(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 September 2014 (25.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/152129 A1

(51) International Patent Classification:
C12Q 1/68 (2006.01) *G01N 31/00* (2006.01)
G01N 33/50 (2006.01) *G06K 9/00* (2006.01)

(21) International Application Number:
PCT/US2014/026982

(22) International Filing Date:
14 March 2014 (14.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/782,033 14 March 2013 (14.03.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

[Continued on next page]

WO 2014/152129 A1

(54) Title: A MATHEMATICAL MUSICAL ORCHESTRAL METHOD FOR PREDICTING CLASSES OF PATIENTS FOR MEDICAL TREATMENT

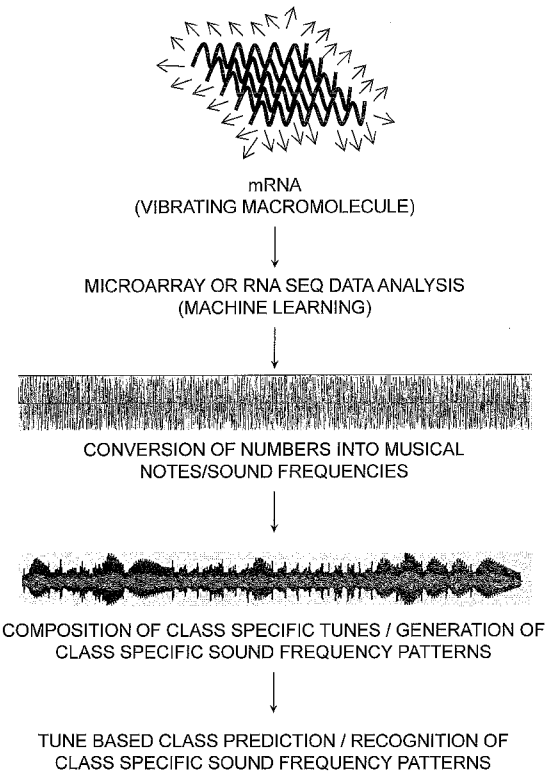


FIG. 1

(57) Abstract: Methods for classifying patients as responders or non-responders to treatment of a disease and predicting recurrence of disease in a patient using audio tunes are provided.

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

A MATHEMATICAL MUSICAL ORCHESTRAL METHOD FOR PREDICTING CLASSES OF PATIENTS FOR MEDICAL TREATMENT

This patent application claims the benefit of priority from U.S. Provisional Application Serial No. 61/782,033 filed March 14, 2013, the content of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a novel method of predicting classes of patients for medical treatment.

BACKGROUND OF THE INVENTION

Gene expression analysis provides the foundation for studying thousands of individual alterations in gene function. These alterations in mRNA expression can be viewed as biomarkers. Whole genome gene expression assays are routinely used to predict treatment responses in human diseases (Xiang et al. *Curr Opin Drug Discov Devel.* 2003; 6:384-95; and Lee J.S. and Thorgeirsso, S.S. *Gastroenterology* 2004; 127:S51-55). A major limitation with the gene expression data analysis methods is the low prediction accuracy with small sample size (Roepman P. *Bioanalysis* 2010; 2:249-62). Studies have indicated that the prediction accuracy can be increased by increasing the sample size. For example, Ein-Dor *et al.* reported that ~3000 samples are needed to get good prediction accuracy necessary for the clinical applications in lung cancer (*Proc Natl Acad Sci U S A* 2006; 103:5923-5928). It has also been proposed that gene expression data can be supplemented with copy number variation and Single Nucleotide Polymorphism (SNP) information to obtain the accuracy required for class prediction (Kalia M. *Metabolism* 2013; 62:S11-14). Using more than one technique, however, will increase the cost of the test and also the complexity associated with the present data analysis methods.

Currently, a supervised clustering method is used to analyze microarray data to classify a patient for treatment response (Speed, T. (Ed.) 2003 Statistical analysis of gene expression microarray data. Chapman and Hall/CRC, NewYork).

The goal of these approaches is to relate gene expression to different target classes and to use this new information to produce a prediction model. Often, this approach is called pattern recognition. There are many different algorithms, such as linear predictors, neural nets, etc. These are very powerful tools, but each has its own advantages and disadvantages. One would need to know how to select the right method, structure, and definition for a given problem. This approach may not provide accurate results to take clinical decision. For example, a prediction model developed by Gordon *et al.* could reach only 74% predicting accuracy with ~400 samples; a good outcome but not excellent result (Gordon et al. *Can Epidemiol Biomarkers Prev* 2003; 12: 905-910).

Musical algorithms have been widely used to compose tunes for entertainment purposes. There is a limited usage in medical musical therapy applications (Carr et al. *PLoS One* 2013; 8:e70252).

SUMMARY OF THE INVENTION

The present invention relates to a method of using a mathematical musical orchestral algorithm, referred to herein as MMOA, to predict response of a patient suffering from a disease to a selected treatment for the disease. As demonstrated herein, this novel MMOA is suitable for small sample size with high prediction accuracy.

Accordingly, an aspect of the present invention relates to a method of classifying a patient suffering from a disease as a responder or a non-responder to a selected treatment for the disease.

In one embodiment, the disease is cancer.

In one embodiment, the disease is lung cancer.

This method comprises first analyzing a tissue sample from the patient with a microarray. The data set generated from the microarray is then filtered using a standard microarray data analysis method and an audio tune and/or sound frequency pattern capturing the filtered data from the microarray is then established via the MMOA. The patient is then classified as a non-responder or responder to the selected treatment based upon the assigned audio tune and/or sound frequency pattern being similar to an audio tune and/or sound frequency pattern already previously identified for known responders or known non-responders.

In one embodiment of the present invention, the MMOA is manually operated.

In another embodiment, a web based program converted from the manually operated MMOA and referred to as sound frequency pattern generation and recognition algorithm or SFPGRA is used.

The classification method of the present invention is also useful in predicting recurrence of a disease such as cancer in a patient.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the methods and materials are described herein. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 provides a schematic of the mathematical musical orchestral algorithm protocol used in the method of the present invention for class prediction. In this embodiment of the present invention, mRNA molecules are considered as the vibrating macromolecules and their vibrations/sound frequency patterns (SFPs) are indirectly estimated from a microarray based gene expression analysis. The fluorescent intensity values obtained from DNA microarrays were converted to musical notes/sound frequencies, and the notes were used to compose class specific tunes/SFPs. Patients suffering from cancer are classified into responder or non-responder based on the tunes/SFPs.

Figure 2 provides a flow diagram of the steps involved in the development of the class prediction model of the present invention. The model was trained and tested with retrospective clinical samples. The model was built with non-responders and responders training data set and fine-tuned with known test data sets. A double blind test was conducted to test and validate the prediction accuracy of the model.

Figures 3A through 3F are musical compositions prepared by SFP generation. Normalized gene expression intensity of top 50 biomarkers was converted into musical notes/sound frequencies. A coherent music/SFP specific to each group (Figure 3A) and patient (Figures 3B and 3C) were composed/generated to train the model. Eight data sets were treated as the "unknowns" and the tunes/SFPs were used to validate the model (Figures 3D-3F). A double blind test was conducted to test and validate the prediction accuracy of the model. Figure 3A is an example of a Reference/Theme/Framework tune/SFP specific to non-responders and responders patients composed/generated using non-responders/responders mean value. The tunes/SFPs were used as the reference tunes/SFPs to compose/generate known tunes/SFPs (training set). Figure 3B shows examples of known non-responder (training set) tunes/SFPs. Three non-responder tunes/SFPs were composed/generated and used as the training set. Figure 3C shows examples of known responder (training set) tunes/SFPs. Three responder tunes/SFPs were composed/generated and used as the training set. Figures 3D-3F show examples of unknown (test set) tunes. Eight tunes/SFPs (4R and 4NR) were composed/generated to validate the MMOA.

Figures 4A through 4G show class specific sound frequency pattern generation and recognition (SFPGR). Steps involved in sound frequency pattern generation and recognition are shown with sample data sets obtained from two unknown patients. Unknown 1 data were obtained from responder patient 8 and Unknown 2 data were obtained from non-responder patient 5. Figure 4A shows the random distribution of microarray signal intensities/numbers. Randomness was observed in the distribution of signal intensities of the top 50 biomarkers obtained by the conventional microarray data analysis. Figures 4B and 4C show random distribution of sound frequencies observed in unknown patient 1 data obtained from responder patient 8 and unknown patient 2 data obtained from non-responder patient 5, respectively. Only one patient in each group is shown as an example. Randomness was also observed in the distribution of signal intensities of the top 50 biomarkers after we converted the signal intensities into sound frequencies. Figures 4D and 4E show class specific sound frequency patterns of unknown patient 1 data obtained from responder patient 8 and unknown patient 2 data obtained from non-responder patient 5, respectively. A unique sound frequency pattern (SFP) specific to each class was generated after the class specific tunes with the top 50 biomarkers were composed. These patterns were stored in a data base

and compared with the SFPs of unknowns to assist in making clinical decisions with respect to a patient. Figures 4F and 4G are spectrograms converted from the sound frequency patterns from unknown patient 1 data obtained from responder patient 8 and unknown patient 2 data obtained from non-responder patient 5, respectively, which are useful for further pattern recognition purposes.

Figure 5 is a schematic of a deconvolution program. As shown, the musical notes/sound frequencies can be readily converted to gene symbol/ID and intensity information and linked to public databases and/or pathway analysis tools.

Figure 6 shows an overview of an embodiment of a data base structure for the present invention. In this embodiment, the data base comprises deidentified patients' clinical information, tissue specification, sample (RNA/DNA) details, microarray data, composed tunes, reference SFPs, and known and unknown SFPs.

Figures 7A through 7C show class prediction and data integration capabilities of MMOA. Flow charts showing the steps involved in the MMOA to discriminate the major classes and sub-classes for personalized medicine applications are depicted in Figures 7A and 7B, respectively. In Figure 7A class prediction was done with top 50 biomarkers specific for surgical treatment response (one parameter). Figure 7B shows use of the algorithm in subclass predictions such as chemotherapy response or radiotherapy or targeted therapy response in non-responder patients who are eligible for adjuvant chemotherapy or radio or targeted therapy. Figure 7C shows use of MMOA in the integration of gene expression data with 3-dimensional voxel intensity obtained from computed tomography (CT) scan image data to discriminate malignant nodules from benign nodules in patients at high risk for lung cancer.

Figure 8 provides an example of final data output from this method. As shown, clinical decision information can be obtained from a first level of the program. Gene list and the pathway information can be obtained from the next level. The details about SFPs are available in the third level. The raw data obtained from the entire gene expression/microarray data can be found in the last level.

Figures 9A through 9L provide an example of the wire frames used to develop the web-based sound frequency pattern generation and recognition algorithm (SFPGRA).

Tables A through K in Example 1 further describe the numbered elements and type as well as additional notations for the wireframes depicted in Figures 9A-9L.

DETAILED DESCRIPTION OF INVENTION AND EMBODIMENTS

Musical algorithms are used widely to compose tunes for entertainment purposes. Usage in medical musical therapy applications has been quite limited.

Since conventional machine learning algorithms cannot achieve the prediction accuracy required in a clinical setting for classifying patients suffering from a disease as responders or non-responders to a selected treatment, in the present invention a mathematical musical orchestral algorithm, referred to herein as MMOA, was integrated into the machine learning process. The MMOA is capable of handling complete gene expression data obtained from whole human genome microarray comprised of ~30,000 human genes. It can be used to analyze more than one clinical parameter such as stage, age, gender and smoking history etc. for class/sub-class predication purposes. It can be also used to predict responses such as, but not limited to, chemotherapy or radiology or targeted therapy response in patients suffering from late stage cancers.

The MMOA can be used for sub-class identification as well. For example, in the first step it can be used to discriminate non-responder from responder after, for example, a surgical treatment. The same algorithm can be used to prediction adjuvant chemotherapy response or radiotherapy or targeted therapy response in non-responder patients who are eligible for adjuvant chemotherapy or radio or targeted therapy.

As shown herein, the combination of mathematical machine learning and MMOA can greatly improve the prediction accuracy of the treatment response in patients suffering from cancer.

In the method of the present invention, a patient suffering from a disease is classified as a responder or a non-responder to a selected treatment for the disease by analyzing a sample from the patient using an RNA, DNA or protein microarray. In one embodiment, if the patient is suffering from cancer, the tumor or a portion thereof is excised from the patient for analysis. Core needle biopsy samples, fine needle aspirations as well as fresh, frozen and formalin-fixed paraffin-embedded tissues samples may also be used.

The data set generated from the microarray is then filtered. An audio tune and/or sound frequency pattern capturing the filtered data from the microarray is then assigned to the patient and the patient is classified as a responder or a non-responder to a selected treatment for the disease based upon the assigned audio tune and/or sound frequency pattern.

The method of the present invention was tested using a Non-Small Cell Lung Cancer (NSCLC) model. At present most of the Stage Ia NSCLC patients are not treated with adjuvant chemotherapy (Qi-Zhu et al. *J Clin Onco* 2010; 28: 4417-4424). Early identification of stage Ia patients likely to recur following surgery will allow the physician to target adjuvant chemotherapy to those patients for whom it is necessary. In stage Ib diseases, most of the patients are treated with adjuvant chemotherapy. However, a subgroup of patients do not recur and hence might not require adjuvant chemotherapy. In stage Ib patients, physician can avoid adjuvant chemotherapy to those who do not require it. Conventional detection and follow-up methods based on the clinical staging and clinic-pathological findings are insufficient to predict recurrence (Sriram et al. *Respirology* 2011; 16: 257-263).

In the present invention, the MMOA was used to convert mRNA signal intensities into musical notes/sound frequencies and class specific tunes/SFPs were composed/generated with the harmonized musical notes/SFPs. By listening and observing the class specific tunes/SFPs, one can discriminate the responders from non-responders of surgical treatment in these NSCLC patients.

While tests were performed on lung cancer patients, as will be understood by the skilled artisan upon reading this disclosure, the method of the present invention provides a simple, sensitive and cost-effective method which can be routinely used in any kind of human disease.

It is important to note that present gene expression data analysis methods considered mRNAs as the inert molecules and use their concentration information (signal intensity) to predict treatment response. In contrast, the present invention considers mRNAs as the vibrating molecules, and uses their macromolecular vibrations/SFPs extracted (from their signal intensity values) for class prediction.

Accordingly, the method of the present invention utilizes what is believed to be the first gene expression algorithm that involves two human senses (i.e. visual and listening) to

predict treatment response in human disease. This is believed to also be the first medical laboratory test that uses two human senses for diagnostics applications.

Since the MMOA predictions are based on the tunes/SFPs, it can be effectively used to predict mRNA extracted from Formalin Fixed Paraffin Embedded (FFPE) samples. Even in the absence of some biomarkers, the tunes/SFPs obtained from the remaining expressed genes can be used to identify the clinical outcome of the patient.

The preferred methods and materials are described below in examples which are meant to illustrate, not limit, the invention. Skilled artisans will recognize methods and materials that are similar or equivalent to those described herein, and that can be used in the practice or testing of the present invention.

EXAMPLES

Example 1: EXPERIMENTS

Conventional gene expression data analysis program uses the concentration/signal intensity information of mRNA to identify the differentially expressed genes for class prediction (Wong et al. *Bioinformatics* 2007; 23:998-1005). In the present invention, an algorithm referred to herein as MMOA was used to convert the signal intensities (numbers) into macromolecular vibrations/sound frequency patterns (SFPs). Class specific tunes/SFPs were composed/generated using coherent music/SFPs. The class specific tune/SFP was used to predict the clinical outcome of unknown patients. The principle of MMOA is shown in Figure 1. The MMOA was tested and validated using samples obtained from NSCLC patients and showed that this application is central to personalized onco-medicine. The functionality specifications of the class prediction model are shown in Figure 2.

Comparison with conventional microarray data analysis

Initially, a conventional microarray data analysis method was used to find out its prediction accuracy. The prediction accuracy of the conventional microarray data analysis was then compared with the MMOA.

Based on the clinical information, patients were classified as a Responder (R) if no recurrence was detected within 5 years after surgery. Otherwise, the patient was considered a Non-responder (NR). Twenty three non-responders and 13 responders were used to build and test the model, and 8 samples were treated as the "unknowns". Total RNA was amplified

and hybridized onto human whole genome microarrays (Affymetrix HGU-133 Plus 2.0). The microarray data was normalized using Robust Multi-array Average (RMA) procedure on Affymetrix GeneChip Operating Software (GCOS). For further analysis, the data was filtered and the probes that do not change were removed from the analysis.

Standard clustering procedures (e.g. hierarchical or sammon map) did not group the samples according to their status of responders or non-responders. Also, according to the limma analysis there were no differentially expressed genes between responders and non-responders group. This indicated that the differences between the two groups is more subtle and has to be addressed using more sophisticated and sensitive analysis. Analysis was performed in R statistical language using standard Bioconductor packages and custom-written code (see http: with the extension //bioconductor.org/ of the world wide web).

The classification model was learned on filtered data from responders (R) and non-responders (NR) using penalized regression procedure. The resulting classifier has a leave one out cross-validation accuracy of 0.89. In other words, the error of misclassification in training data is 0.11 implying that 9 out of 10 patients/samples are predicted correctly.

A confusion matrix of the classifier is given by the following:

		True	
	Object	**NR**	**R**
	NR	**22**	**3**
	R	**1**	**10**

One out of 23 non-responders (NR) 1 was incorrectly predicted, and 3 out of 13 responders (R) were incorrectly classified in a leave-one-out cross-validation procedure.

Classifier built on the training dataset was applied to predict the clinical outcome of the 8 unknown patients.

Mathematical Musical Orchestral Algorithm (MMOA)

A conversion rule was formulated to decipher the numbers (gene expression data/signal intensities) into musical notes/sound frequencies (see Table 1). After converting the numbers into pitches with rhythms, the notes were looked as a whole group. A pattern generation algorithm was created to generate sound frequency patterns (SFPs) ex: a string of

eight notes from G to E or recurring notes ex: a lot of G or F. A key/tonal center i.e. G major and F minor respectively were selected to compose the music/generate SFPs. A coherent piece of music/SFP was composed/generated by observing and listening to the music. A reference/theme/framework tune or reference SFP was composed/generated using the NR and R mean values (see Figure 3A). Known NR and R tunes/SFPs were composed/generated to fine tune the reference SFPs to train the model (Figure 3B and 3C). The tunes/SFPs were finalized by listening and observing to the composition/patterns, and fine tuned to match with the reference SFP/theme music by adjusting the location of the note or tempo etc. Microarray data from 8 patients were considered as the "unknown" test data set. A double blind test was performed to identify clinical outcome of 8 unknowns after fine tuned the model (Figures 3D-F). Steps involved in sound frequency pattern generation and recognition are shown with sample data set obtained from two unknown patients (unknown 1/responder patient 8 and unknown 2/non-responder patient 5) (see Figures 4A-4G). The tunes/SFPs are readily converted back to signal intensity and gene symbol/ID using a deconvolution program and can be linked to other public data bases (Figure 5). A data base was created with reference and known SFPs and were compared with unknown SFPs for class prediction (see Figure 6). The MMOA is a very versatile program and can handle more than one clinical parameter to classify a patient (see Figure 7A). The application of MMOA to discriminate sub-classes for personalized medicine is shown in Figure 7B. In addition MMOA can be used to integrate data obtained from two or more technologies. An example of an integration approach for radiogenomic application is shown in Figure 7C. Final data structure obtained from MMOA is shown in Figure 8. Clinical decision (responder or non-responder) can be obtained from the first level. Gene list, signal intensity and pathway information can be obtained from the second level. The details about SFPs are available in the third level. The raw data obtained from all the genes can be found in the last level. The manually operated MMOA program was converted into cloud/web based computer program which was named Sound Frequency Pattern Generation and Recognition Algorithm (SFPGRA). The wire frames used for the SFPGRA are shown in Figures 9A-9L. Tables A through K below further describe the numbered elements and type as well as additional notations for the wireframes depicted in Figures 9A-9L.

