J Digit Imaging
DOI 10.1007/s10278-016-9938-1

ENABLE (Exportable Notation and Bookmark List Engine): an Interface to Manage Tumor Measurement Data from PACS to Cancer Databases

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Abstract Oncologists evaluate therapeutic response in cancer trials based on tumor quantification following selected "target" lesions over time. At our cancer center, a majority of oncologists use Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 quantifying tumor progression based on lesion measurements on imaging. Currently, our oncologists handwrite tumor measurements, followed by multiple manual data transfers; however, our Picture Archiving Communication System (PACS) (Carestream Health, Rochester, NY) has the ability to export tumor measurements, making it possible to manage tumor metadata digitally. We developed an interface, "Exportable Notation and Bookmark List Engine" (ENABLE), which produces prepopulated RECIST v1.1 worksheets and compiles cohort data and data models from PACS measurement data, thus eliminating handwriting and manual data transcription. We compared RECIST v1.1 data from eight patients (16 computed tomography exams) enrolled in an IRB-approved therapeutic trial with ENABLE outputs: 10 data fields with a total of 194 data points. All data in ENABLE's output matched with the existing data. Seven staff were taught how to use the interface with a 5-min explanatory instructional video. All were able to use ENABLE successfully without additional guidance. We additionally assessed 42 metastatic genitourinary cancer patients with available RECIST data within PACS to produce a best response waterfall plot. ENABLE manages tumor measurements and associated metadata exported from PACS, producing forms and data models compatible with cancer databases, obviating handwriting and the manual re-entry of data. Automation should reduce transcription errors and improve efficiency and the auditing process.

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Published online: 10 January 2017

Keywords Clinical oncology · Data collection · Efficiency · Multimedia · PACS · RECIST · Data management · PACS metadata

Background

The most common method of assessing tumor burden in cancer trials is determining size change of select metastatic lesions on cross-sectional anatomical imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. RECIST is the criteria used in a majority of our cancer therapeutic clinical trials at the National Institutes of Health Clinical Center (NIH CC) [1] and requires metastatic lesion selection at initiation of treatment with subsequent analysis of lesion size changes over time. This produces enormous amounts of data that need careful management throughout the trial.

RECIST v1.1 quantifies tumor progression based on linear measurements in two dimensions (axial images) of selected patient "target" metastatic lesions (up to five) for each CT or MRI exam [2, 3]. There can be up to 10 metadata values per lesion used in RECIST (see Fig. 1 for an example RECIST form), with an additional 17 data points per set of select images tracked over time. For example, a clinical trial with 50 patients, each of whom has 5 CT exams with three target lesions per exam, results in over 10,000 data points (see Appendix 1 for detailed calculation) that must be managed throughout the trial. These are currently handwritten, typed into medical records, and then retyped at least once into a research information database (see Fig. 2), making this process error-prone and extremely inefficient.

To address these challenges, we have built a computational strategy through a collaboration with our Picture Archiving Communication System (PACS) vendor for image measurements, to be automatically saved for each patient in bookmark lists that are exportable files (e.g., as Excel spreadsheets). This allows for digital management from a single source of truth (SSOT), as opposed to inefficient and error-prone manual data management.

We developed an interface we term "Exportable Notation and Bookmark List Engine" (ENABLE) which extracts verified data from files that have been directly exported as standalone files from PACS and which performs RECIST calculations (percent tumor size change), compiles patient cohort data in a single document (with all pertinent calculations), and auto-populates a summary document (an NCI RECIST worksheet, see Fig. 1a) that is used in our cancer center.

We also built ENABLE to produce data which is natively compatible with Labmatrix (BioFortis, Columbia, MD), one of the research information databases in use in the NIH CC. This allows direct uploading of patient tumor measurement data into Labmatrix, promoting digital management of data at the source of input and aiming to improve efficiency and minimize transcriptional transfer errors.

Current Data Flow

Following CT or MRI acquisition on cancer patients, radiologists report findings (the traditional clinical report), often including "index" lesion measurements (not necessarily "target" lesions). It is well known that radiologists often do not include the necessary quantification of imaging on cancer patients required for tumor assessments on clinical trials [4, 5]. When oncologists review tumor images on CT or MRI without target lesion measurements, they proceed to measure these lesions themselves or request consultations with radiologists to ensure objective and verified measurement of target lesions.

Our oncologists perform RECIST calculations manually for each patient visit, followed by data entries into multiple databases (for example: handwritten RECIST worksheets, the electronic medical record, research databases, and onsite files such as Excel for further analysis). This inefficient flow of information is outlined in Fig. 2. In addition to being extremely inefficient, this repeated transcription process is inherently error-prone and promotes incorrect or discrepant tumor measurements [6]. ENABLE encourages (rather than "resists") radiologists and oncologists to collaborate in patient tumor assessment [5].

Many oncologists also produce visual analytics such as waterfall plots [7, 8] to show each patient's overall best response to report on therapeutic efficacy according to RECIST guidelines. This is one of many analytic displays driving the need for patient data to be automatically batched into one source with correct RECIST calculations.

Improving the Data Flow

Our PACS system allows radiologists and oncologists to co-register several cross-sectional exams from two or more time points [9], allowing measurements to be automatically or semi-automatically related over time based on their location and surrounding anatomy [10]. Moreover, multimedia-enhanced radiology reports with hyperlinked measurements [11] and the inclusion of a radiologist assistant (radiology postdoc, fellow or technologist that verifies baseline date and relates known target lesions over time) has been shown to increase measurement consistency among radiologists and oncologists [12]. This makes it easier to verify data—a prerequisite to semi-automated data management.

