be processed simultaneously, provided all corresponding LIVS and FSA files are present within the selected folder, including those in nested folders.

Important: Do not edit FSA files generated by the ABI 3500xL platform. These FSA files are validated with LIVS files from the software. Uploading files incorrectly will halt analysis process. An error message window will pop-up with a corresponding error code. (See Table 3) Sample results are generated at this time. These results are for Research Use Only purposes and should not be used for any determination of medical diagnosis.

4. Select samples for report generation ()
 - Click checkbox () to toggle the selection of any run report or sample report
 - If a run is invalid, no sample reports will be selectable for samples from that run.
5. Click Generate Reports. Select directory for reports to be saved, Click Select Folder.
 - A report password is set by the Admin user and is required to view the PDF reports.
 - Results are grouped by Sample Name
6. A Run Report is generated by the software for every run selected following analysis.
 - Traceable run information and control validity is recorded on Page 1 of the Run Report generated by the software
 - A summary of samples included in a run is included starting on Page 2 of the Run Report generated by the software
7. A Sample Report is generated by the software for every sample selected following analysis.
 - Sample information and sample result are recorded in the Sample Report generated by the software.
 - Run information is included in the Sample Report to provide traceability

8. Available Products

Catalog Number	Description	Quantity
12070101	T-Cell Receptor Gamma Gene Rearrangement Assay 2.0	33 reactions
12070111	T-cell Receptor Gamma Gene Rearrangement Assay 2.0 MegaKit	330 reactions
S1000001	IdentiClone® RUO TCRG 2.0 Software	1 software package

These products are for Research Use Only. Not for use in diagnostic procedures.

References 1. Cushman-Vokoun, AM *et al.*, (2010) *Journal of Molecular Diagnostics* 12(6):787-796. doi: 10.2353/jmoldx.2010.090183 | 2. Derrioux, C *et al.*, (2019) *Journal of Molecular Diagnostics* 21(1): 111-122. doi: <https://doi.org/10.1016/j.jmoldx.2018.08.006> | 3. Armand, M *et al.*, (2019) *Hemasphere* 3(3): e255. doi: 10.1097/HS9.0000000000000255 | 4. Langerak, A *et al.*, (2012) *Leukemia* 26, 2159–2171. doi: <https://doi.org/10.1038/leu.2012.246>. | 5. van Krieken, J *et al.*, (2007) *Leukemia* 21, 201–206. doi: <https://doi.org/10.1038/sj.leu.2404467> | 6. van Dongen, J *et al.*, (2003) *Leukemia* 17, 2257–2317. doi: <https://doi.org/10.1038/sj.leu.2403202> | 7. Applied Biosystems 3500/3500xL Genetic Analyzer User Guide (Part Number 4401661 Version: c). <https://tools.thermofisher.com/content/sfs/manuals/4401661.pdf>