TABLE A: Corresponds to the Wireframe of Figure 9A

Title	Home
Version	1.0
Note:	

No.	Element	Type	Description
1	Forgot?	Link	Redirect the user to forgot username page
2	Forgot?	Link	Redirect the user to forgot password page
3	Login	Button	Authenticate the user's credentials

TABLE B: Corresponds to the Wireframe of Figure 9B

Title	Home
Version	1.0
Note:	

No.	Element	Type	Description
1	Username	Text	From database
2	Secret question	Text	From database
3	Secret answer	Input box	User will enter the secret answer to their question. Secret question will be asked only when user logs in and the cookie dropped during the last visit is not found.

TABLE C: Corresponds to the Wireframe of Figure 9C

Title	Compose home page
Version	1.0
Note: This page is available to users with composer role.	

No.	Element	Type	Description
1	Welcome username	Text	Compose username will have an option of dropdown list
2	Dropdown list	Dropdown list	From Settings user can change username, password and email address
3	Link	Link	This is landing page for composer
4	Dropdown list	Dropdown list	On the rollover of My Tunes options list will come.
5	Data grid	Data grid	List of Reference tunes.
6	Select Data version	Dropdown list	This will list the version of data set uploaded A data set is a collection 3 files uploaded by the admin or site user. These three files are "mean NR and R", known NR and R" and "Unknowns" Changing the value from the list will load the data from selected data set.

TABLE D: Corresponds to the Wireframe of Figure 9D

Title	Composer Reference Non-Responder OncoTune
Version	1.0
Note: Composer will compose the Reference Non-Responder OncoTune. The Reference Non-Responder OncoTune will be used in class prediction.	

No.	Element	Type	Description
1	Last updated	Text/ Date time	Date on which this version was last updated. This value gets updated when composer clicks Save this version button.
2	Comments	Text	Comments about tune
3	Mean NR notes	Staff	Notes generated from the Mean NR data uploaded.

			Using these notes composer will create reference NR tune.
4	Player	Music player	Play the notes from Mean NR notes
5	Reference NR OncoTune	Staff	On this staff composer will create new music by • Double clicking to copy the note. • Deleting notes from Tunes.
6	Copy all Notes from Mean NR to NR Tune	Button	Copy all notes from Mean NR to Ref NR OncoTune.
7	Clear NR Tune	Button	Clear Ref NR OncoTune staff
8	Bin	Image	Select a note and click bin delete it.
9	Save Changes	Button	Saves the Reference NR Tune

TABLE E: Corresponds to the Wireframe of Figure 9E

Title			Composer Reference Non-Responder OncoTune
Version			1.0
Note:			
No.	Element	Type	Description
10	Plays Together	Player	Plays all the tunes on the page
11	Check to apply composition rules	Checkbox	When checked the composition rules will be applied and notes will be highlighted. When unchecked composition rules will be removed and

			notes will come in normal/default colors.
12	Check to track the gene	Checkbox	When checked and composer rollovers mouse cursor on a notes it will show a popup at the mouse position with Gene information. When unchecked this feature will be turned off.

TABLE F: Corresponds to the Wireframe of Figure 9F

Title			Composer Reference Responder OncoTune
Version			1.0
Note: Composer will compose the Reference Responder OncoTune. The Reference Responder OncoTune will be used in class prediction.			
No.	Element	Type	Description
1	Last updated	Text/ Date time	Date on which this version was last updated. This value gets updated when composer clicks Save this version button.
2	Comments	Text	Comments about tune
3	Mean R notes	Staff	Notes generated from the Mean R data uploaded. Using these notes composer will create reference R tune.
4	Player	Music player	Play the notes from Mean R notes
5	Reference R OncoTune	Staff	On this staff composer will create new music by • Double clicking to copy the note. • Deleting notes from Tunes.
6	Copy all Notes from	Button	Copy all notes from Mean R to Ref R OncoTune.

	Mean R to R Tune		
7	Clear R Tune	Button	Clear Ref R OncoTune staff
8	Save Changes	Button	Saves the Reference R Tune

TABLE G: Corresponds to the Wireframe of Figure 9G

Title	Compose Known NR tune from NR Reference tune
Version	1.0

Note:
- On this page composer will compose known NR tunes from Reference Non-Responder OncoTune
- Composer can change either of the four tunes on this page.
- Composer can select known NR from the dropdown list 1

No.	Element	Type	Description
1	Known NR list	Dropdown list	List of all known NR. By default first items will be selected
2	Ref NR notes	Staff	Ref NR notes. This is read only.
3	Known NR	Staff	Known NR notes. These are for the known NR selected from the dropdown list 1
4	Compose Known NR	Staff	Initially this will be blank. Composer will create a new tune from known NR here.
5	Save Changes	Button	Save changes
6	Show All Known Non-Responders	Button	Open or Pop up a new screen that will list all the Known Non-Responders

TABLE H: Corresponds to the Wireframe of Figure 9H

Title	Known NR or R list
Version	1.0

Note:			
No.	Element	Type	Description
1	Close	Button	This will take the user back to the previous screen, which are Know Non-Responder or Known Responder
2	Pagination	Pagination	Pagination will come only where there are more than 10 Known Non-Responders

TABLE I: Corresponds to the Wireframe of Figure 9I

Title	Compose Known R tune from R Reference tune
Version	1.0

Note:
- On this page composer will compose known R tunes from Reference Responder OncoTune
- Composer can compose one known R tune at a time.
- Composer can select known R from the dropdown list 1

No.	Element	Type	Description
1	Known R list	Dropdown list	List of all known R. By default first items will be selected
2	Ref R notes	Staff	Ref R notes. This is read only.
3	Known R	Staff	Known R notes. These are for the known R selected from the dropdown list 1
4	Compose Known R	Staff	Initially this will be blank. Composer will create a new tune from known R here.
5	Save Changes	Button	Save changes

TABLE J: Corresponds to the Wireframes of Figure 9J and 9K

Title	Class prediction of Unknown patients
Version	1.0
Note: On this page composer will predict the unknown patients based on Reference tunes.	

No.	Element	Type	Description
1	Unknowns	Dropdown list	List of all Unknown biomarkers Change the value will load that biomarkers in 5
2	Result	Radio buttons	This will a three values Not know yet Non-Responder Responder
3	Reference Non-Responder	Staff	Reference Non-Responder tune
4	Reference Responder	Staff	Reference Responder tune
5	Unknown	Staff	Unknown notes that composer will compose to match either with Reference Non-Responder or Reference -Responder tunes
6	Save Changes	Button	Save changes

TABLE K: Corresponds to the Wireframe of Figure 9L

Title	Tracking
Version	1.0
Note: This page will track the changes made to the uploaded data	

No.	Element	Type	Description
1	Tracking	Data grid	List the original biomarkers and changes made to them to create a tune
2	Select Unknown	Dropdown list	List of all the unknowns and All option to list all the unknowns

Example 2: METHODS

In step 1, a conversion rule was formulated to decipher the numbers (gene expression data) into musical notes/sound frequencies (see Table 1 below).

Table 1: The conversion rule used for the transfer of gene expression data (log 2 signal intensity) in to sound frequencies/musical notes.

Intensity value (whole number)	Note	Intensity value (Decimal)	Rhythm
1	Tonic	0	Sixteenth
2	Supertonic	1	Sixteenth
3	Mediant	2	Sixteenth
4	Subdominant	3	Eight
5	Dominant	4	Eight
6	Sudmediant	5	Quarter
7	Leading Tone	6	Quarter
8	Tonic'	7	Half
9	Supertonic'	8	Half
10	Mediant'	9	Whole
11	Subdominant'		
12	Dominant'		

Other: Sharps (#) and Flats (b) as well as rests may be at Composer's discretion

In step 2, after converting the numbers into pitches with rhythms, the notes were looked at as a whole group.

In step 3, a composition/pattern generation algorithm was created to generate SFPs with the notes/sound frequencies and the rules for composition as follows:

a) Conversion vertical data into horizontal format.

b) Search a set of data for any patterns (ex: 5.4, 6.4, 7.4, 6.4) that are apparent *without* changing the order of the set.

c) Search for any outliers and mark them to not be used in composition.

d) Figure out which number(s) occur most often and use that number/note as a tonic or a reciting tone.

e) With the tonic note in mind, use any patterns discovered in #2 to create small sets of pitch orders (4-12 notes) with which to work with

f) Use the pitch orders to create a motif or theme that can be used or repeated throughout the composing process

g) Add rhythms and rests into the motif to make a more musical (*sing-able*) melody.

h) If a common chord progress (IV-V-I) becomes apparent or is useful as a basis for the melody, it is a good option to use this when available.

i) Always attempt to end a melody on a tonic or dominant

j) Repeat steps a-i for each data set, being sure to relate all of the melodies to the main theme composed from the average data set.

A coherent piece of music/SFP was composed/generated by observing the SFPs and listening to the music.

In step 4, a reference/theme/framework music/SFP specific to each group (NR reference and R reference) was composed/generated using non-responders and responders mean values (see Figure 3A), respectively.

In step 5, the theme/framework tune/SFP was used as the reference music/SFP to compose/generate the training sets (i.e. known non-responder and responder tunes/SFPs) to train the model (see Figure 3B and 3C).

In step 6, the tunes/SFPs were finalized by listening to the composition and observing the SFPs, and further refined to match with the reference/theme music/SFP by adjusting the location of the note or tempo, etc.

In step 7, data from 8 patients were considered as the test data set (i.e. unknowns). A double blind test was performed to identify clinical outcome of the unknowns after composing/generating the tune/SFP (see Figures 3D-3F). The clinical outcome was predicted correctly by observing the SFPs and listening to the musical notes. 100% prediction accuracy was achieved using the current model of the present invention.

In step 8, initially the entire gene expression data were converted into musical notes using excel program and with the help of a music composer. Manual MMOA took a longer time for class prediction. The manually operated MMOA program was converted into

cloud/web based software (SFPGRA). The program can be operated using any of the following programs. The wire frames used for the SFPGRA are listed in Figures 9A through 9L and their numbered elements and type as well as additional notations for the wireframes depicted in Figures 9A-9L are provide in Tables A through K above.

	Microsoft Internet Explorer	7.x+
	Mozilla Firefox	9.x +
	Google Chrome	16.x +
	Apple Safari	5.x+

Audio Files

The tunes/SFPs can be listened to by playing any musical instrument mode using any musical software. For these tests, the audios (midi files) were recorded in violin and piano playing mode. Two tunes/SFPs (NR reference and R ref) were composed as the reference/theme tunes/SFPs. Three NR tunes/SFPs and three R tunes/SFPs were composed/generated as the training set. Eight tunes (4NR and 4R) were composed/generated to test and validate the model.

Deconvolution of musical notes/sound frequencies to signal intensity and gene symbol/ID

The tunes/SFPs are readily converted back to signal intensity and gene symbol/ID using a deconvolution program. It can be linked to pathway analysis tools and public data bases. The schematic detail of the deconvolution program is shown in Figure 5.

Example 3: RESULTS

Conventional Microarray data analysis:

The microarray data was normalized using Robust Multi-array Average (RMA) procedure on Affymetrix GeneChip Operating Software (GCOS). For further analysis, the data was filtered and the probes that do not change were removed from the analysis. The data was further analyzed in R statistical language using standard Bioconductor packages and custom written codes. The top 50 biomarkers and their signal intensities used for class prediction are shown in Table 2.

Classifier built on the training dataset was applied to predict the clinical outcome of the 8 unknown patients (unknown test data set). The results are show in Table 3. To determine prediction accuracy, sample and data permutations were performed. Each sample was removed, and about 80% percent of genes were randomly sampled 1000 times from the filtered data-set. Each time the classifier learning procedure was repeated and then applied to unknown patients to predict the outcome. Prediction accuracies for 7 unknown patients are very high, around or higher than 95% (with about 2-3% confidence interval). The sample unknown 4 predicted as non-respondent with confidence accuracy within 61%-72%. The prediction accuracy was later compared with the original clinical outcome of the patients (Table 3). The prediction accuracy was found to be 62.5%. Three samples (marked *) out 8 samples were predicted incorrectly.

Table 2. Top 50 biomarkers differentially expressed in responders and non-responders of surgical treatment. NR mean: Non-responders mean (n=23); R mean: Responders mean (n=13); NR and R means were used to composed/generate reference tunes/reference SFPs. KNR1, KNR2 and KNR4: Known non-responders testing set. KR3, KR6 and KR7: Known responders testing set. UN1/R8: Unknown 1/Responder 8; UN2/NR5: Unknown 2/Non-responder 5. Data for other 6 unknowns (3 NR and 3 R) samples are not shown.

Affy_Probe ID	NR Mean	R Mean	KNR 1	KNR 2	KNR 4	KR3	KR6	KR7	UN1/R 8	UN2/NR 5
201830_s_at	10.07	9.69	7.78	8.83	9.97	8.95	6.83	7.78	9.12	10.33
215078_at	3.91	4.25	5.14	3.80	3.99	8.05	8.10	8.74	6.98	4.17
241272_at	4.13	4.36	4.33	4.00	4.19	4.06	7.14	8.04	6.91	5.39
200656_s_at	10.91	10.70	10.97	11.14	10.01	10.95	8.77	8.68	8.56	8.83
213915_at	6.41	6.61	6.12	7.01	7.02	8.63	10.86	7.45	5.77	7.59
243256_at	6.50	6.70	6.72	6.87	7.18	7.28	9.25	8.60	8.45	8.09
243819_at	3.78	3.98	3.75	4.00	4.51	4.07	6.62	5.10	4.53	5.45
240265_at	3.43	3.62	3.51	3.63	4.26	3.08	6.38	5.62	4.72	5.62
232311_at	5.48	5.67	5.90	5.62	6.05	6.17	10.18	9.52	8.77	9.49
236725_at	5.61	5.80	5.48	5.51	5.56	6.59	9.00	7.77	7.62	7.29
211794_at	5.82	6.00	6.40	6.20	6.03	6.58	8.99	8.33	6.81	7.43
244777_at	5.25	5.43	5.22	5.37	5.90	5.58	7.72	6.44	5.11	5.49
238575_at	4.16	4.35	3.75	4.08	4.10	3.68	8.81	4.67	3.92	5.14
204103_at	7.83	7.99	7.25	7.93	8.62	9.82	11.78	9.70	8.43	8.69
242946_at	5.35	5.51	5.53	5.55	6.56	5.75	8.60	7.71	6.63	7.19

224582_s_at	9.04	8.88	8.66	8.61	8.88	8.94	5.57	5.60	6.17	6.77
230110_at	5.50	5.66	5.29	5.93	6.31	5.94	8.73	6.91	6.47	6.55
238063_at	5.82	5.97	6.31	6.04	5.95	6.01	8.42	7.91	6.82	6.64
236495_at	3.87	4.02	4.58	3.73	3.68	4.80	7.88	8.82	6.90	5.64
230006_s_at	7.87	7.73	7.40	7.82	7.58	8.38	5.23	5.68	7.70	7.40
227182_at	5.48	5.62	5.10	5.50	5.87	5.23	7.59	5.59	5.05	5.42
240260_at	4.86	5.00	4.62	5.22	5.38	4.73	7.12	7.19	5.79	5.65
201417_at	11.61	11.48	11.26	11.40	11.78	11.25	8.22	10.48	11.57	10.75
240652_at	3.97	4.10	3.76	4.05	4.30	4.21	6.17	6.07	5.35	4.83
1559037_a_at	4.05	4.18	4.27	4.19	4.52	3.73	6.11	6.37	4.48	5.76
206296_x_at	5.52	5.65	5.39	5.86	5.73	5.44	7.68	6.63	7.17	6.40
239205_s_at	4.37	4.50	5.10	5.26	4.32	5.76	9.04	6.82	4.72	4.93
233204_at	4.74	4.87	5.02	4.69	4.50	4.74	6.89	6.54	6.11	5.98
210549_s_at	4.49	4.62	4.67	4.45	5.45	4.71	8.77	5.25	4.36	5.79
1569369_at	4.02	4.14	3.83	4.43	3.64	6.06	7.20	5.60	4.67	5.83
1557797_a_at	4.05	4.17	3.78	4.61	5.11	3.88	6.56	5.78	5.30	5.64
1557578_at	2.92	3.05	2.80	2.56	3.40	3.12	6.31	6.04	3.69	3.33
213958_at	7.14	7.26	7.07	7.41	7.57	7.25	8.45	7.51	7.34	7.54
244357_at	4.28	4.40	4.31	4.43	4.37	4.10	7.37	6.75	6.43	6.31
227677_at	6.80	6.91	6.56	7.07	7.08	6.98	9.26	8.32	7.63	7.68
214369_s_at	4.25	4.37	4.79	4.68	4.69	4.04	6.03	5.50	4.52	4.98
204485_s_at	9.27	9.16	9.77	9.36	8.57	9.44	6.60	7.03	8.62	8.64
234640_x_at	3.43	3.54	4.09	3.45	3.69	3.84	4.80	6.02	3.62	3.57
236301_at	5.19	5.31	4.67	5.39	5.73	5.73	8.06	5.88	5.17	6.21
241505_at	4.53	4.64	4.19	4.61	5.26	4.53	6.38	6.25	6.26	5.31
1556472_s_at	4.11	4.22	3.84	4.26	4.25	4.02	6.58	4.66	4.47	4.73
1560706_at	4.70	4.81	4.70	4.49	5.32	5.25	6.84	5.56	5.81	5.53
235040_at	6.38	6.27	6.62	6.30	5.75	6.19	5.03	5.60	6.13	5.94
201428_at	8.83	8.72	6.94	8.50	8.99	6.81	4.74	7.06	8.48	9.67
224676_at	9.53	9.42	9.86	9.13	9.48	8.87	7.96	7.91	8.59	8.54
214219_x_at	5.51	5.61	5.37	5.74	5.91	5.35	7.45	6.55	6.78	6.33
1555259_at	4.13	4.23	4.03	3.98	3.83	5.29	8.39	4.95	4.77	4.97
210988_s_at	7.29	7.18	7.22	7.40	6.58	7.48	4.74	5.25	6.52	5.51
210225_x_at	7.74	7.84	7.87	7.89	8.03	8.33	9.00	8.80	7.98	7.72
206804_at	5.45	5.55	5.48	5.61	5.68	5.88	9.80	6.93	6.50	7.20

Table 3. Prediction accuracy of conventional data analysis method was calculated by comparing the predicted outcomes with the original clinical outcome.