Target lesion measurements and associated metadata are all stored within our PACS in an organized, exportable database known as a Bookmark List that is easy to export and digitally manage in a structured format, obviating the need for handwriting and duplicating data

a

MEDICAL RECORD	Tumor Measurements/RECIST Criteria

Protocol Number:	Course#:	Baseline	Or Follow-up

Comments:

LESIONS

Lesion #	Site/Description	Target	New Lesion or Progression	Modality	Contrast	S/I#	RECIST Diam (cm)	Date of Test

Overall Response and Criteria Evaluation Definitions:

CR = Complete Response
PR = Partial Response
PD = Progressive Disease
SD = Stable Disease
IR = Indeterminate Response

RECIST Criteria Evaluation (Targeted) *

PD = Current: Sum >20% increase from the best response
PR = Current: sum >30% decrease from baseline sum
SD = Anything else except complete response
CR = All lesions gone and tumor markers normal

RECIST Criteria Evaluation (Non-Targeted) **

PD = Any new lesions or worsening non-targeted lesions
CR = No non-targeted lesions
IR/SD = Anything else

Overall Response Evaluation Table ***

Targeted	Non-Targeted	Overall
PD	Any	PD
Any	PD	PD
CR	CR	CR
CR	SD	PR
PR	SD	PR
PR	CR	PR
SD	SD	SD
SD	CR	SD

Current Targeted Lesion Sum	
Targeted Lesion Baseline Sum	
Targeted lesion best Response Smallest Sum	
% change from Best Response	
% change from Baseline	
Targeted Lesions Response*	
Non-targeted Lesions Response**	
OVERALL RESPONSE*** (use Overall Response Evaluation table on left to determine)	
Date Measured:	
Measured By:	
Recorded By:	
Verified By:	

Patient Identification

Tumor Measurement/RECIST Criteria Section: Measurements, Other

b

MEDICAL RECORD	Tumor Measurements/RECIST Criteria

Protocol Number: 12-L-1234	Course#:	Baseline	Or Follow-up	X

Comments:

LESIONS

Lesion #	Site/Description	Target	New Lesion or Progression	Modality	Contrast	S/I#	RECIST Diam (cm)	Date of Test
1	F01/ Target 1 LT lung mass	T		CT		4/90	3	**DATE**
2	F02/ Target 2 LT lower lung mass	T		CT		4/121	1.9	**DATE**
3	F03/ NT peritoneal mass	NT		CT		2/70	2.5	**DATE**

Overall Response and Criteria Evaluation Definitions:

CR = Complete Response
PR = Partial Response
PD = Progressive Disease
SD = Stable Disease
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RECIST Criteria Evaluation (Targeted) *

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IR/SD = Anything else

Overall Response Evaluation Table ***

Targeted	Non-Targeted	Overall
PD	Any	PD
Any	PD	PD
CR	CR	CR
CR	SD	PR
PR	SD	PR
PR	CR	PR
SD	SD	SD
SD	CR	SD

Current Targeted Lesion Sum	4.9
Targeted Lesion Baseline Sum	4.4
Targeted lesion best Response Smallest Sum	4.9
% change from Best Response	11.4
% change from Baseline	11.4
Targeted Lesions Response*	SD
Non-targeted Lesions Response**	SD
OVERALL RESPONSE*** (use Overall Response Evaluation table on left to determine)	SD
Date Measured: **DATE**	
Measured By: Dr. Bob Jones	
Recorded By:	
Verified By:	

Patient Identification
John Doe
MRN#1234567

Tumor Measurement/RECIST Criteria Section: Measurements, Other

Fig. 1 Blank (*left*, **a**) and prepopulated RECIST sheet (*right*, **b**). **a** (*left*) Unpopulated (blank) digital RECIST worksheet used at our research center. **b** (*right*) Populated RECIST worksheet semi-automatically generated by ENABLE as one of several output possibilities. These sheets can be saved in Word or a PDF and electronically signed and imported into our EMR

entry steps from the workflow. Utilizing our PACS capability to export this tumor data in a consistent format, we developed ENABLE to automate a majority of the data management aspects of the tumor assessment workflow.

Methods

Testing Data

As part of a quality improvement initiative, we retrospectively assessed CT scans of the chest, abdomen, and pelvis and reviewed previously measured metastatic lesions from eight sarcoma patients enrolled in an IRB-approved therapeutic trial (NCT01343043) with available RECIST tumor measurement data within PACS from November 2013 to August 2016 in order to make calculations and data comparison (group 1). All data was managed in a HIPAA-compliant manner on a secure server (see Appendix 2 for more details).

For best-response waterfall plot construction, we additionally assessed 42 metastatic genitourinary cancer patients enrolled in a separate IRB-approved therapeutic clinical trial (NCT01688999) with available RECIST data within PACS from September 2015 to February 2016 (group 2).

The Bookmark List

Tumor data is stored in our PACS within the *Bookmark List* in a structured manner, separated into columns based on user configurable categories. For the purpose of automation and to meet our cancer trial needs, we configured the view for all radiologists and assistants to a standardized bookmark list displaying the following necessary tumor data categories:

> *Study description, Patient name, Follow-up designator, Annotation name, Tool used, Lesion description, Target, Lesion subtype (liver, lung, lymph, other), Series number, Slice number, Long diameter (cm), Short diameter (cm), RECIST diameter (cm)*, and name of provider making the annotation (*creator*).

For standardization and minimization of errors, we used centimeters (cm) to one tenth of a centimeter (rather than millimeters (mm)) and hence configured our PACS to manage measurements similarly. Our radiology reports on cancer patients presenting measurements only

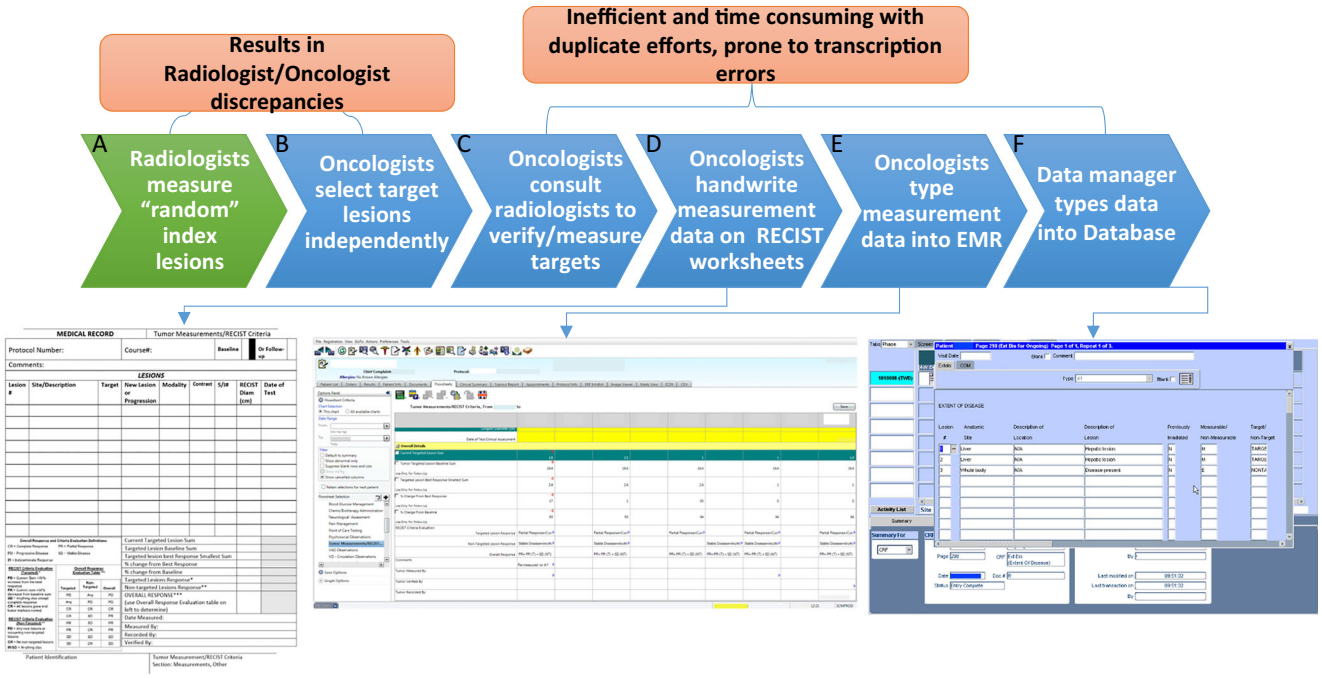

Fig. 2 Current example of information flow. The *flowchart* above outlines the current tumor assessment process involving manual calculations, handwriting, and repeated data entry: *A* Radiologists measure some of the clinically relevant subjective arbitrary lesions on CT. *B* Oncologists often independently select the same or different target lesions and measure them or, if target lesions were reported by radiologists (becoming more common now with multimedia reporting), extract these from reports. *C* Oncologists often consult with radiologists to obtain/verify measurements of target lesions. *D* Research nurse or study research coordinators then handwrite measurement data on RECIST worksheets. *E* This is followed by typing measurement data into our EMR. *F* Finally, data managers re-type the same data into multiple databases (since they are currently incompatible systems at our hospital). Thanks to multimedia reporting and new workflows, radiologists are now measuring target lesions more consistently, resulting in fewer consultations for target lesion selection. Additionally, steps D through F are essentially combined when using ENABLE interface and workflow. See Fig. 7 for streamlined digital workflow

in centimeters, also to a tenth of a centimeter (and not mm). Although measurements are currently exported from our PACS in millimeters, ENABLE converts them to centimeters.

Two additional parameters constitute the filename when exporting the Bookmark List from PACS, which are patient identifiers (*Medical Record Number*) and research study (*Protocol Number*).

To ensure sustainability and longevity of this solution, other data fields necessary in cancer criteria and oncology decisions can also be handled by the interface. Oncologists often request for volumetric analysis; for example, some of our cancers are followed by the Viable Tumor Volume method [13], which is available in our bookmark tools for exportation as *Volume* cm^3 with all HU values reflecting their necrosis (Table 1).

Within the bookmark list, separate scan data are delimited by a *study header* that contains data regarding the exam date, time, modality, and other data used for storage and organization within PACS. Within each exam, the data for each lesion is reproduced in a table within a row corresponding to the lesion.

An example bookmark list (as seen in PACS) is shown in Fig. 3, showing the "export table" capability to save as Excel, resulting in a structured file (shown in Fig. 4).

ENABLE Algorithm Outline

Our proof-of-concept interface ENABLE was developed in the widely available Microsoft (Redmond, WA) Visual Basic for Applications (VBA) language, which fit our program's needs, allowing for easy manipulation of the structured bookmark lists in Excel. ENABLE automatically performs calculations (e.g., RECIST v1.1 criteria), compiles patient cohort data, creates populated data models, and allows for data to be managed digitally. The interface algorithm is outlined in the flowchart in Fig. 5.

The interface has the ability to process single or sets of files of patient measurement data. Files are imported into the interface as separate Excel files, and the data inside each file is copied by the interface into a separate spreadsheet within an Excel workbook.