S. No	Status	Clinical outcome	Predicted with Bio-Conductor
1	Unknown 1	Responder	**Non-Responder***
2	Unknown 2	Non-Responder	Non-Responder
3	Unknown 3	Non-Responder	Non-Responder
4	Unknown 4	Responder	**Non-Responder***
5	Unknown 5	Responder	Responder
6	Unknown 6	Responder	Responder
7	Unknown 7	Non-Responder	**Responder***
8	Unknown 8	Non-Responder	Non-Responder

*Three samples out 8 were predicted incorrectly

Prediction accuracy of MMOA is shown in **Table 4**. Eight tunes/SFPs were composed to validate the algorithm and they were predicted with 100% accuracy in double blind studies.

Table 4: Comparison of prediction accuracy of conventional microarray analysis method with MMOA.

S. No	Status	Clinical outcome	Predicted with Bio-Conductor	Predicted with MMOA
1	Unknown 1	Responder	**Non-Responder**	Responder
2	Unknown 2	Non-Responder	Non-Responder	Non-Responder
3	Unknown 3	Non-Responder	Non-Responder	Non-Responder
4	Unknown 4	Responder	**Non-Responder**	Responder
5	Unknown 5	Responder	Responder	Responder
6	Unknown 6	Responder	Responder	Responder
7	Unknown 7	Non-Responder	**Responder**	Non-Responder
8	Unknown 8	Non-Responder	Non-Responder	Non-Responder

WHAT IS CLAIMED IS:

1. A method of classifying a patient suffering from a disease as a responder or a non-responder to a selected treatment for the disease, said method comprising

analyzing a sample from the patient using an RNA, DNA or protein microarray;

filtering a data set generated from the microarray;

assigning an audio tune and/or sound frequency pattern capturing the filtered data to the patient; and

classifying the patient as a responder or a non-responder utilizing the audio tune and/or sound frequency pattern.

2. The method of claim 1 wherein the patient is suffering from cancer.

3. The method of claim 1 wherein the patient is suffering from lung cancer.

4. The method of claim 1 wherein the audio tune capturing the filtered data from the microarray is assigned manually using a mathematical musical orchestral algorithm.

5. The method of claim 1 wherein the sound frequency pattern capturing the filtered data from the microarray is assigned using a web based sound frequency pattern generation and recognition algorithm.

6. The method of claim 1 further comprising obtaining a tissue sample from the patient for analysis.

7. A method of predicting recurrence of a disease in a patient, said method comprising:

analyzing a sample from the patient using an RNA, DNA or protein microarray;

filtering a data set generated from the microarray;

assigning an audio tune or sound frequency pattern capturing the filtered data to the patient; and

predicting recurrence of the disease in the patient utilizing the audio tune.

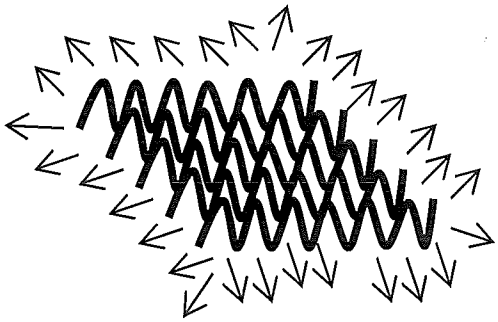
8. The method of claim 7 wherein the patient is suffering from cancer.

9. The method of claim 7 wherein the patient is suffering from lung cancer.

10. The method of claim 7 wherein the audio tune capturing the filtered data from the microarray is assigned manually using a mathematical musical orchestral algorithm.

11. The method of claim 7 wherein the audio tune capturing the filtered data from the microarray is assigned using a web based sound frequency pattern generation and recognition algorithm.

12. The method of claim 7 further comprising obtaining a tissue sample from the patient for analysis.

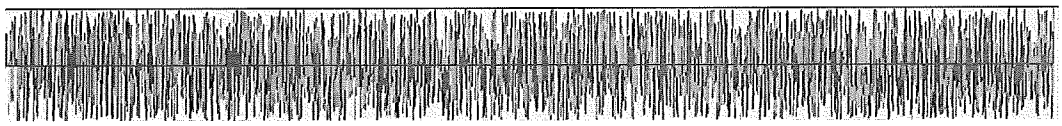


mRNA
(VIBRATING MACROMOLECULE)

↓

MICROARRAY OR RNA SEQ DATA ANALYSIS
(MACHINE LEARNING)

↓



CONVERSION OF NUMBERS INTO MUSICAL
NOTES/SOUND FREQUENCIES

↓

COMPOSITION OF CLASS SPECIFIC TUNES / GENERATION OF
CLASS SPECIFIC SOUND FREQUENCY PATTERNS

↓

TUNE BASED CLASS PREDICTION / RECOGNITION OF
CLASS SPECIFIC SOUND FREQUENCY PATTERNS

FIG. 1

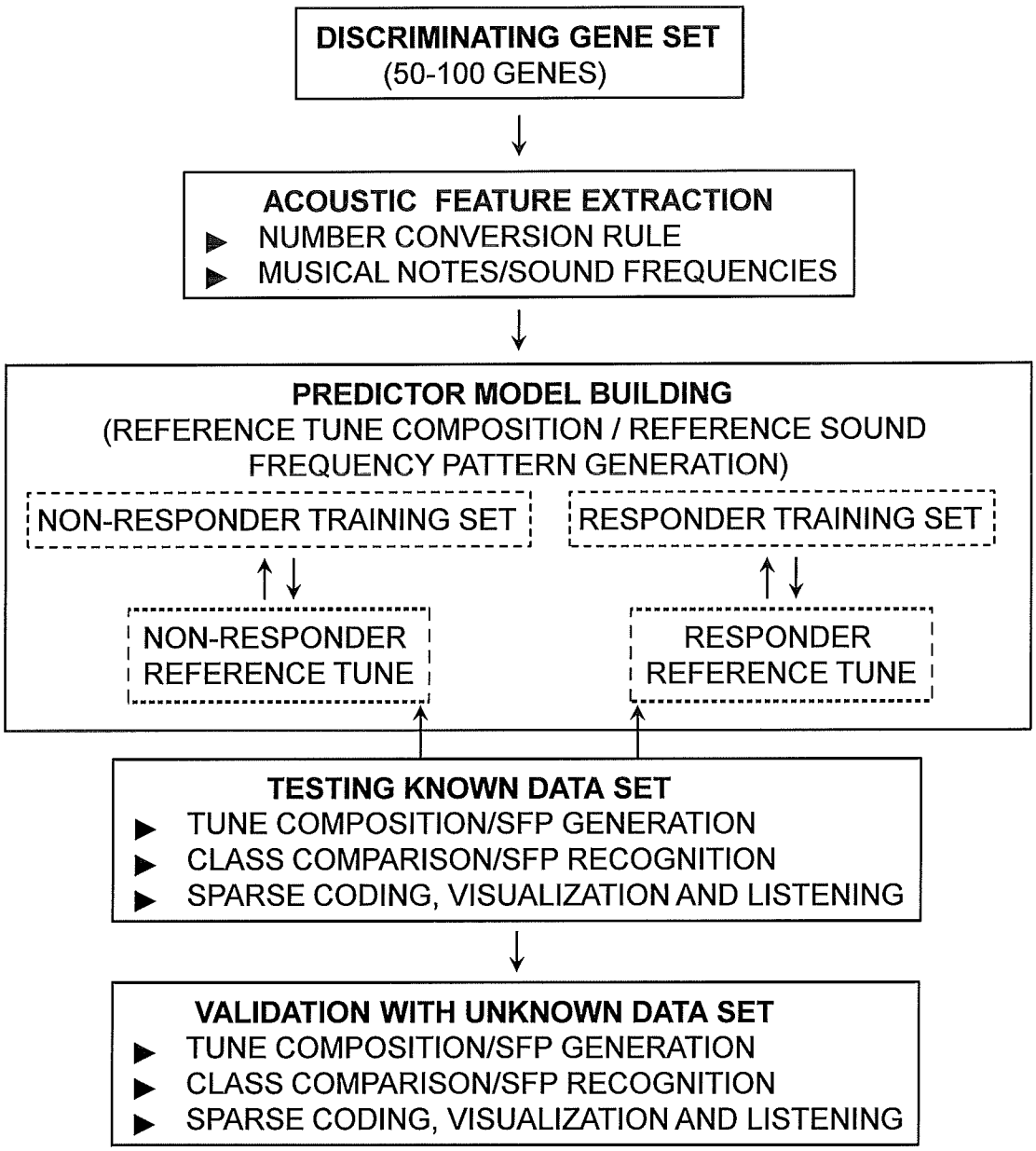

DISCRIMINATING GENE SET
(50-100 GENES)
ACOUSTIC FEATURE EXTRACTION
NUMBER CONVERSION RULE
MUSICAL NOTES/SOUND FREQUENCIES
PREDICTOR MODEL BUILDING
(REFERENCE TUNE COMPOSITION / REFERENCE SOUND FREQUENCY PATTERN GENERATION)
NON-RESPONDER TRAINING SET
RESPONDER TRAINING SET
NON-RESPONDER REFERENCE TUNE
RESPONDER REFERENCE TUNE
TESTING KNOWN DATA SET
TUNE COMPOSITION/SFP GENERATION
CLASS COMPARISON/SFP RECOGNITION
SPARSE CODING, VISUALIZATION AND LISTENING
VALIDATION WITH UNKNOWN DATA SET
TUNE COMPOSITION/SFP GENERATION
CLASS COMPARISON/SFP RECOGNITION
SPARSE CODING, VISUALIZATION AND LISTENING

FIG. 2

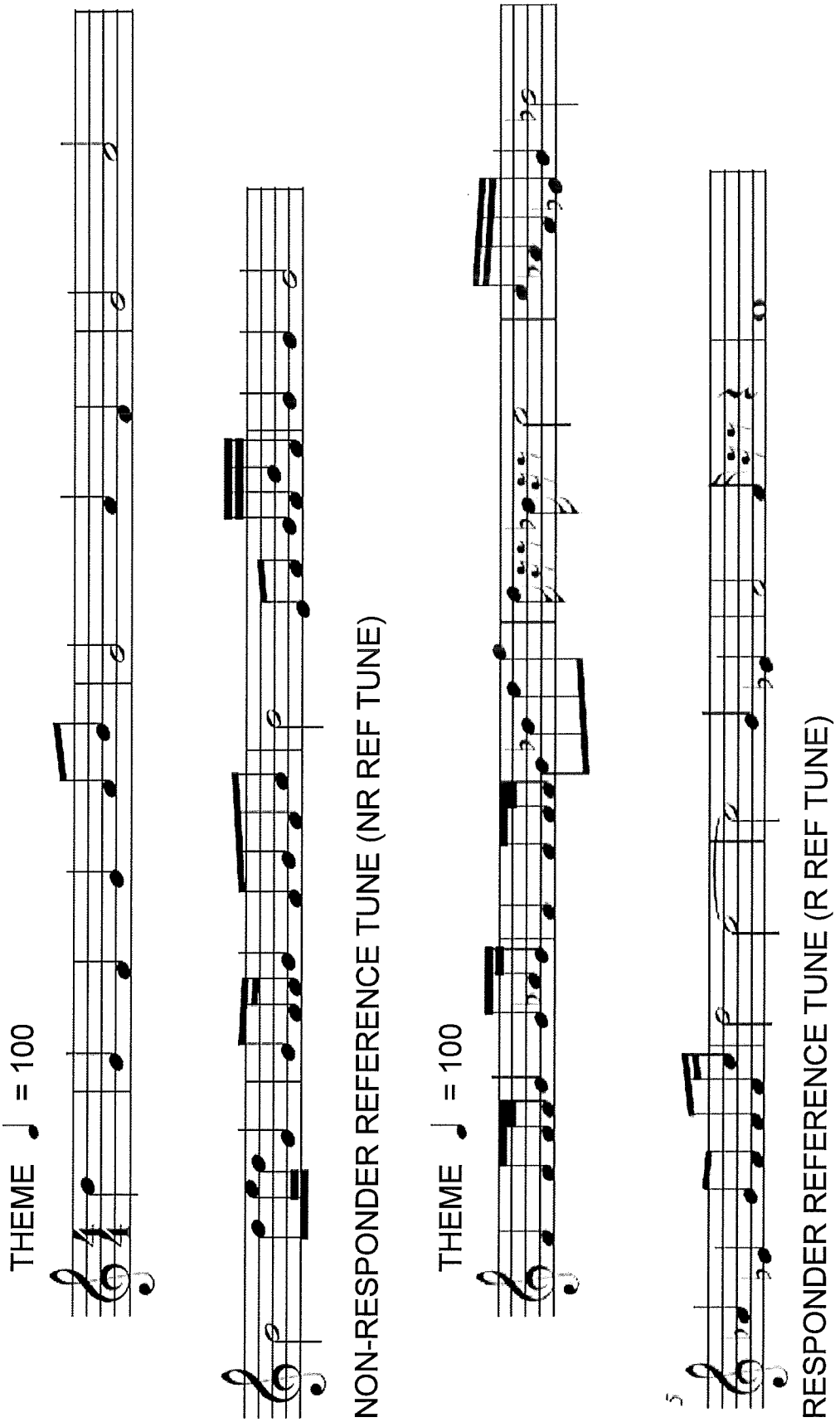

THEME ♩ = 100
NON-RESPONDER REFERENCE TUNE (NR REF TUNE)
THEME ♩ = 100
RESPONDER REFERENCE TUNE (R REF TUNE)

FIG. 3A


KNOWN NON-RESPONDER TUNE 1 (KNRT1)
KNOWN NON-RESPONDER TUNE 2 (KNRT2)
KNOWN NON-RESPONDER TUNE 4 (KNRT4)

FIG. 3B

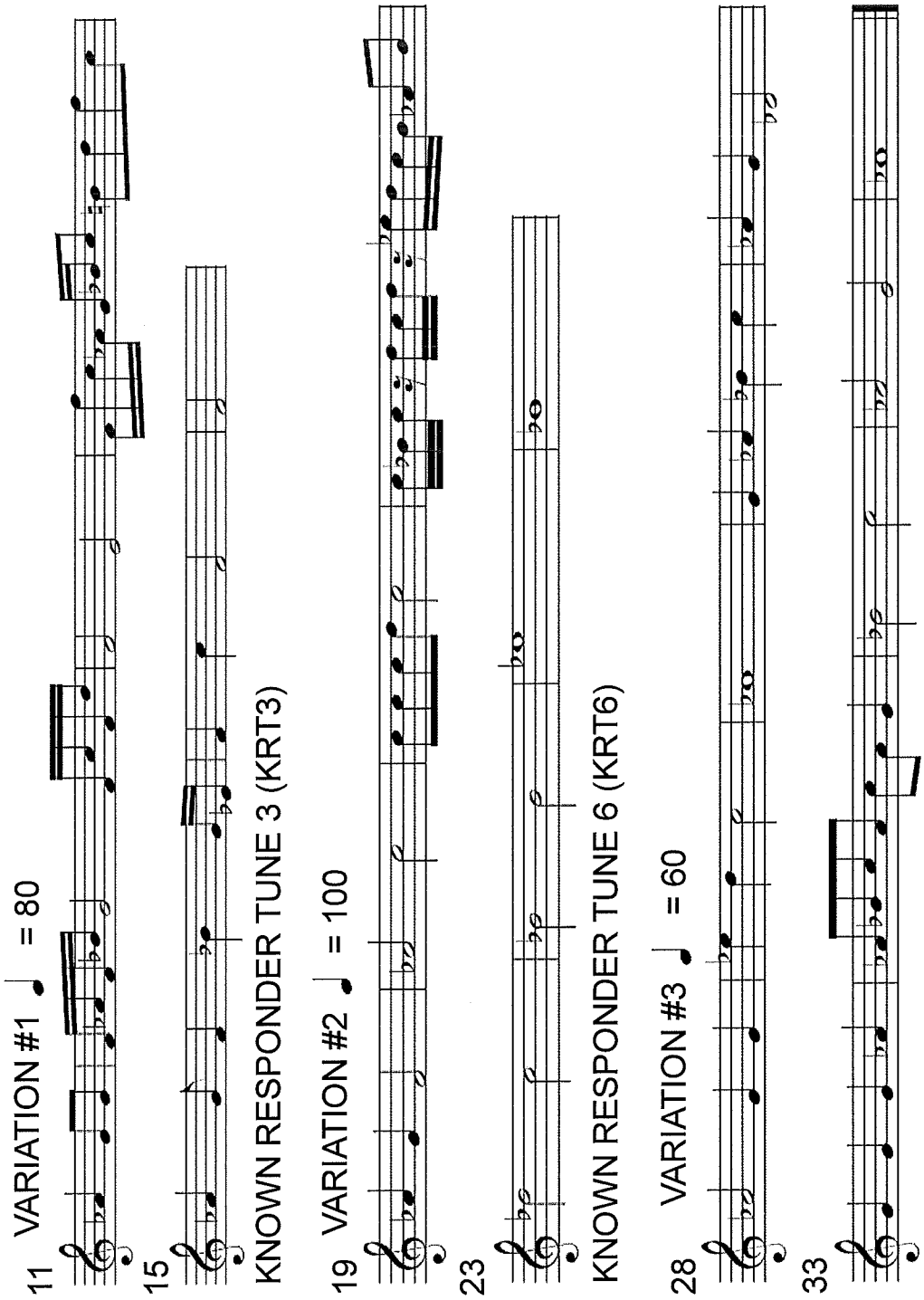

11 VARIATION #1 ♩ = 80
15 KNOWN RESPONDER TUNE 3 (KRT3)
19 VARIATION #2 ♩ = 100
23 KNOWN RESPONDER TUNE 6 (KRT6)
28 VARIATION #3 ♩ = 60
33 KNOWN RESPONDER TUNE 7 (KRT7)