Table 1 Data fields managed by ENABLE

Field label	Purpose and available options	Example
Study description	Date, time, and type of exam (CT, MRI, PET). This information is saved as tab delimited along each of the data element rows	Jun 23, 2014 2:08 p.m., CT, (251 days from baseline)
Patient name	Patient first, middle, and last name	John R. Doe
Follow-up	Indicates the lesion's follow-up designator over time. When a measurement of the same anatomic location is available for two or more time points, it is set as a follow-up series, numbered in sequential order.	F01, F02, F03
Name	Name of the annotation (measurements, arrows, etc.), used for identification in each time point. It is set automatically in sequential order by PACS and to streamline audit trails	B01, B02, etc.
Tool	Indicates the measurement tool utilized (e.g., one-diameter, two-diameter, linear, segmentation, etc.)	Two-diameter
Lesion description	Qualitative description of the lesion	"Left hilar node"
Target	Indicates if lesion is target, non-target, or unspecified	Target
Lesion subtype	Indicates lesion type (lymph, lung, liver, other) and affects the RECIST diameter	Lymph
Series number	Axial image series on which the measurement was made	3
Slice number	Slice number on which the measurement was made	191
RECIST diameter (cm)	Lesion diameter required for RECIST calculations dependent on subtype: lymph node would be short diameter, all others will be long axis	2.3 cm
Long diameter (cm)	The longest axial diameter of the lesion	2.3 cm
Short diameter (cm)	The largest diameter perpendicular to the longest diameter (AKA "short axis")	1.5 cm
Creator of measurement	Name of the provider who made the measurement	Dr. Bob Jones
Medical record number	Unique patient identifier	1234567
Protocol number	Research protocol identifier	12-L-3456
Volumetric size (cm^3)	Volumetric size	53.2 cm^3
Hounsfield unit (HU) mean	Hounsfield unit mean determined for region of interest (ROI) and/or volume of interest (VOI)	32 Hu
Product of diameters	Product of lesion diameters (long × short diameter)	25 cm^2

Also included are volumetric size (cm^3), Hounsfield unit (HU) mean (from region of interest (ROI) or volume of interest (VOI)), and product of diameters, all of which could be necessary in the research setting

To apply the RECIST v1.1 criteria, the columns pertaining to this data are identified and their indices are stored. Since bookmark lists contain all metadata fields (shown in Table 1) made on a patient's imaging study (e.g., CTs, MRI, etc.), there is a large amount of extraneous data that is not pertinent to tumor burden assessment and is thus removed (this is configurable) to improve readability while allowing data flow to be more manageable.

To accomplish this, the interface parses the lesion data in each row of the table, identifying rows for removal. Lesions not marked as "Target" or "Non-Target" are removed, since only Target and Non-Target lesion measurements are used for RECIST v1.1 calculations.

Calculations are performed once all extraneous data are removed (Table 2). For each patient, the sums of the RECIST diameters are computed for Target lesions on baseline exam and each subsequent exam. The percent changes in the sums are then computed in reference to the baseline sum and best response, which is the CT exam with the smallest sum of target diameters achieved during the study (without new lesion present). All of the RECIST data are stored in the corresponding patient spreadsheet.

ENABLE allows for a streamlined creation of waterfall plots digitally since the RECIST data is available in the master spreadsheet. Overall responses of all patients are available at-a-glance and are based on the smallest sum of all target lesions according to RECIST.

Sustainability

To assure ease of use, seven users with a range of education (from college students to physicians) were taught how to use the interface with a brief instructional video. The output of the interface after their use was verified to determine if the staff members used it correctly.

Data Comparison Method

We compared existing RECIST data from group 1 (the eight sarcoma patients) recorded by oncologists with the RECIST outputs generated by ENABLE these patients' bookmark lists

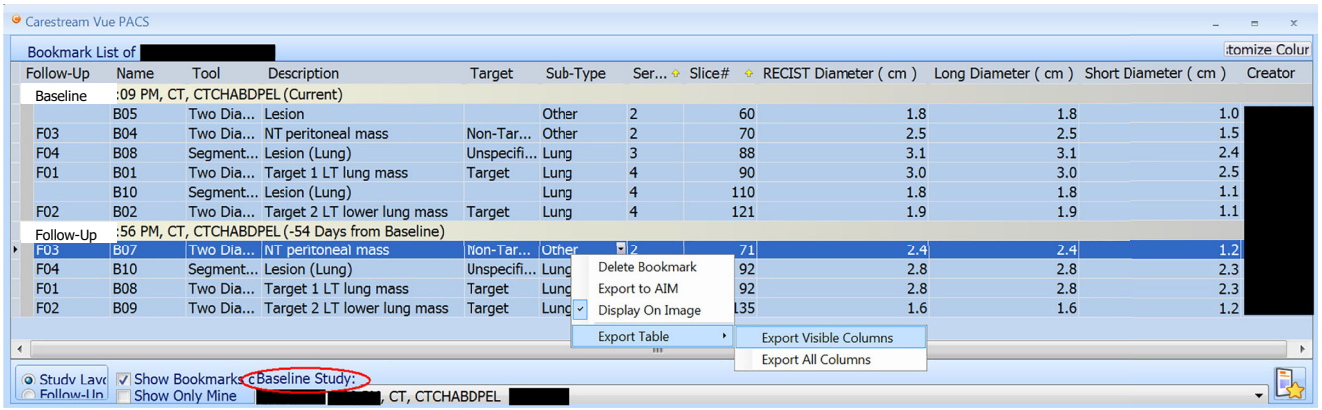

Fig. 3 Bookmark list in PACS. Figure 3 shows a PACS Bookmark List where all annotation data for a patient's exams appear. In this example, there is one baseline exam and one follow-up, each with two target lesions and one non-target lesion measured and related in the current time point to prior lesion (F01 and F02 as targets and F03 a non-target lesion). Also, note the baseline date (blacked out along with private patient data) at the *bottom of the table* (*circle in red* for clarification). The "Export table" option to "Export Visible Columns" results when one right clicks the list, resulting in the Excel document shown in Fig. 4 (color figure online)

exported from PACS. The following information was considered for comparison:

> Patient name, lesion description, Target or Non-Target classification, series number, slice number, RECIST diameter, date, follow-up or baseline selection, target lesion RECIST sum of current exam, and the percentage target lesion size change from baseline.