FIG. 3C

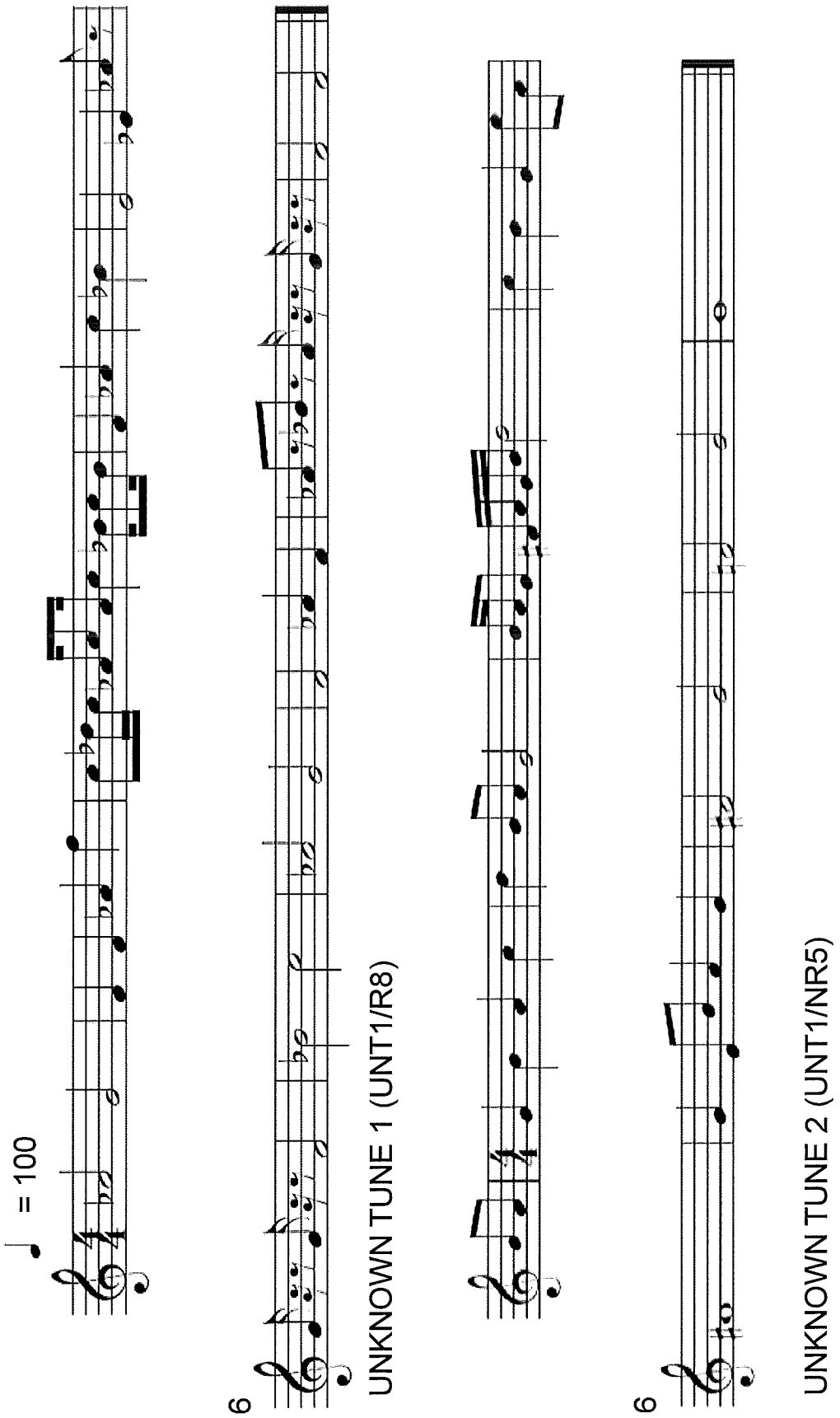


FIG. 3D

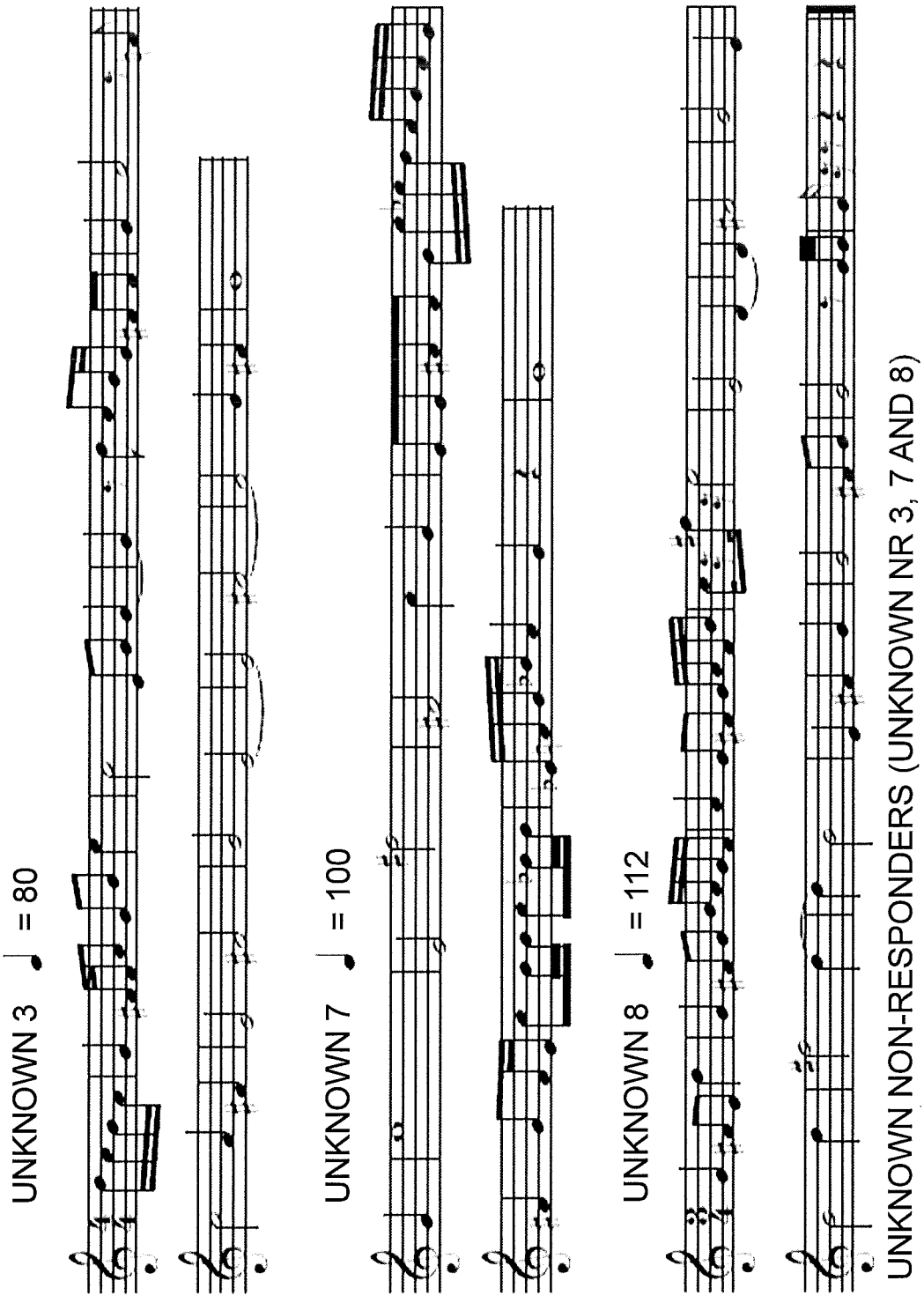

UNKNOWN 3 ♩ = 80
UNKNOWN 7 ♩ = 100
UNKNOWN 8 ♩ = 112
UNKNOWN NON-RESPONDERS (UNKNOWN NR 3, 7 AND 8)

FIG. 3E

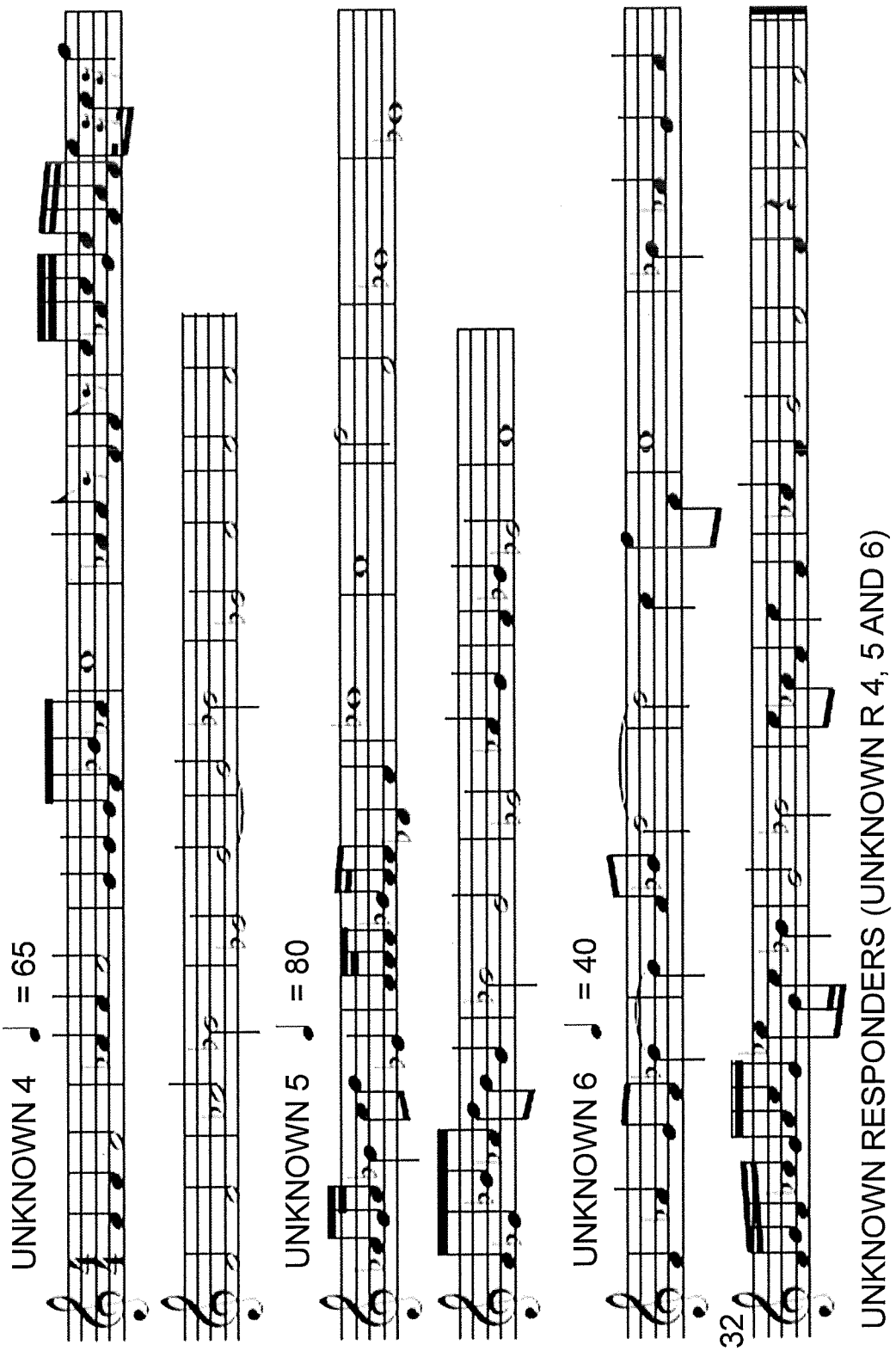

UNKNOWN 4 ♩ = 65
UNKNOWN 5 ♩ = 80
UNKNOWN 6 ♩ = 40
32
UNKNOWN RESPONDERS (UNKNOWN R 4, 5 AND 6)

FIG. 3F

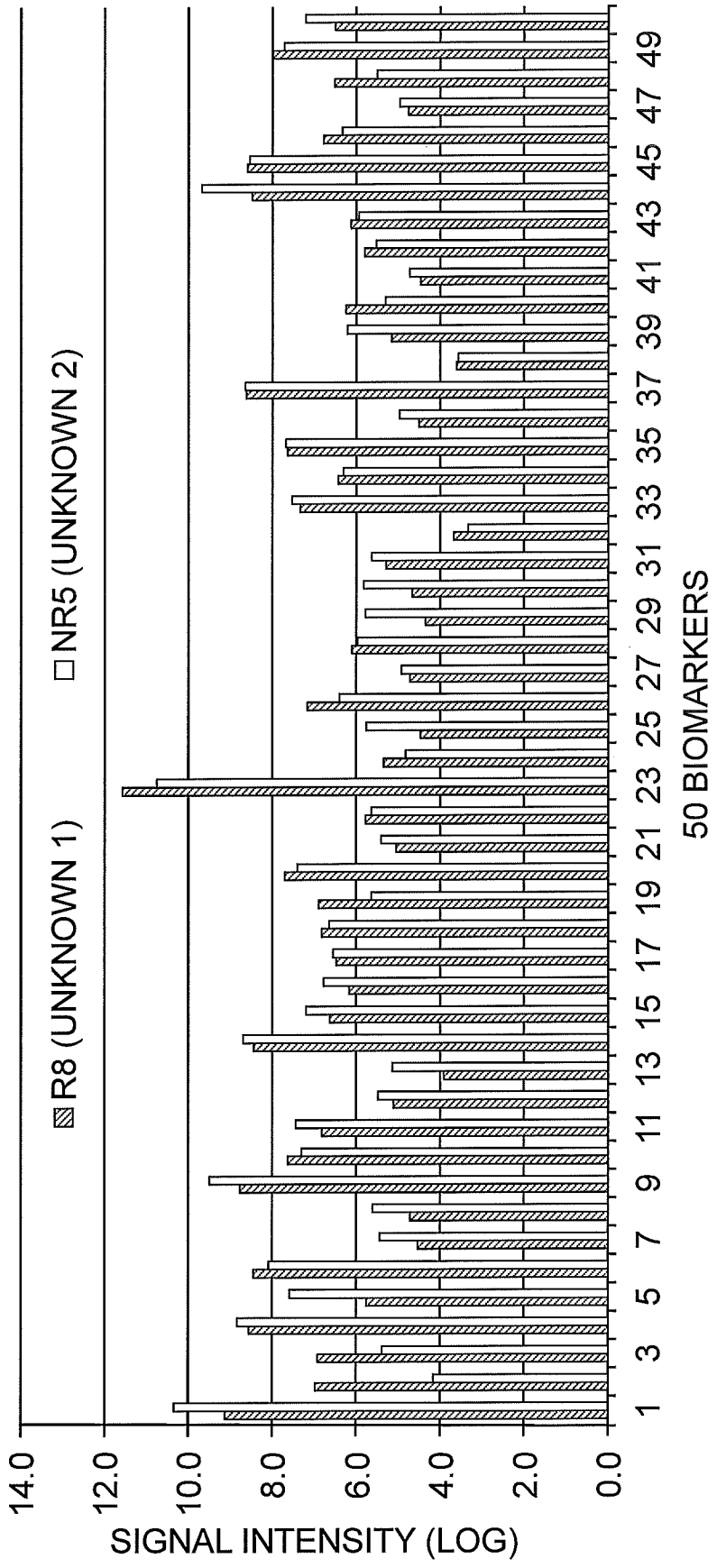

R8 (UNKNOWN 1)
NR5 (UNKNOWN 2)
SIGNAL INTENSITY (LOG)
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
50 BIOMARKERS
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45 47 49