There were a total of 27 unique lesions with 6 corresponding data points each (RECIST diameter, series number, slice number, exam date, target or non target selection, lesion descriptor) and 4 data points corresponding to each of the 8 patients compared (patient name, protocol number, medical record number, baseline, or follow-up exam), yielding a total of 194 data points which were compared.

Waterfall Plot-Batched Files

We created a waterfall plot from 42 patients' data in group 2. We then checked that the data output by the interface matched with the data used to manually create the plot by comparing: baseline sum, best response sum, and percent change.

Results

Testing Data

To use the interface, users saved the bookmark lists in a common location on a secure server. The three outputs (RECIST worksheets, compiled data, and Labmatrix model) were exported onto the secure server, in the same location where

	Study Description	Patient Name	Follow-Up	Name	Tool	Description	Target	Sub-Type	Series	Slice#	RECIST Diameter (cm)	Long Diameter (cm)	Short Diameter (cm)	Creator
1														
2	STUDY INSTANCE UID: 12345671234567123456 7													
3	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name	F01	B01	Two Diameters	Target 1 LT lung mass	Target	Lung	4	90	3	3	2.5	Dr name
4	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name	F02	B02	Two Diameters	Target 2 LT lower lung mass	Target	Lung	4	121	1.9	1.9	1.1	Dr name
5	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name	F03	B04	Two Diameters	NT peritoneal mass	Non-Target	Other	2	70	2.5	2.5	1.5	Dr name
6	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name		B10	Segmentation	Lesion (Lung)		Lung	4	110	1.8	1.8	1.1	Dr name
7	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name		B08	Segmentation	Lesion (Lung)		Lung	3	88	3.1	3.1	2.4	Dr name
8	"EXAM DATE" 1:09 PM, CT, CTCHABDPEL	Patient Name		B05	Two Diameters	Lesion		Other	2	60	1.8	1.8	1	Dr name
9	STUDY INSTANCE UID: 12345671234567812345 8													
10	"EXAM DATE" 2:56 PM, CT, CTCHABDPEL	Patient Name	F01	B08	Two Diameters	Target 1 LT lung mass	Target	Lung	4	92	2.8	2.8	2.3	Dr name
11	"EXAM DATE" 2:56 PM, CT, CTCHABDPEL	Patient Name	F02	B09	Two Diameters	Target 2 LT lower lung mass	Target	Lung	4	135	1.6	1.6	1.2	Dr name
12	"EXAM DATE" 2:56 PM, CT, CTCHABDPEL	Patient Name	F03	B07	Two Diameters	NT peritoneal mass	Non-Target	Other	2	71	2.4	2.4	1.2	Dr name
13	"EXAM DATE" 2:56 PM, CT, CTCHABDPEL	Patient Name		B02	Line			Line	3	-1	15.7			Dr name

Fig. 4 The structured bookmark list (exported from bookmark list in Fig. 3). The data exported using the "Export Visible Columns" option appears as shown. The data are separated into columns pertaining to the fields described in Table 1. Each set of exam data is separated by study headers, which can be seen in *rows 2* and *9* (*gray rows*). Please note that figs. 3 and 4 were captured at different points in time, resulting in minor discrepancies in the lesions present in the images. For example, F04 does not appear in figure 4 whereas it is present in fig. 3, since it did not require follow up

the bookmark lists were saved, then edited or uploaded to predetermined locations.

Bookmark List

All patients bookmark lists were exported containing the necessary columns, and prior to exportation the target and non-target lesions were correctly related over time. Also, target and non-target lesion location was described under the "Lesion description" field in order to ensure verified measurement exportation for the interface (e.g., "Target 1 Left lower lobe nodule"). See Appendix 3 for more details.

Interface Implementation

Outputs

Once all calculations are performed, ENABLE generates three main outputs: (1) prepopulated RECIST worksheets, (2) compiled cohort data, and (3) data models for upload to research information databases (see Figs. 5 and 6).

1. Electronic RECIST sheets are generated by printing all relevant tumor and RECIST data to a digital version of the RECIST sheet (a Word document) ready for electronic signature. It is optional to convert to a PDF for upload to electronic medical record systems. An example is shown in Figs. 1b and 6(1).
2. Two files of cohort data are compiled:
    a. First, all of the individual patient spreadsheets are compiled into a single spreadsheet which can be useful for multicenter trials, outside institutes, or industry, also helping to streamline the auditing process.
    b. The second set of compiled data contains patient identifiers and specific information such as percent change from baseline. This document can be used for further research and statistical analyses, as well as to create cohort analytics and informative displays such as waterfall plots.
3. The final output of the interface is a dataset which contains the information for all of the patients in a study and which conforms to the data model of a research information database used by the research team. For example, ENABLE produces a compatible data model which can be uploaded directly into Labmatrix, a commercially available database used at the NIH CC that also contains all clinical and research data (lab values, clinical notes, genetic data, etc.).

We are currently working to incorporate more databases in the future such as the Cancer Clinical Center (C3D Oracle Clinical, Oracle, Redwood City, CA) since this is also used at the NIH CC.

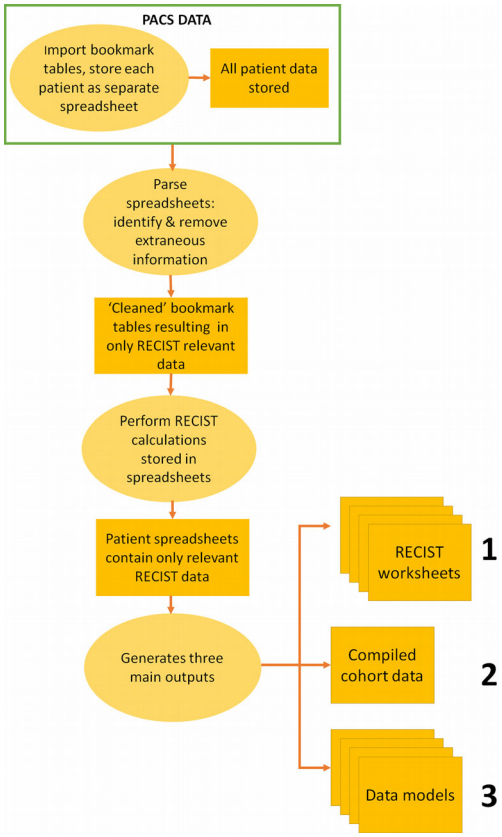

Fig. 5 *Flowchart algorithm* outlining interface data processing. *Rectangles* represent data or information, and *ovals* represent processes. The *flowchart* describes how the input data are manipulated to produce the three interface outputs 1) RECIST worksheets, 2) compiled cohort data, and 3) data models)

Interface Performance

Computer Specifications We ran ENABLE on an Intel Xeon E5-2603 workstation (2 cores) with 16GB RAM, running 64-bit Windows 7 Enterprise Service Pack 1.

Sustainability: Ease of Use

All seven of the staff who viewed the tutorial were able to use it successfully with consistent outputs, showing promise that this is a sustainable solution.

Data Comparison

Data Flow Comparisons

Interface-driven flow of information is outlined in Fig. 5.

Table 2 RECIST calculations produced by ENABLE

Lesion	Target	RECIST diameter (cm)	Target RECIST sum (cm)	Target RECIST percent change (%)	Non-target RECIST sum (cm)	Non-target RECIST percent change (%)	Best response sum (cm)	Target response	Non-target response	Overall response	Exam type	Patient name	MRN	Protocol no.
Follow-up 2			6.7	−37	5.5	4	6.7	PR	SD	SD	CT		1234567	12-L-12
Target lesion 1	Target	4.2												
Target lesion 2	Target	2.5												
Non-target lesion 1	Non-target	4.6												
Non-target lesion 2	Non-target	0.9												
Follow-up 1			10.3	−3	7.3	38					CT			
Target lesion 1	Target	7.5												
Target lesion 2	Target	2.8												
Non-target lesion 1	Non-target	6.5												
Non-target lesion 2	Non-target	0.8												
Baseline			10.6		5.3						CT			
Target lesion 1	Target	8.7												
Target lesion 2	Target	1.9												
Non-target lesion 1	Non-target	4.7												
Non-target lesion 2	Non-target	0.6												

This table shows examples of RECIST diameters and calculations often performed by oncologists. This example shows a baseline study and two follow-up CT exams with two target and two non-target lesions. In the "Lesion" column is the lesion name (these characters were entered manually in PACS, for example, "left upper lobe", etc.). Column "Target" depicts whether it is a target or a non-target lesion, "Target RECIST sum" represents sum of target RECIST diameters, and "Target RECIST percent change" is the percentage change of target lesions from baseline to determined time point (the same with non-target lesion in lasts two columns)