FIG. 4A

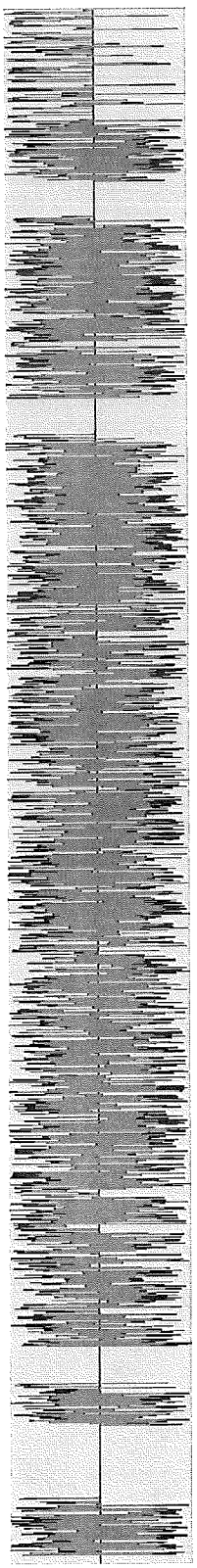


FIG. 4B

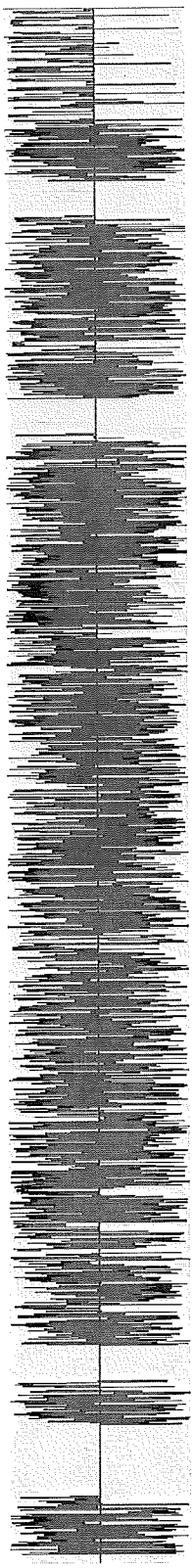


FIG. 4C

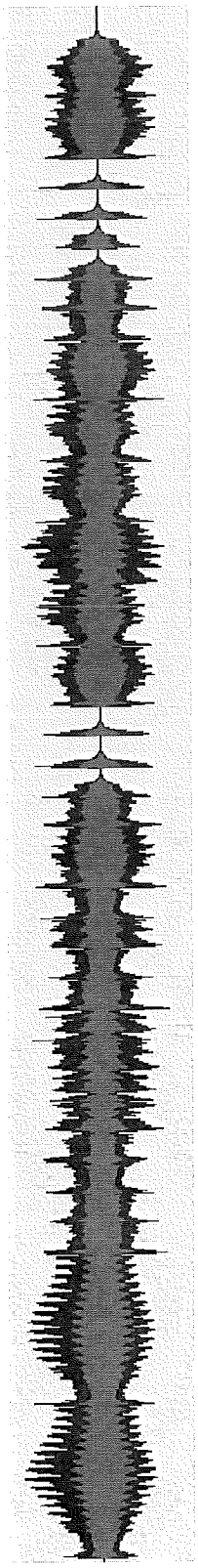


FIG. 4D

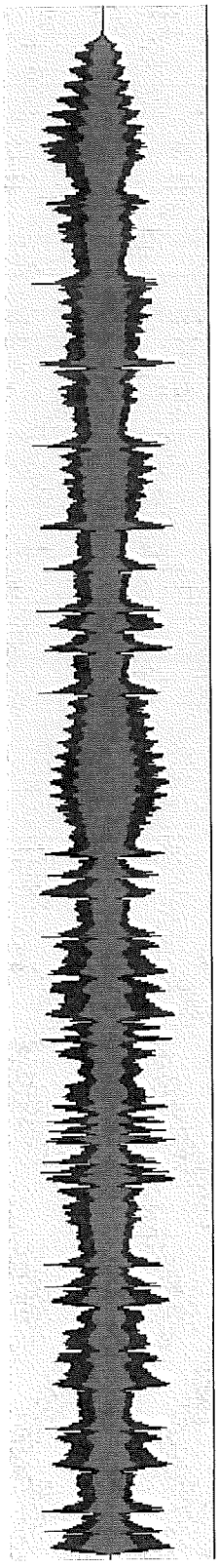


FIG. 4E

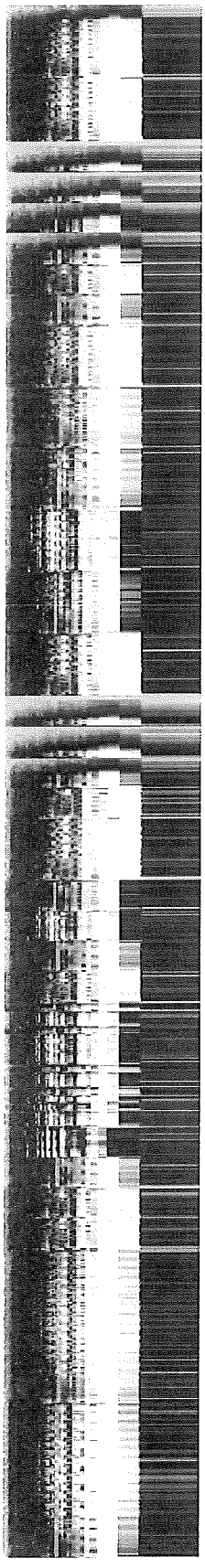


FIG. 4F

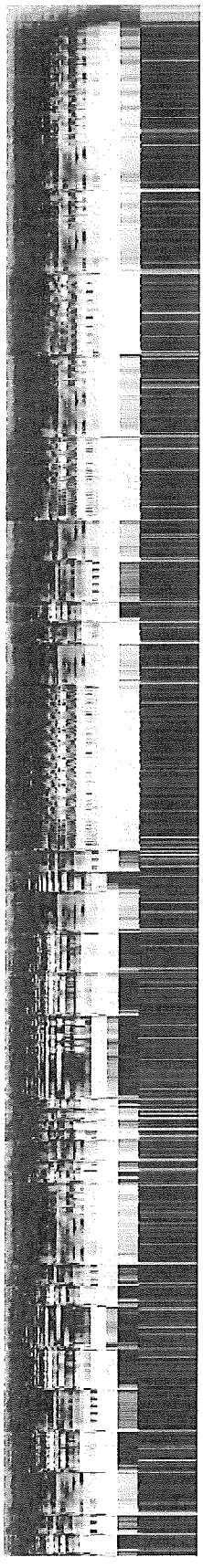


FIG. 4G

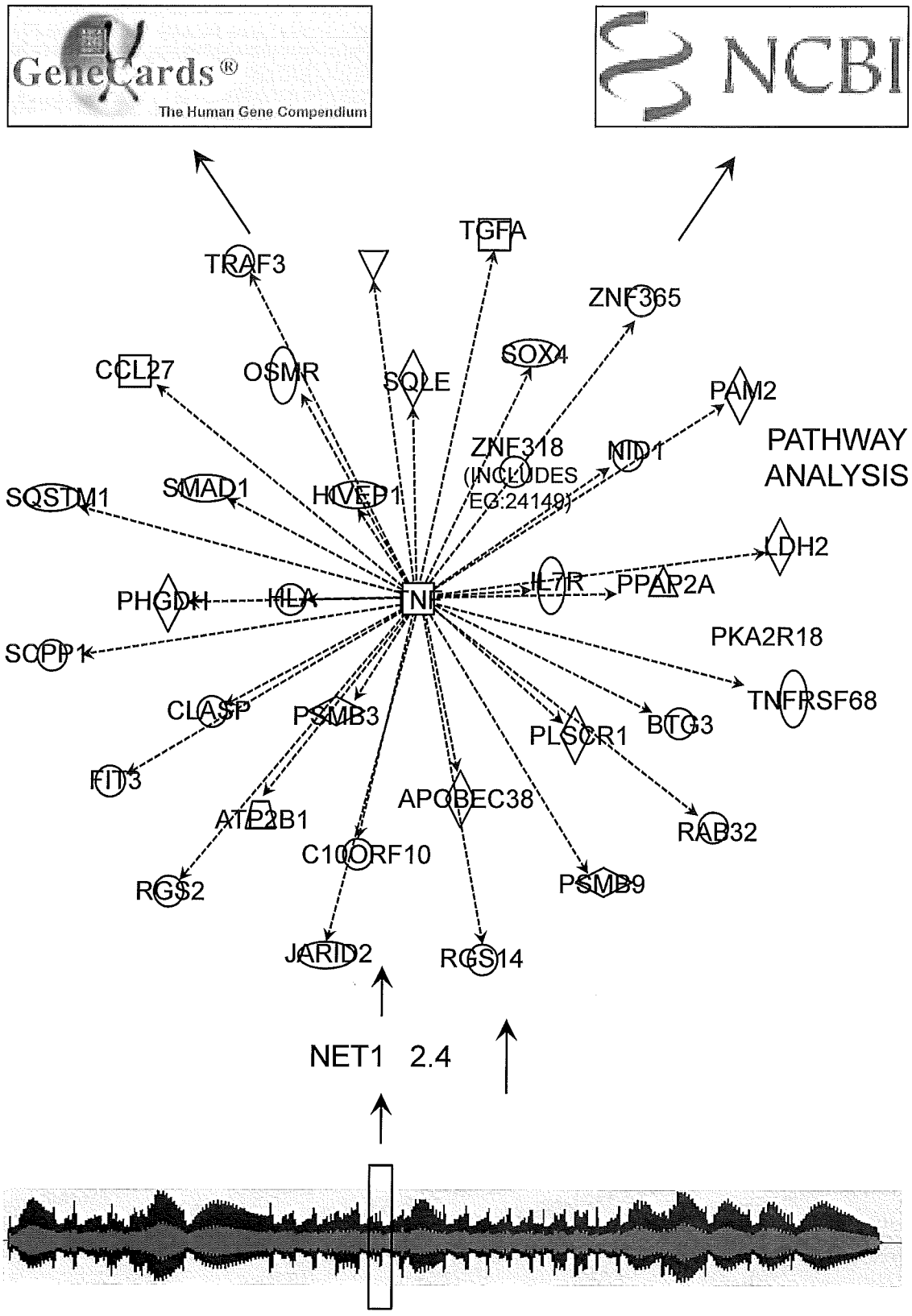

GeneCards®
The Human Gene Compendium
NCBI
TRAF3
TGFA
ZNF365
CCL27
OSMR
SQLE
SOX4
PAM2
ZNF318
(INCLUDES
EG:24149)
NID1
PATHWAY
ANALYSIS
SQSTM1
SMAD1
HIVEP1
LDH2
PHGDH
HLA
IL7R
PPAP2A
SCPP1
PKA2R18
CLASP
PSMB3
TNFRSF68
BTG3
PLSCR1
FIT3
APOBEC38
ATP2B1
RAB32
C10ORF10
RGS2
PSMB9
JARID2
RGS14
NET1 2.4

FIG. 5

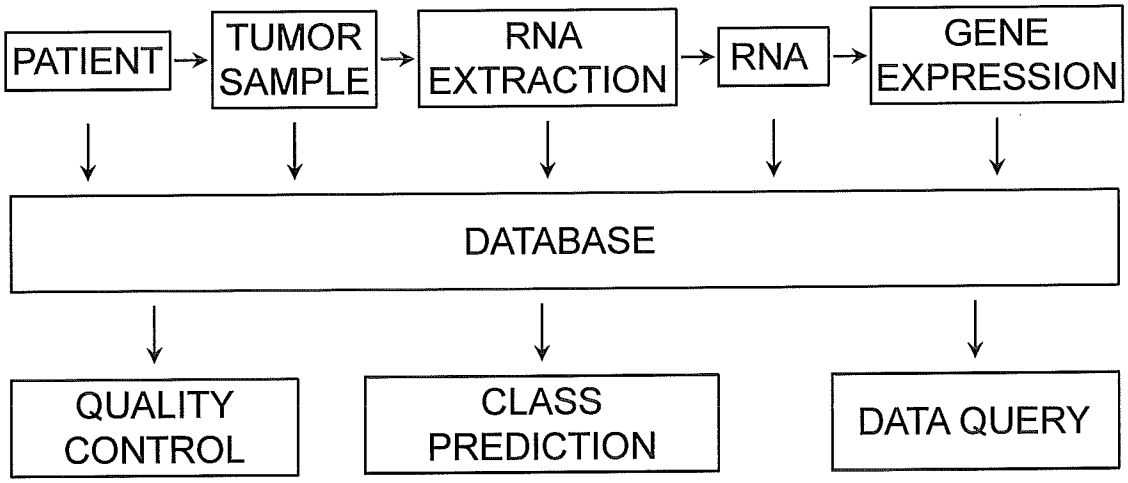

PATIENT
TUMOR SAMPLE
RNA EXTRACTION
RNA
GENE EXPRESSION
DATABASE
QUALITY CONTROL
CLASS PREDICTION
DATA QUERY

FIG. 6

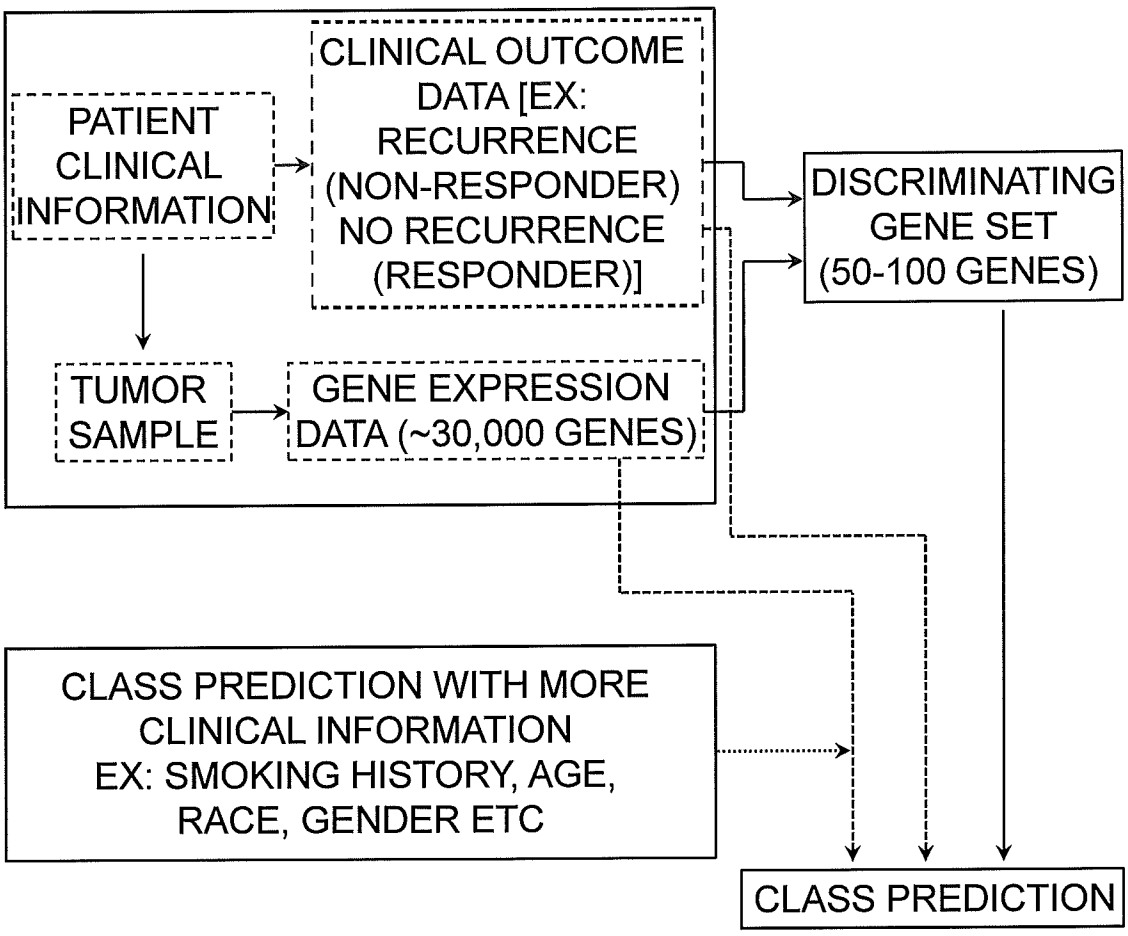

PATIENT CLINICAL INFORMATION
CLINICAL OUTCOME DATA [EX: RECURRENCE (NON-RESPONDER) NO RECURRENCE (RESPONDER)]
DISCRIMINATING GENE SET (50-100 GENES)
TUMOR SAMPLE
GENE EXPRESSION DATA (~30,000 GENES)
CLASS PREDICTION WITH MORE CLINICAL INFORMATION EX: SMOKING HISTORY, AGE, RACE, GENDER ETC
CLASS PREDICTION

FIG. 7A

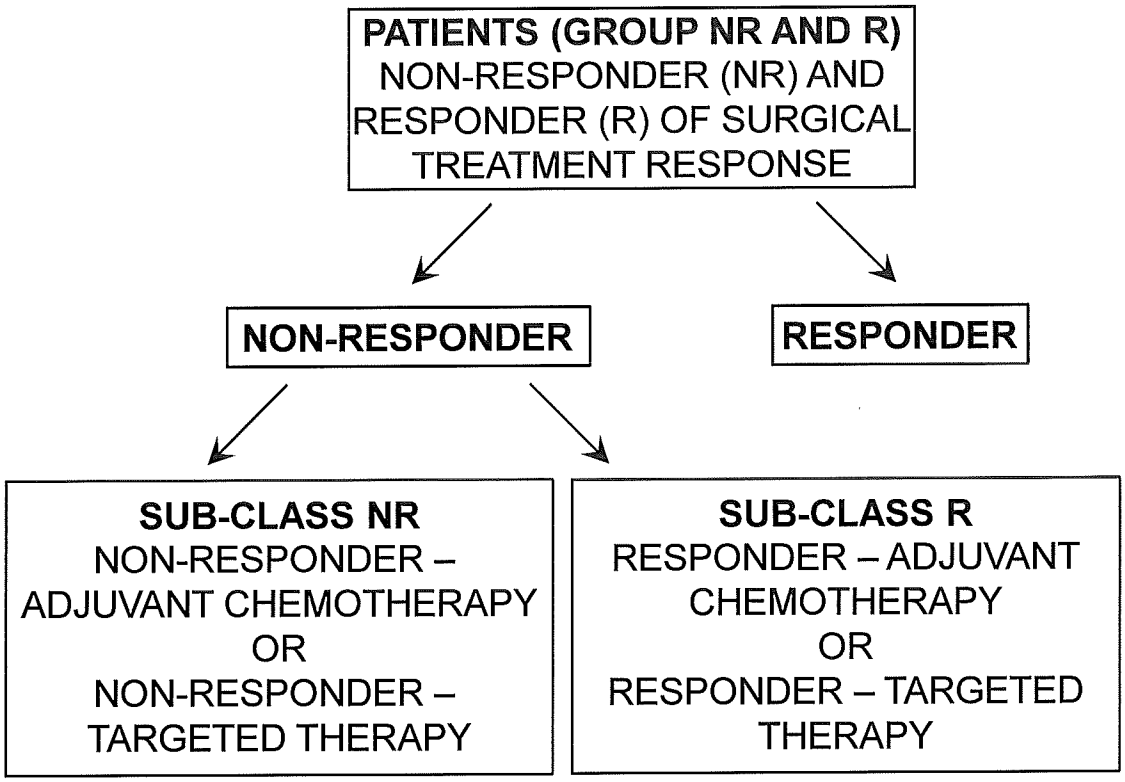

PATIENTS (GROUP NR AND R)
NON-RESPONDER (NR) AND RESPONDER (R) OF SURGICAL TREATMENT RESPONSE
NON-RESPONDER
RESPONDER
SUB-CLASS NR
NON-RESPONDER – ADJUVANT CHEMOTHERAPY
OR
NON-RESPONDER – TARGETED THERAPY
SUB-CLASS R
RESPONDER – ADJUVANT CHEMOTHERAPY
OR
RESPONDER – TARGETED THERAPY

FIG. 7B

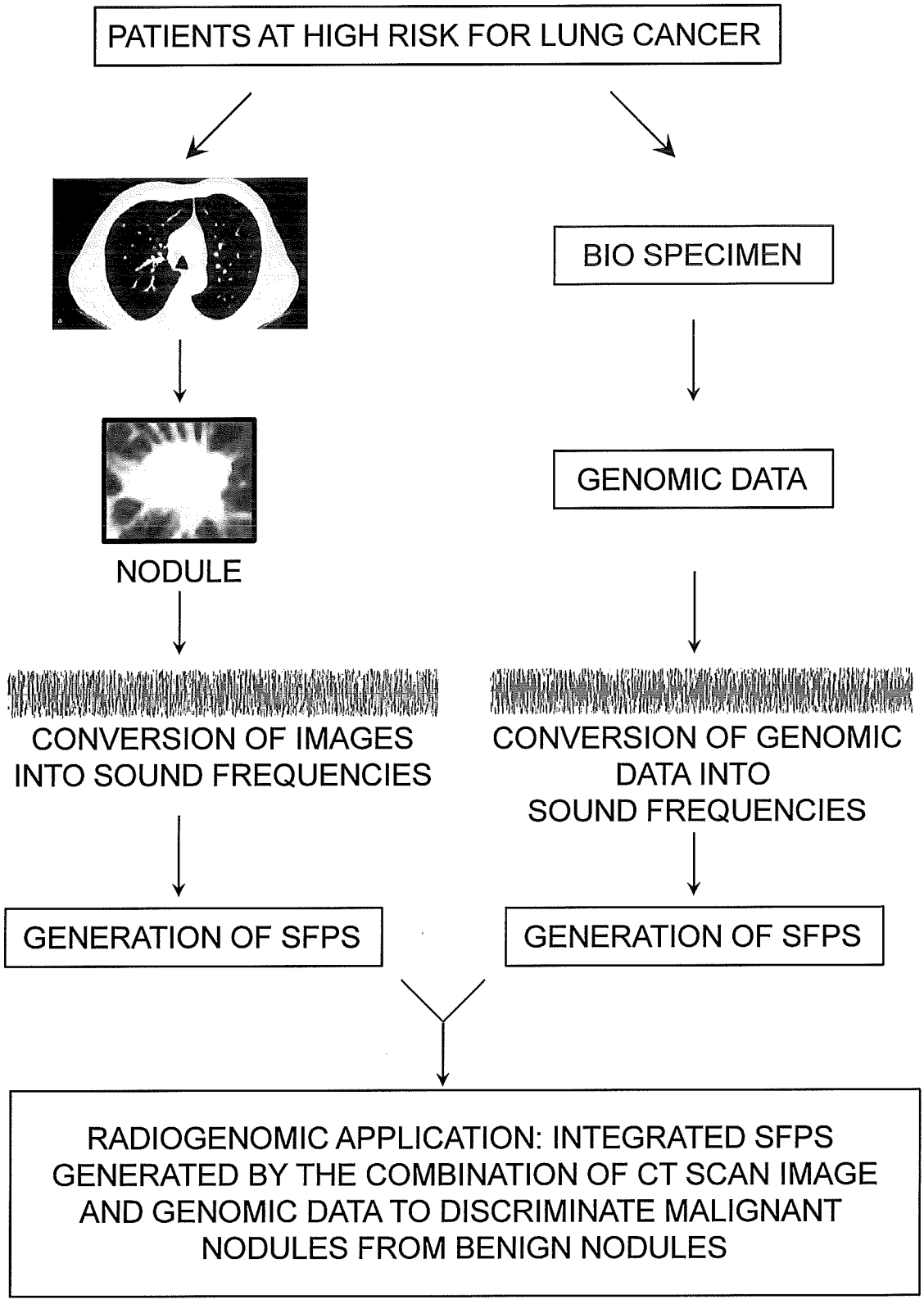

PATIENTS AT HIGH RISK FOR LUNG CANCER
BIO SPECIMEN
NODULE
GENOMIC DATA
CONVERSION OF IMAGES INTO SOUND FREQUENCIES
CONVERSION OF GENOMIC DATA INTO SOUND FREQUENCIES
GENERATION OF SFPS
GENERATION OF SFPS
RADIOGENOMIC APPLICATION: INTEGRATED SFPS GENERATED BY THE COMBINATION OF CT SCAN IMAGE AND GENOMIC DATA TO DISCRIMINATE MALIGNANT NODULES FROM BENIGN NODULES