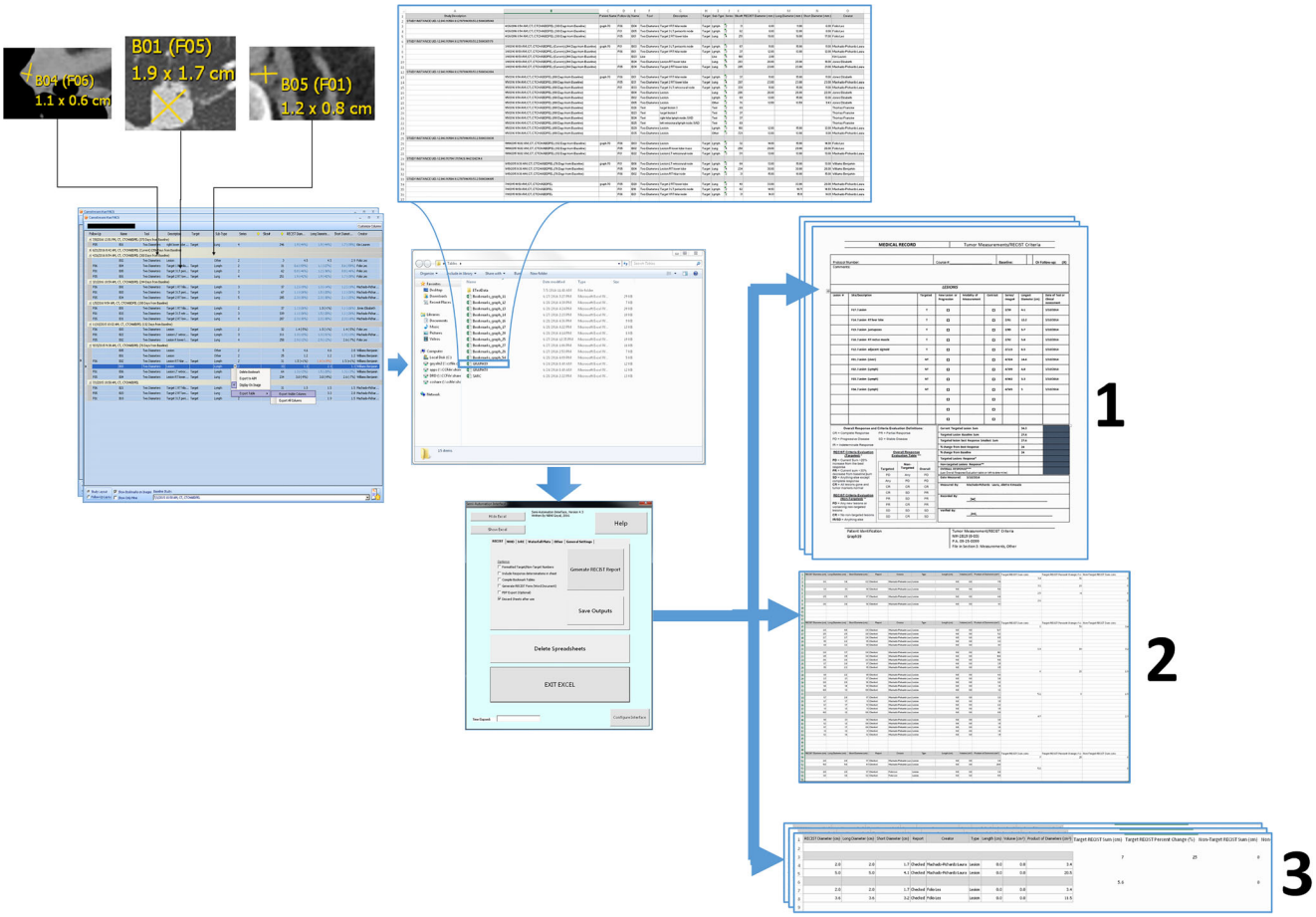

Fig. 6 Visualization of data flow with ENABLE. Lesion measurements made on PACS and stored in individual bookmark lists in PACS are exported using the "Export Visible Columns" option and saved as spreadsheet files in a common folder. ENABLE batch processes bookmark lists: (1) Auto-populated RECIST forms are created as Word documents allowing remaining fields to be filled, and stored in a common location, ready for electronic signatures. These can be converted to PDF files and uploaded to the EMR. (2) Compiled cohort data. Single spreadsheet with each patient's verified measurements and pertinent calculations. It is created if the program has single or batched bookmark lists as input. (3) Resultant model structured for archiving with other clinical data into databases such as Labmatrix

The entire process from lesion measurements to exporting data from PACS, importing it to the interface, and generating outputs is shown graphically in Fig. 6.

Streamlined new workflow compared to traditional tumor assessment workflow is shown in Fig. 7.

Data Concordance

Out of the eight patients in group 1 (16 CT exams and 27 lesions overall) for which we compared 194 data points from the oncology records, the interface produced an identical 194 data points.

Waterfall Plot Creation

The interface was able to organize batched patient data (group 2), selecting each patient's greatest RECIST percentage reduction from baseline, aligning from highest positive number to lowest negative number (also including zero) in excel columns. This format would quickly display the data and allow an oncologist to easily transfer each patient's best response into a waterfall plot. Our interface does not yet include all RECIST guidelines for determining overall best response, such as excluding a patient's exam where a new lesion is present. Thus, when comparing our interface results to those that were manually determined by the oncologist, there were discrepancies in the overall response calculation.

Discussion

Benefits and Workflow Improvements

Using ENABLE, the management of information in the tumor burden assessment workflow can be significantly automated by exporting data directly from PACS and managing it