FIG. 7C

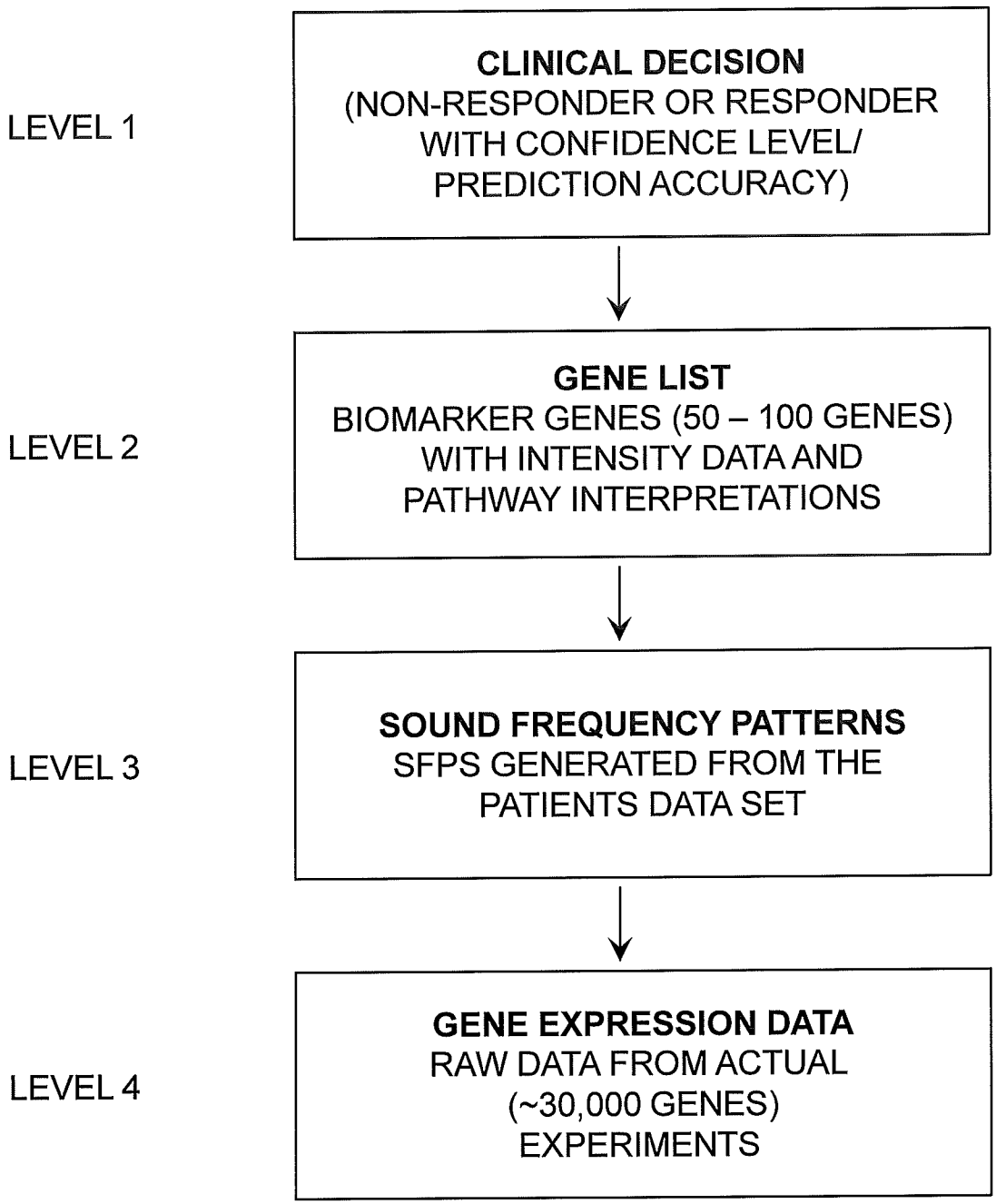
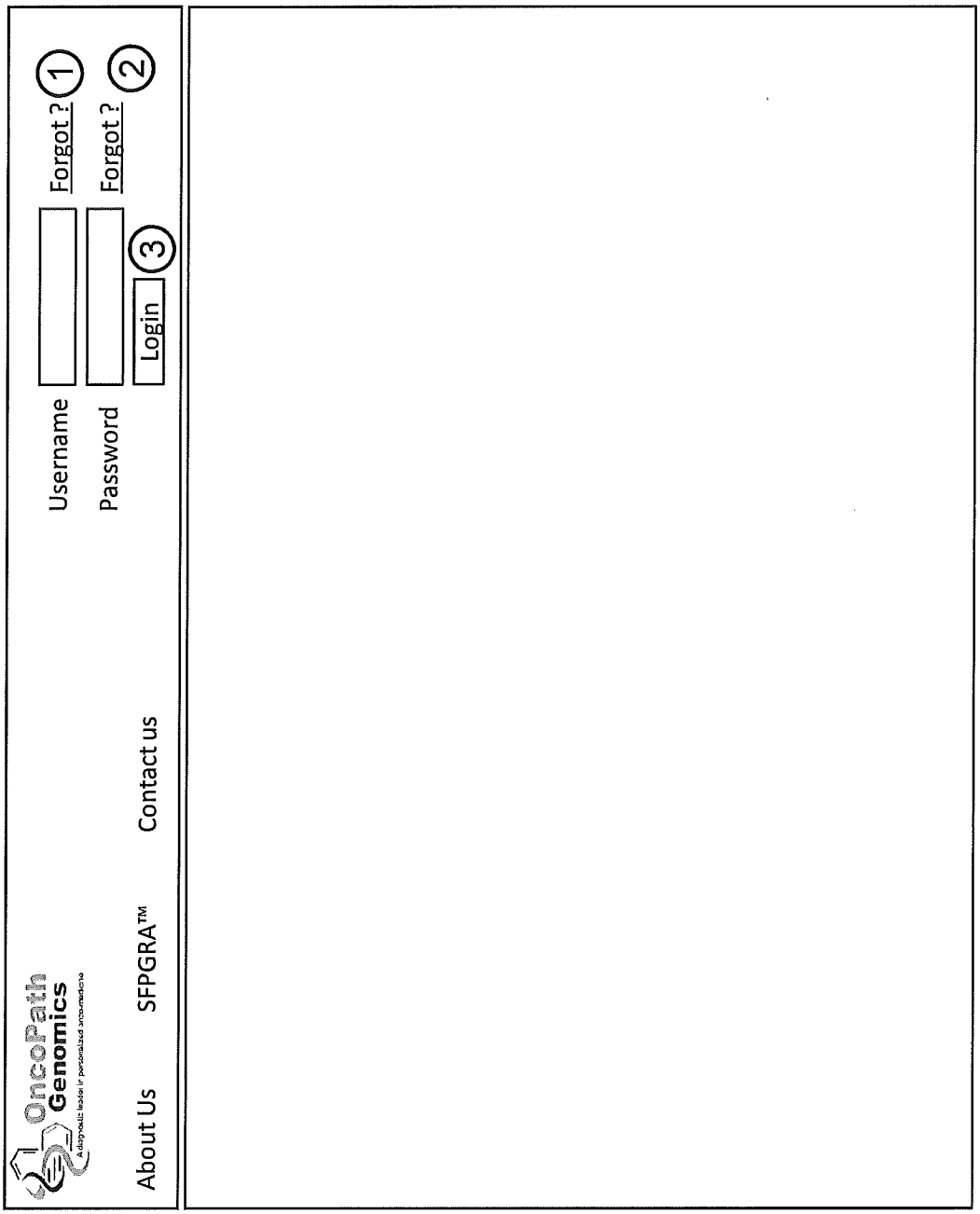

LEVEL 1
CLINICAL DECISION
(NON-RESPONDER OR RESPONDER
WITH CONFIDENCE LEVEL/
PREDICTION ACCURACY)
LEVEL 2
GENE LIST
BIOMARKER GENES (50 – 100 GENES)
WITH INTENSITY DATA AND
PATHWAY INTERPRETATIONS
LEVEL 3
SOUND FREQUENCY PATTERNS
SFPS GENERATED FROM THE
PATIENTS DATA SET
LEVEL 4
GENE EXPRESSION DATA
RAW DATA FROM ACTUAL
(~30,000 GENES)
EXPERIMENTS

FIG. 8


OncoPath Genomics
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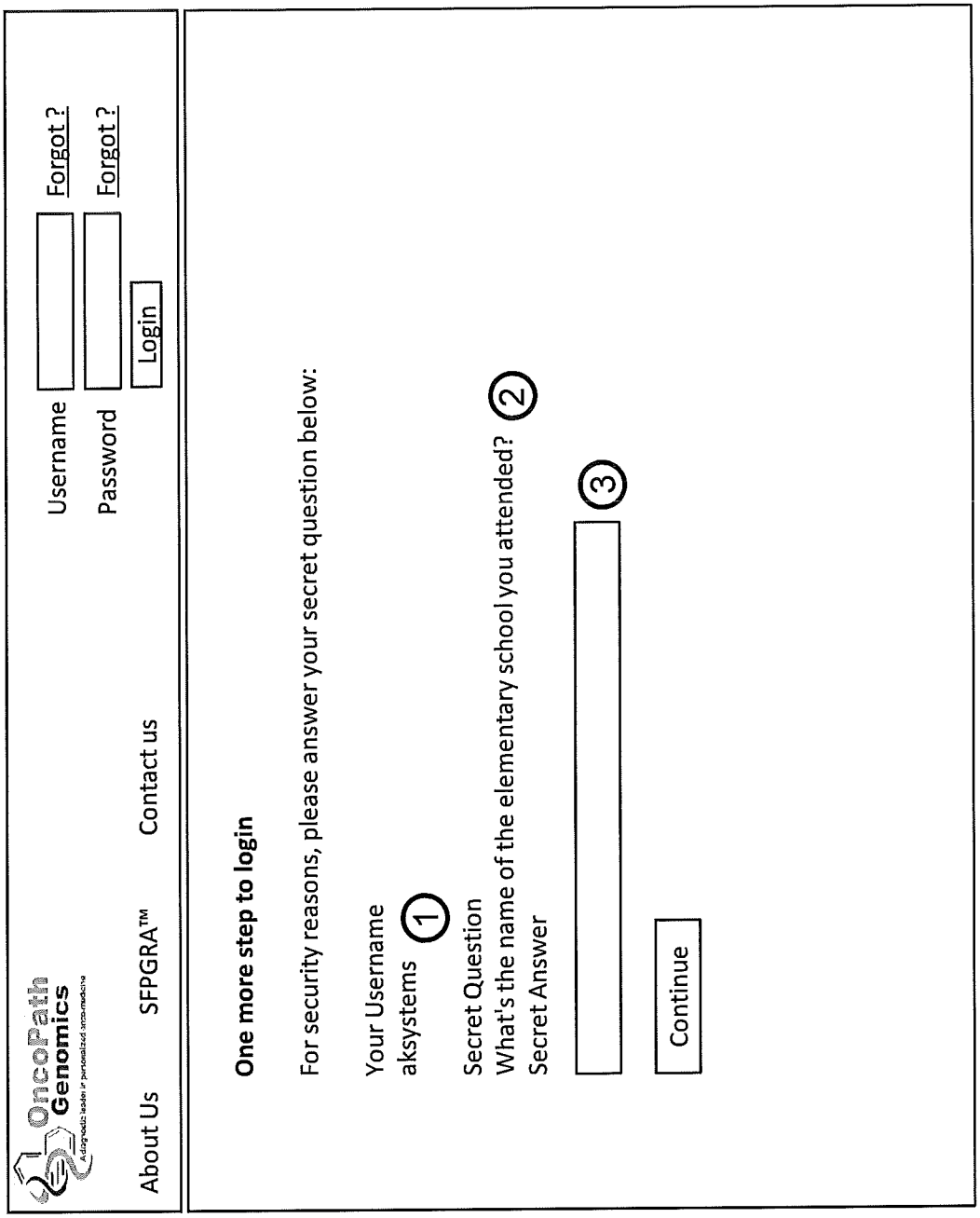
About Us
SFPGRA™
Contact us
Username
Password
Login
Forgot ?
Forgot ?
1
2
3

FIG. 9A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Username
Forgot ?
Password
Forgot ?
Login
One more step to login
For security reasons, please answer your secret question below:
Your Username
aksystems
1
Secret Question
What's the name of the elementary school you attended?
2
Secret Answer
3
Continue

FIG. 9B

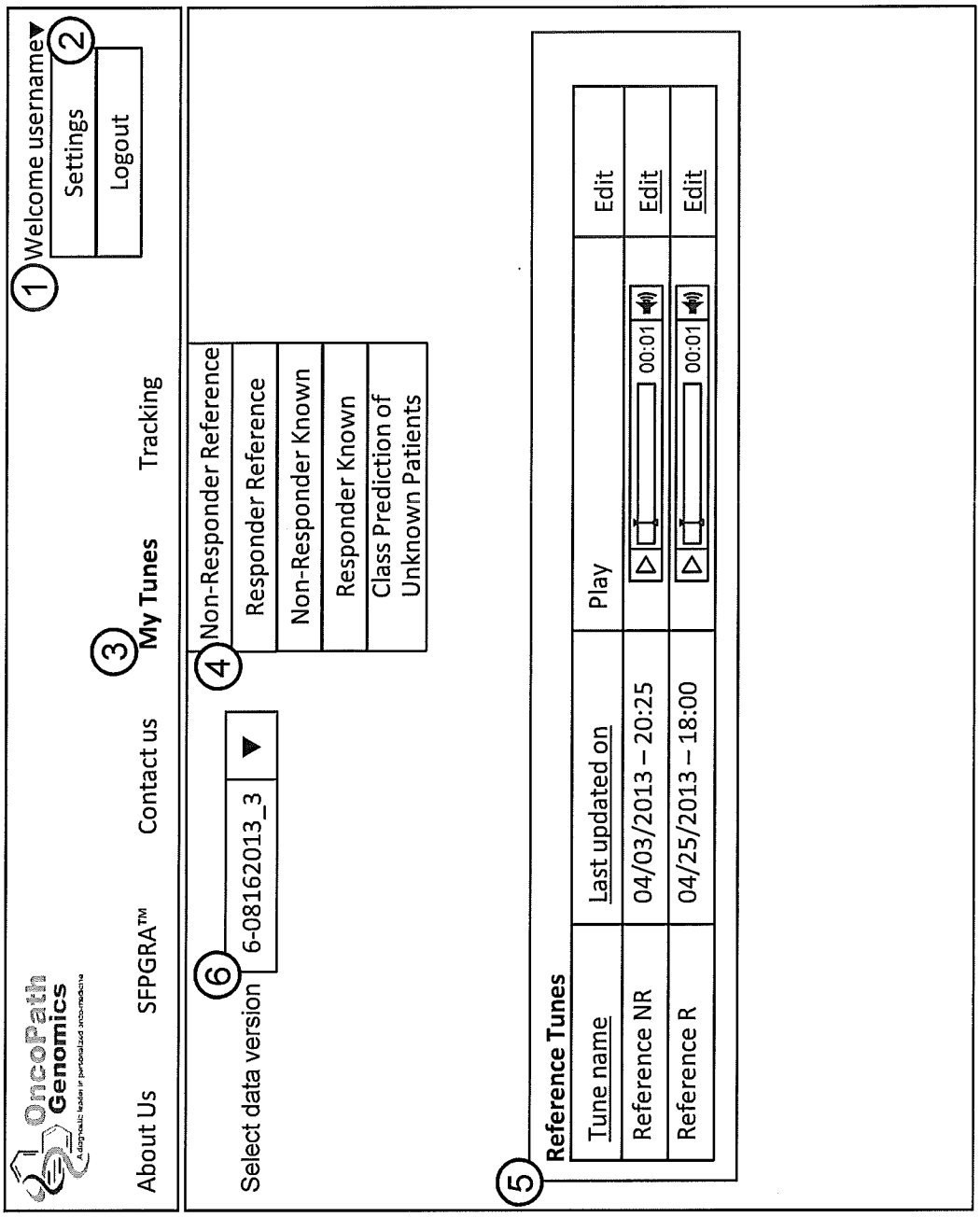
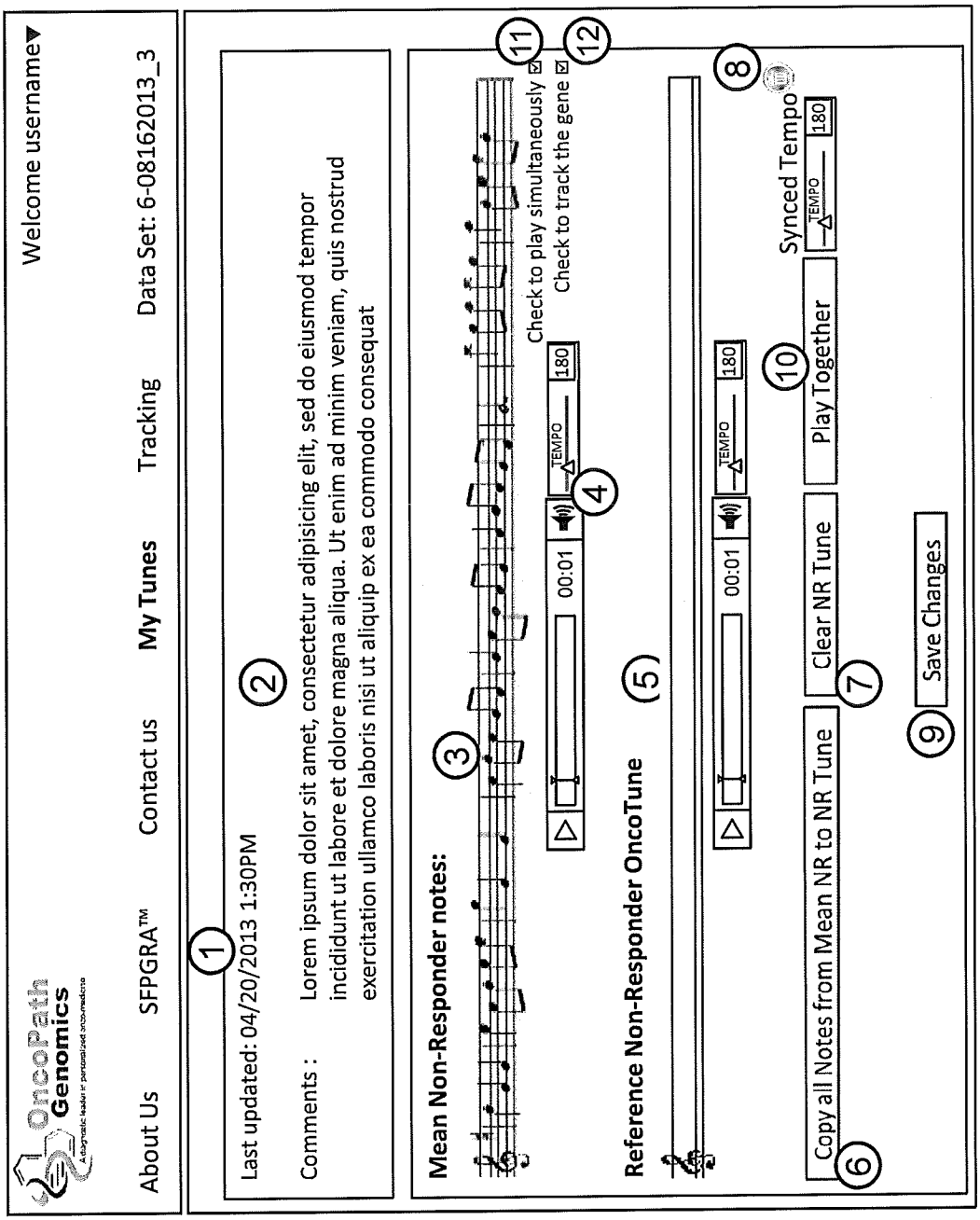

OncoPath Genomics
About Us
SFPGRA™
Contact us
My Tunes
Tracking
1 Welcome username
2 Settings
Logout
3
4 Non-Responder Reference
Responder Reference
Non-Responder Known
Responder Known
Class Prediction of Unknown Patients
6 Select data version 6-08162013_3
5 Reference Tunes
Tune name
Last updated on
Play
Edit
Reference NR
04/03/2013 – 20:25
00:01
Edit
Reference R
04/25/2013 – 18:00
00:01
Edit

FIG. 9C


OncoPath Genomics
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Welcome username
About Us
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Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
1
Last updated: 04/20/2013 1:30PM
2
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Mean Non-Responder notes:
3
11
Check to play simultaneously
12
Check to track the gene
00:01
TEMPO
180
4
Reference Non-Responder OncoTune
5
8
00:01
TEMPO
180
10
Synced Tempo
Play Together
TEMPO
180
6
Copy all Notes from Mean NR to NR Tune
7
Clear NR Tune
9
Save Changes

FIG. 9D

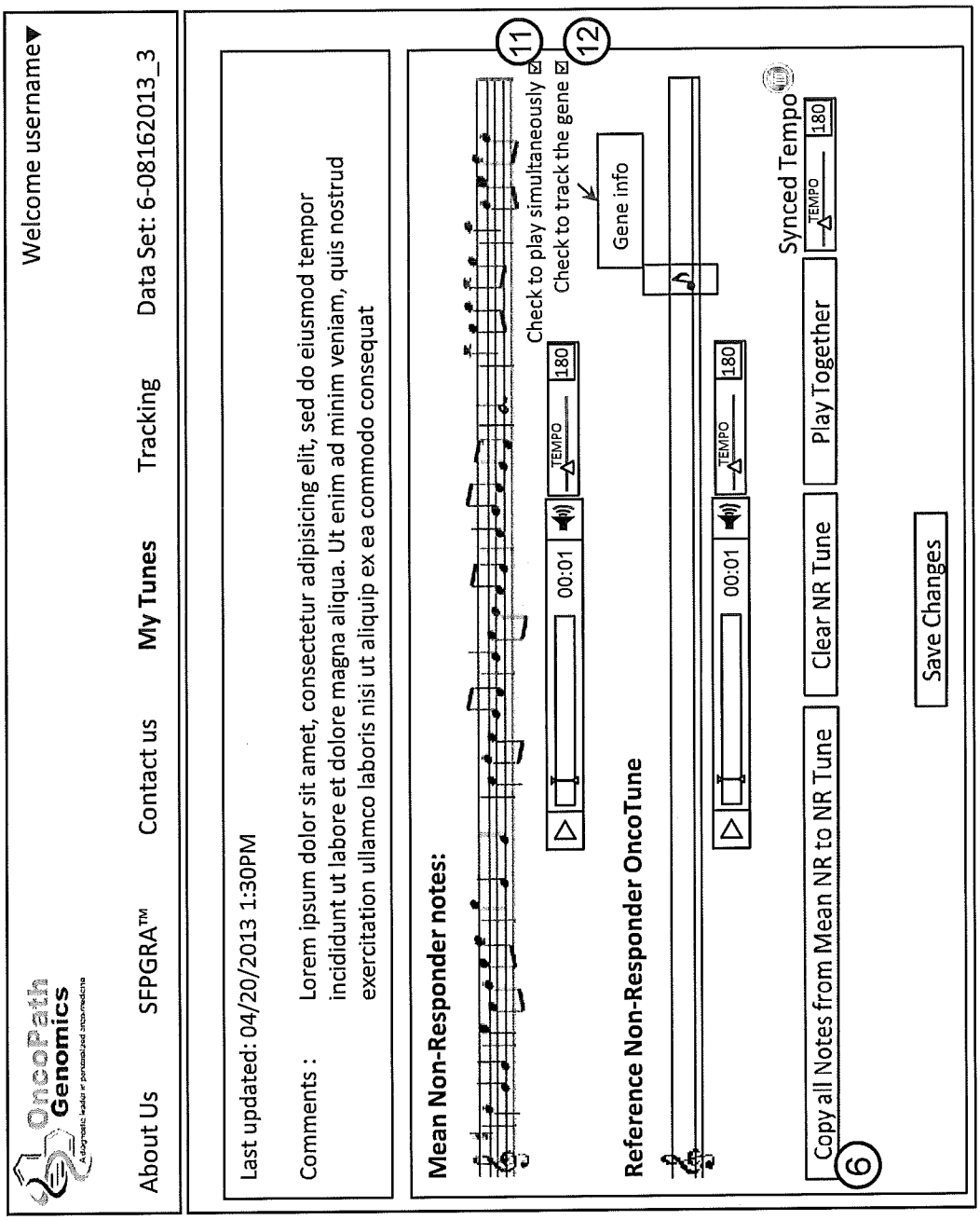
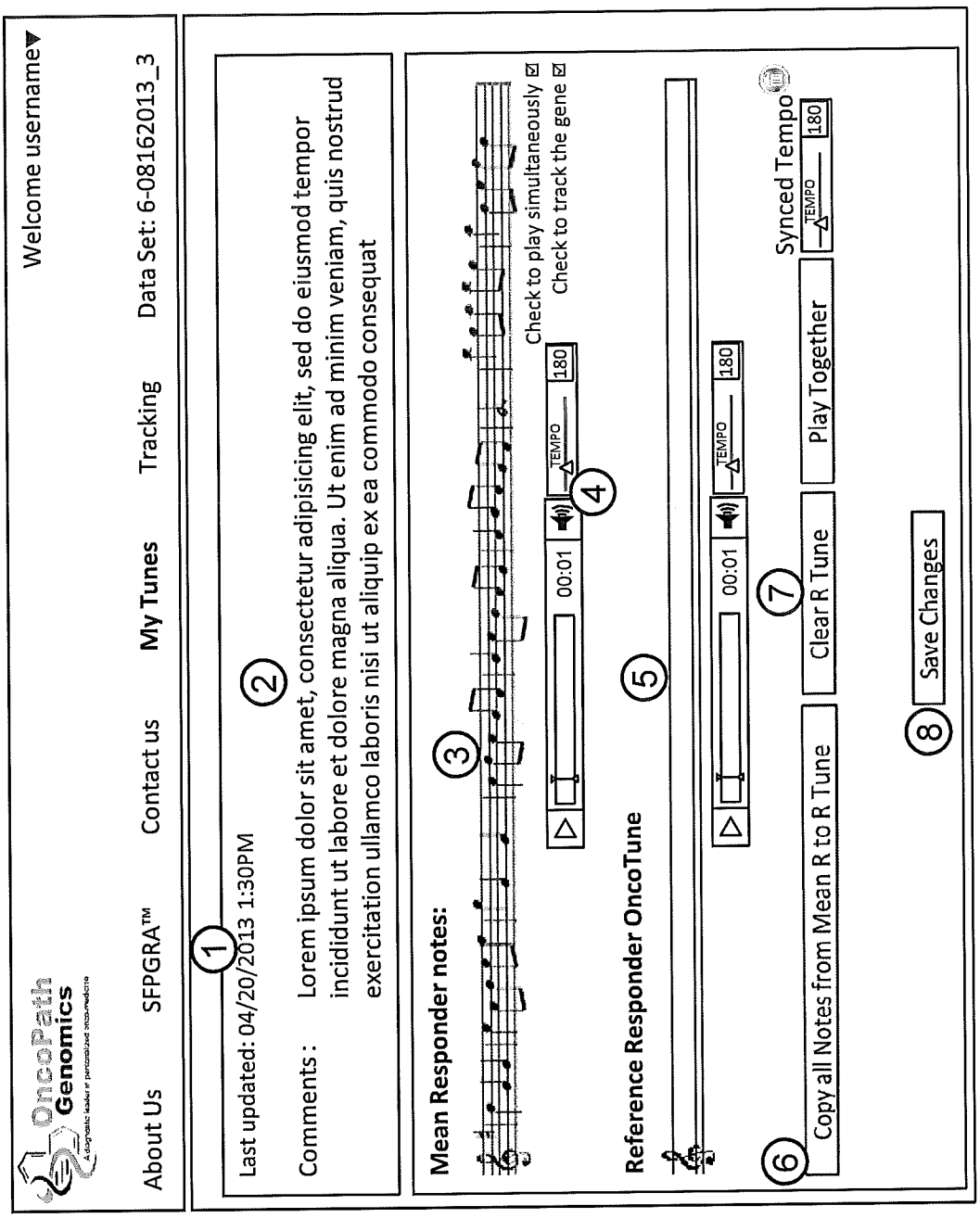

OncoPath Genomics
Welcome username
About Us
SFPGRA™
Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Mean Non-Responder notes:
11
12
Check to play simultaneously
Check to track the gene
TEMPO
180
00:01
Gene info
Reference Non-Responder OncoTune
Synced Tempo
Copy all Notes from Mean NR to NR Tune
Clear NR Tune
Play Together
Save Changes
6

FIG. 9E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My Tunes
Tracking
Data Set: 6-08162013_3
1
Last updated: 04/20/2013 1:30PM
2
Comments :
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Mean Responder notes:
3
Check to play simultaneously
Check to track the gene
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4
Reference Responder OncoTune
5
00:01
TEMPO
180
Synced Tempo
TEMPO
180
6
Copy all Notes from Mean R to R Tune
7
Clear R Tune
Play Together
8
Save Changes

FIG. 9F

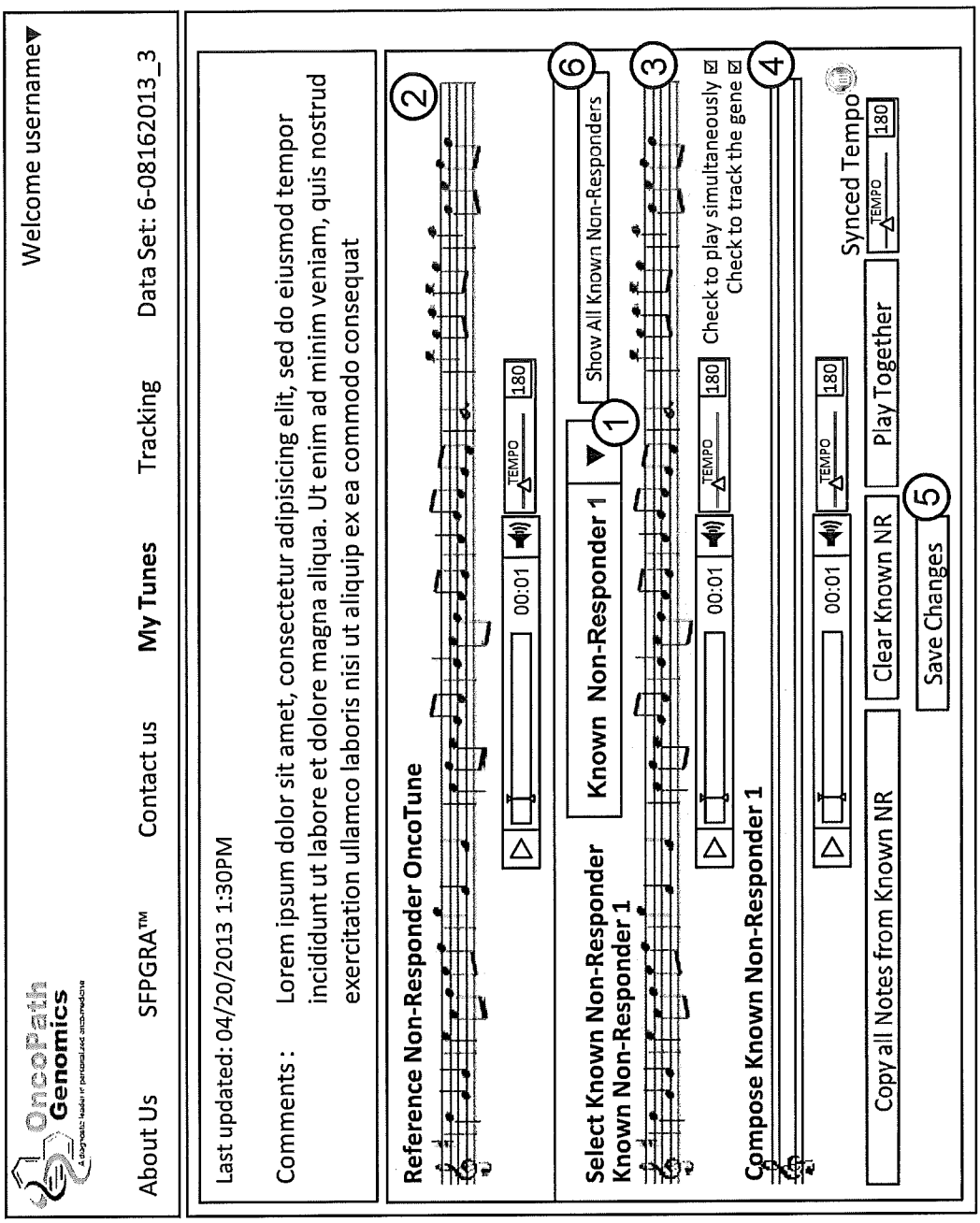
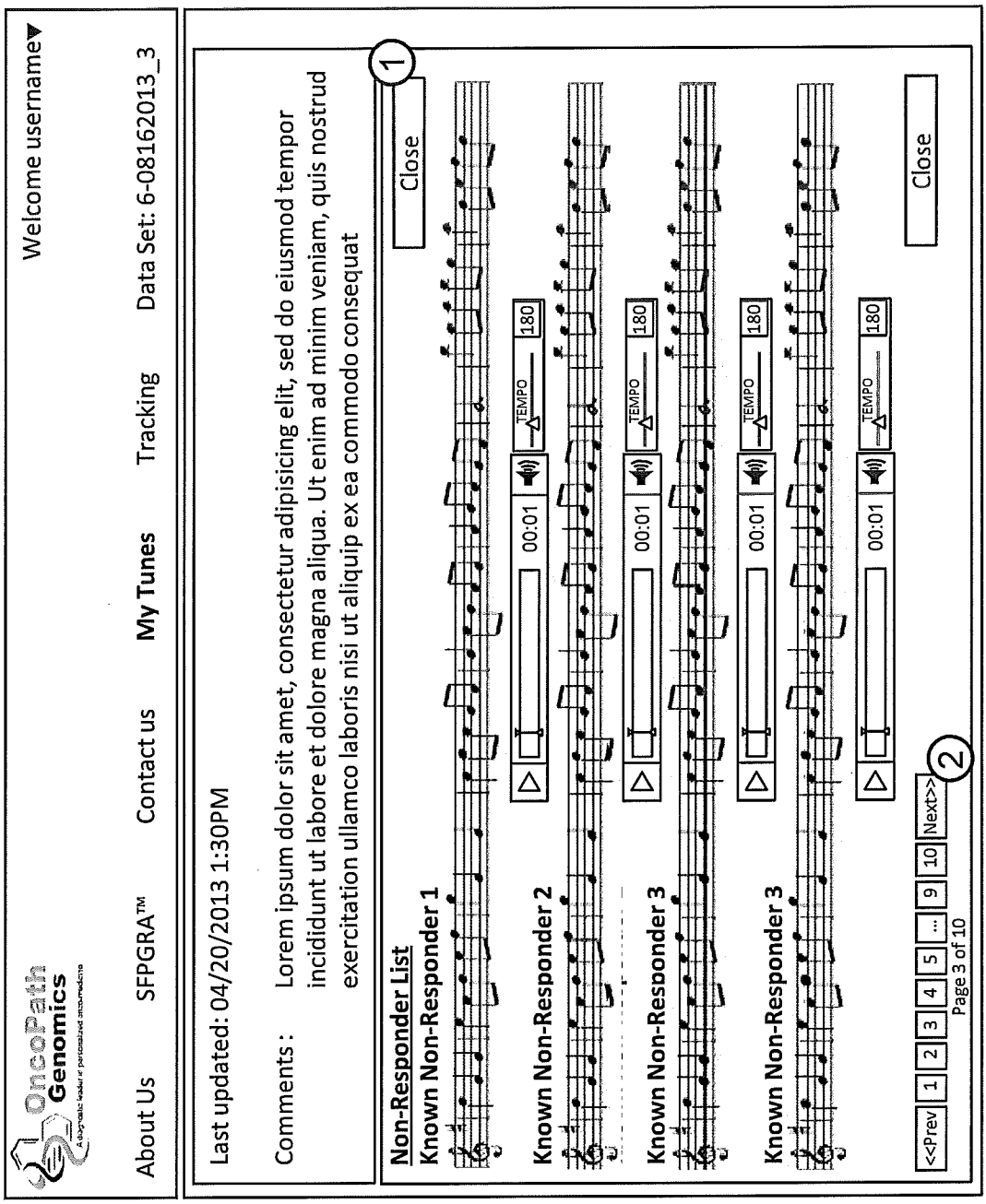

OncoPath Genomics
Welcome username
About Us
SFPGRA™
Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Reference Non-Responder OncoTune
Select Known Non-Responder
Known Non-Responder 1
Compose Known Non-Responder 1
Known Non-Responder 1
Show All Known Non-Responders
Check to play simultaneously
Check to track the gene
TEMPO
180
00:01
Synced Tempo
Copy all Notes from Known NR
Clear Known NR
Play Together
Save Changes
1
2
3
4
5
6

FIG. 9F


OncoPath Genomics
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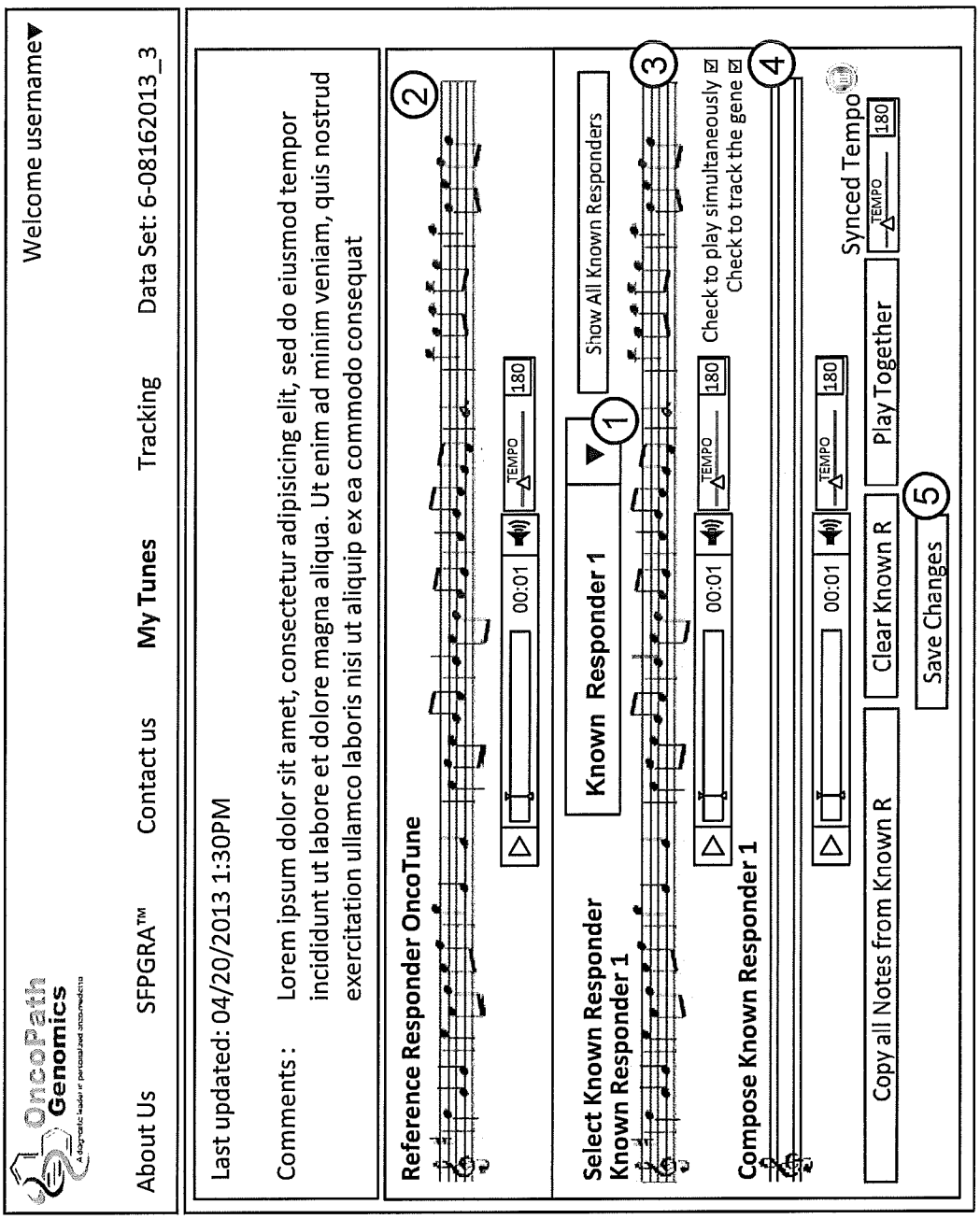
Welcome username
About Us
SFPGRA™
Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Non-Responder List
Close
1
Known Non-Responder 1
Known Non-Responder 2
Known Non-Responder 3
Known Non-Responder 3
00:01
TEMPO
180
<<Prev
1
2
3
4
5
...
9
10
Next>>
2
Page 3 of 10
Close

FIG. 9H


OncoPath Genomics
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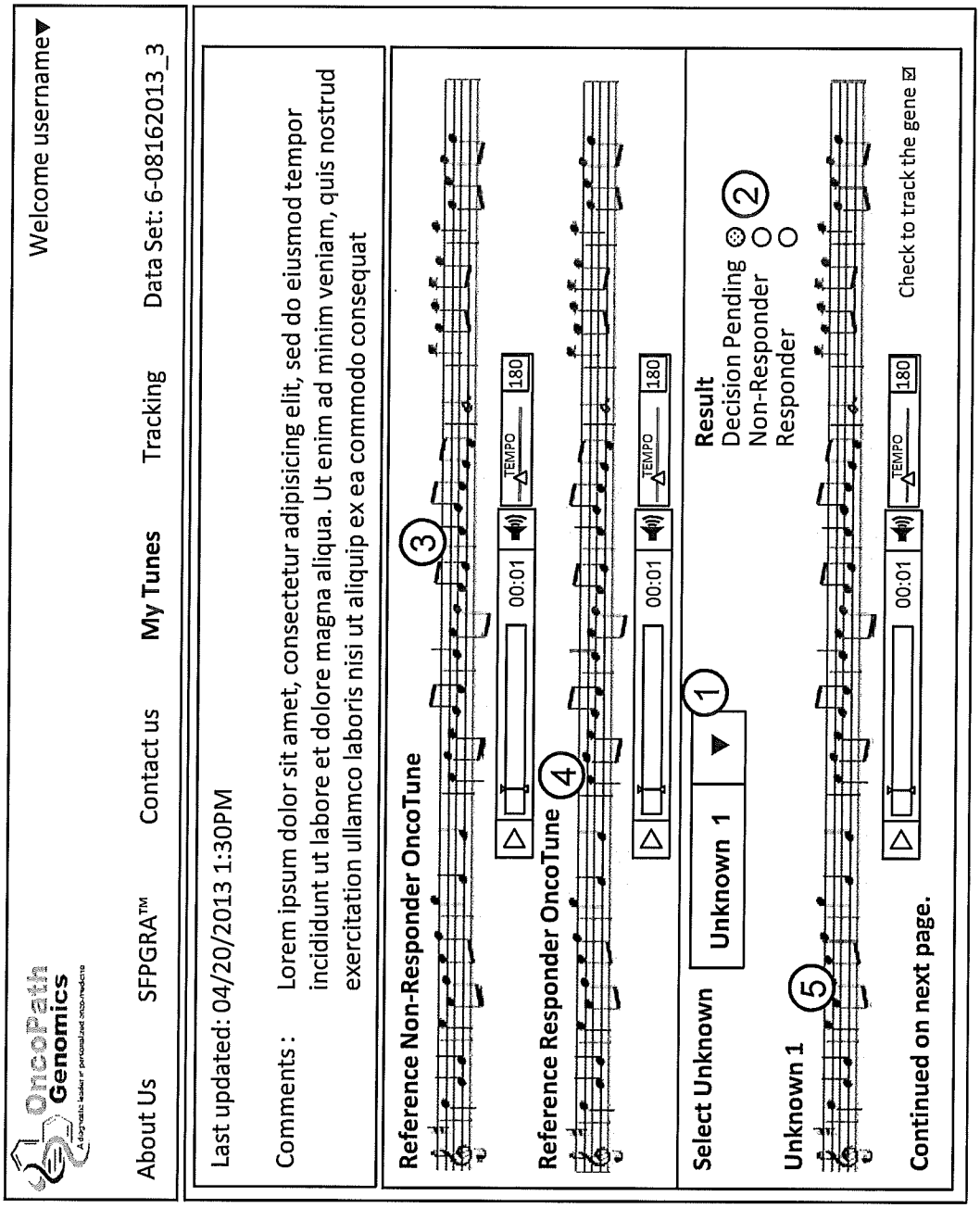
Welcome username
About Us
SFPGRA™
Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Reference Responder OncoTune
00:01
TEMPO
180
Select Known Responder
Known Responder 1
Known Responder 1
Show All Known Responders
Check to play simultaneously
Check to track the gene
Compose Known Responder 1
Synced Tempo
Copy all Notes from Known R
Clear Known R
Play Together
Save Changes
1
2
3
4
5

FIG. 9I


OncoPath Genomics
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Welcome username
About Us
SFPGRA™
Contact us
My Tunes
Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Reference Non-Responder OncoTune
3
TEMPO
180
00:01
Reference Responder OncoTune
4
TEMPO
180
00:01
Select Unknown
Unknown 1
1
Result
Decision Pending
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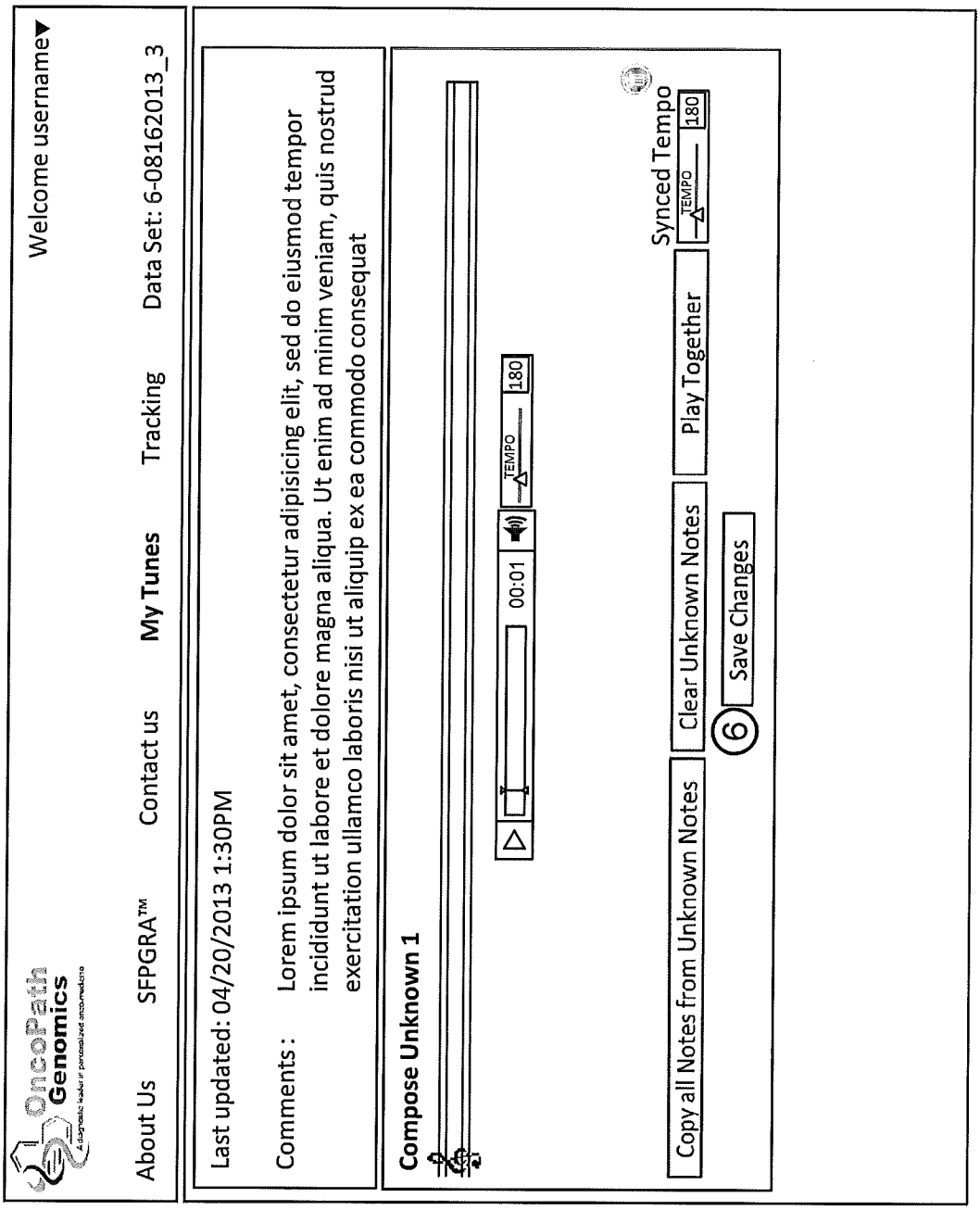
Responder
2
Unknown 1
5
TEMPO
180
00:01
Check to track the gene
Continued on next page.

FIG. 9J


OncoPath Genomics
Welcome username
About Us
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Contact us
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Tracking
Data Set: 6-08162013_3
Last updated: 04/20/2013 1:30PM
Comments :
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat
Compose Unknown 1
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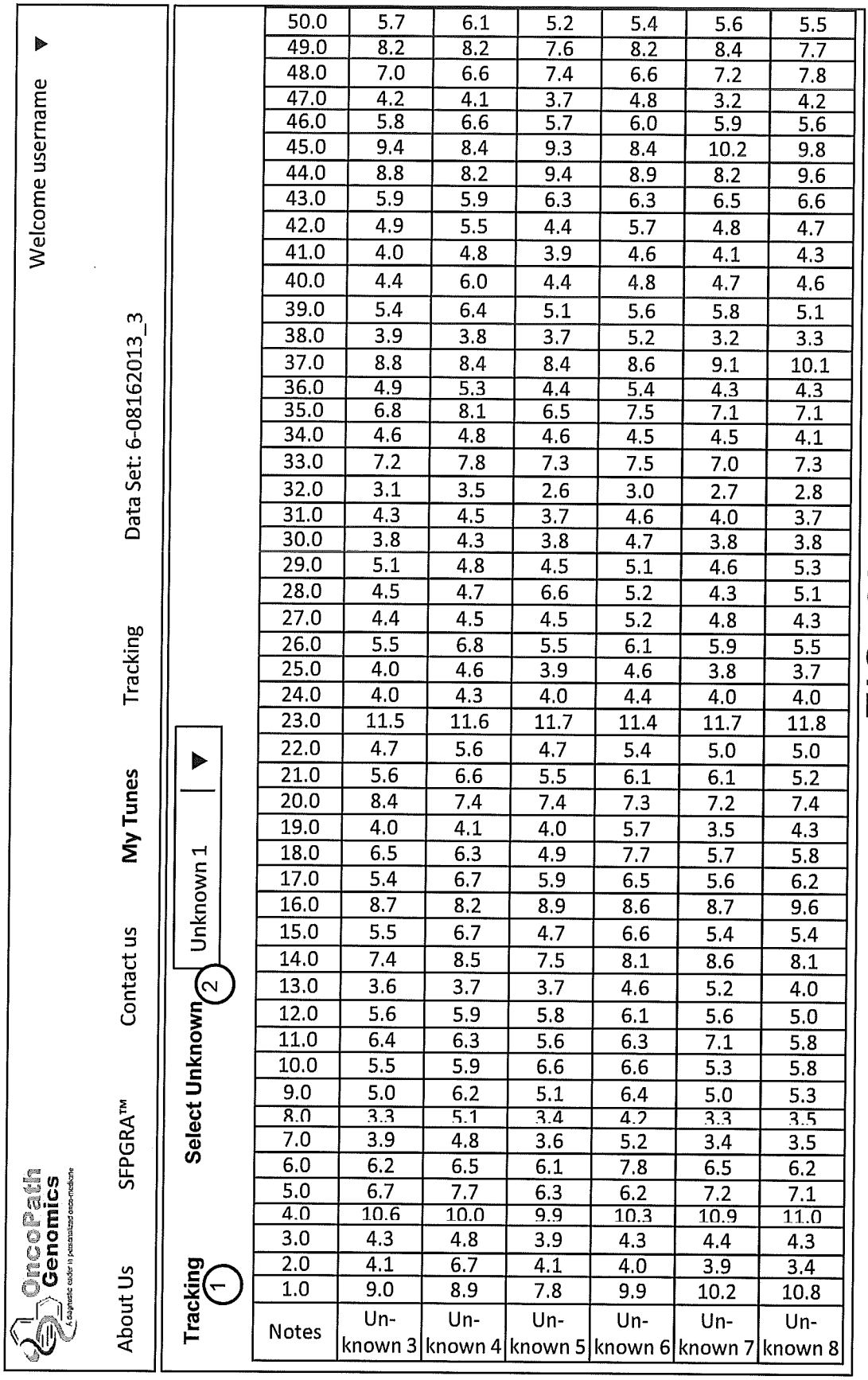
Synced Tempo
TEMPO
180
Copy all Notes from Unknown Notes
Clear Unknown Notes
Play Together
6
Save Changes

FIG. 9K



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48.0	7.0	6.6	7.4	6.6	7.2	7.8
47.0	4.2	4.1	3.7	4.8	3.2	4.2
46.0	5.8	6.6	5.7	6.0	5.9	5.6
45.0	9.4	8.4	9.3	8.4	10.2	9.8
44.0	8.8	8.2	9.4	8.9	8.2	9.6
43.0	5.9	5.9	6.3	6.3	6.5	6.6
42.0	4.9	5.5	4.4	5.7	4.8	4.7
41.0	4.0	4.8	3.9	4.6	4.1	4.3
40.0	4.4	6.0	4.4	4.8	4.7	4.6
39.0	5.4	6.4	5.1	5.6	5.8	5.1
38.0	3.9	3.8	3.7	5.2	3.2	3.3
37.0	8.8	8.4	8.4	8.6	9.1	10.1
36.0	4.9	5.3	4.4	5.4	4.3	4.3
35.0	6.8	8.1	6.5	7.5	7.1	7.1
34.0	4.6	4.8	4.6	4.5	4.5	4.1
33.0	7.2	7.8	7.3	7.5	7.0	7.3
32.0	3.1	3.5	2.6	3.0	2.7	2.8
31.0	4.3	4.5	3.7	4.6	4.0	3.7
30.0	3.8	4.3	3.8	4.7	3.8	3.8
29.0	5.1	4.8	4.5	5.1	4.6	5.3
28.0	4.5	4.7	6.6	5.2	4.3	5.1
27.0	4.4	4.5	4.5	5.2	4.8	4.3
26.0	5.5	6.8	5.5	6.1	5.9	5.5
25.0	4.0	4.6	3.9	4.6	3.8	3.7
24.0	4.0	4.3	4.0	4.4	4.0	4.0
23.0	11.5	11.6	11.7	11.4	11.7	11.8
22.0	4.7	5.6	4.7	5.4	5.0	5.0
21.0	5.6	6.6	5.5	6.1	6.1	5.2
20.0	8.4	7.4	7.4	7.3	7.2	7.4
19.0	4.0	4.1	4.0	5.7	3.5	4.3
18.0	6.5	6.3	4.9	7.7	5.7	5.8
17.0	5.4	6.7	5.9	6.5	5.6	6.2
16.0	8.7	8.2	8.9	8.6	8.7	9.6
15.0	5.5	6.7	4.7	6.6	5.4	5.4
14.0	7.4	8.5	7.5	8.1	8.6	8.1
13.0	3.6	3.7	3.7	4.6	5.2	4.0
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11.0	6.4	6.3	5.6	6.3	7.1	5.8
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7.0	3.9	4.8	3.6	5.2	3.4	3.5
6.0	6.2	6.5	6.1	7.8	6.5	6.2
5.0	6.7	7.7	6.3	6.2	7.2	7.1
4.0	10.6	10.0	9.9	10.3	10.9	11.0
3.0	4.3	4.8	3.9	4.3	4.4	4.3
2.0	4.1	6.7	4.1	4.0	3.9	3.4
1.0	9.0	8.9	7.8	9.9	10.2	10.8
Notes	Un-known 3	Un-known 4	Un-known 5	Un-known 6	Un-known 7	Un-known 8

FIG. 9L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/26982

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; G01N 33/50, 31/00; G06K 9/00 (2014.01)
USPC - 435/6.1, 6.11, 6.14, 702/19, 23; 382/128, 129
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C12Q 1/68; G01N 33/50, 31/00; G06K 9/00 (2014.01)
USPC: 435/6.1, 6.11, 6.14, 702/19, 23; 382/128, 129

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6.1, 6.11, 6.14, 702/19, 23; 382/128,129 704/231, 352/19 (text search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic data bases: PatBase, Google Scholar, Google Patents
Search terms: spectral conversion image or light to sound, algorithm microarray, expression profile, heat map, treatment response, responder, non-responder, patient classification, recurrence, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0247580 A1 (COCHE et al.) 30 September 2010 (30.09.2010). Especially para [0091], [0108], [0109].	1-6
A	US 2006/0132714 A1 (NEASE et al.) 22 June 2006 (22.06.2006). Especially abstract.	1-12
A	WO 2011/055309 A1 (AMEDI et al.) 12 May 2011 (12.05.2011). Especially abstract.	1-12
A	US 2007/0129952 A1 (KENYON et al.) 07 June 2007 (07.06.2007). Especially abstract.	1-12
A	US 2011/0136683 A1(DAVICIONI). 09 June 2011 (09.06.2011). Especially para [0016], [0017], pg 171 table 4.	7-12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 July 2014 (07.07.2014)	01 AUG 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)