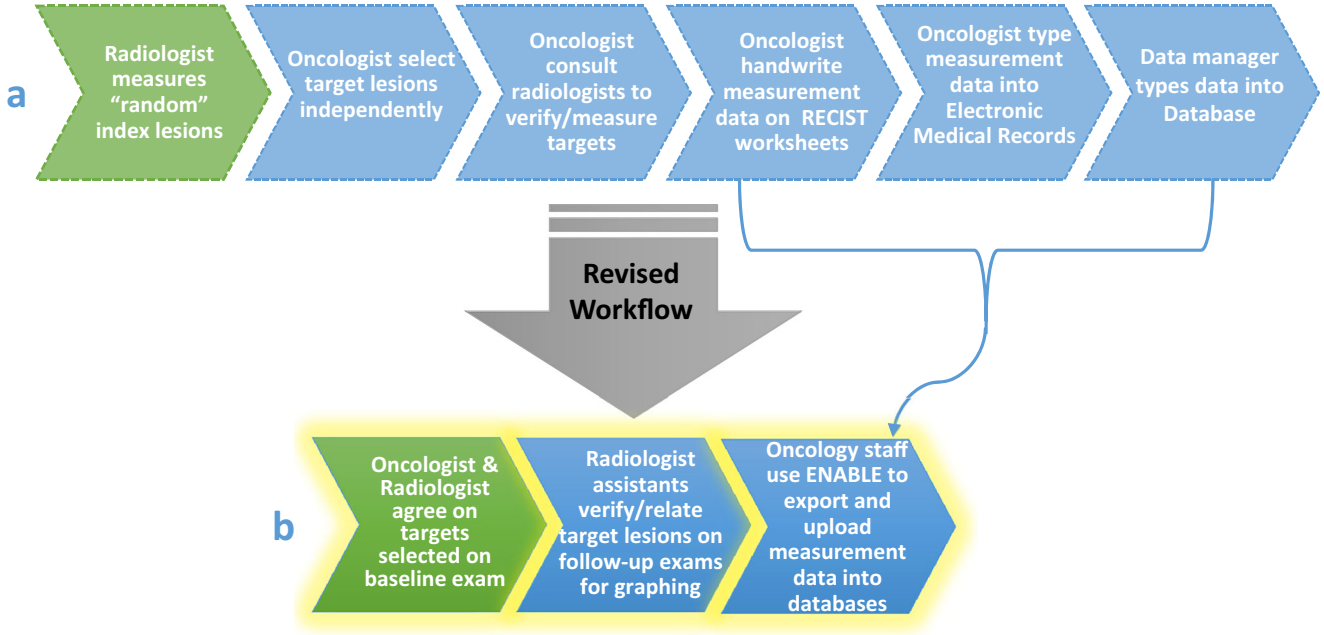

Fig. 7 **a** Traditional *workflow* explained in Fig. 2. **b** Revised and new *workflow* where oncologists and radiologists agree on target lesions on baseline exam with a radiologist assistant verifying and relating selected lesions over time. Oncology staff uses ENABLE for verified data exportation and RECIST calculation. This results in a semi-automated process, obviating handwriting while minimizing transcription errors

digitally. Users can electronically sign the digital RECIST worksheets and upload them as PDF to electronic medical records.

With this interface and advanced PACS tools [14], workflow efficiency will undoubtedly improve with fewer errors. The largest time savings should be achieved when the manual entry of data into databases is replaced by the digital upload of data using our interface. Thus, this improvement (the creation of digital RECIST forms) represents only a fraction of potential time-saving improvements. ENABLE presents a potentially cost-neutral (and potentially cost-saving) solution, which could shift current downstream data management to upfront data acquisition to conform to Information Technology single source of truth doctrine, ensuring optimal data quality.

Handwriting can be eliminated from workflows, allowing for data to be managed digitally with fewer errors [15] from PACS to databases. We hope to eventually manage and store all data in an Annotation Image Markup (AIM) [16] compliant manner, for optimal interoperability with other PACS vendors and institutions.

Limitations

Potential errors which cannot be addressed with data automation include radiologists' interobserver tumor measurement differences and target lesion discrepancies where oncologists may have selected and measured separately from radiologists. Thus, the interface depends on preselected, agreed-upon, and verified inputs. Discrepant data will naturally result in errors at the output. This is where radiologist assistants or oncology staff can work in the background verifying target lesion selection and measurement data.

Utilizing the interface creates a new workflow necessity (resources that could come from downstream data management), namely, that a radiologist assistant or research nurse verifies all preselected target and non-target lesion measurements in PACS before they are exported. This assures that correct lesion exportation with lesion subtype, baseline date, measurements, and other associated metadata are correct from the start, minimizing downstream error propagation.

In addition, ENABLE was designed based on our PACS system and is currently vendor-dependent. However, the structure and design of the program should be adaptable to suit other PACS vendors, a proposition which we plan on testing.

Both the output format of the bookmark table from PACS and the import format for research information databases may change over time, necessitating dedicated IT staff to maintain the interface. In addition, oncologist or study requirements vary, and in order to meet those needs, new features may need to be implemented in the interface code.

Since this "middle ground" data management solution is dependent on running an Excel VBA script, it is not fully automatic, in that a human operator must input the data for the script to run. To help achieve full automation, the interface would need to be ported to a server-based language like Java, Perl, or Node, ideally integrated into PACS.

In its current state, our interface only functions on computers that run the Windows operating system, and have Excel and Word. With some small modifications to the source code, the interface could be made to function on other operating systems and computers, e.g., macOS (Apple Inc. Cupertino, CA).

In the future, we hope to integrate ENABLE directly into our (and other) PACS, allowing oncologists to generate all of the interface outputs directly from PACS. This will eliminate the need for maintenance of the interface and potential compatibility conflicts between various systems and would provide a fully sustainable solution that can be replicated by other PACS systems.

The structured nature of the reports with hyperlinks from image data to radiologist labeling should also lead to improved natural language processing searching for data analytics [17]. Finally, the data can be uploaded directly into cancer center databases as well as the researcher's own information databases.

Conclusion

We developed a scalable interface called ENABLE that digitally manages tumor measurement and associated metadata, obviating handwriting and repetitive data entry, resulting in a digitally driven workflow.

In addition to being more efficient, automation of digital measurement data will undoubtedly reduce transcription errors and streamline auditing, with the end state of improved assessment of metastatic tumor burden in therapeutic cancer trials. We believe that our efforts will help encourage (ENABLE, rather than "resist") radiologists and oncologists to include the quantification needed (e.g. RECIST).

Utilizing this interface provides an efficient way to obtain useful information that helps oncologists make clinical decisions from the raw measurement data (SSOT) provided by radiologists in their reports and radiologist extenders in the bookmark list.

Acknowledgements The authors are grateful to Donna Bernstein, Isabel Palacios-Yance for facilitating data management workflow information and patient data as well, and Nicole Davarpanah for intellectual input in the realization of this paper.

Compliance with Ethical Standards

Disclosures Les R. Folio and Laura Machado are associate investigators in a research agreement with Carestream Health (Rochester, NY). This research was supported [in part] by the Intramural Research Program of the NIH Clinical Center. The content is the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This is an HIPAA-compliant IRB exempt study. This study was submitted to SIIM 2017.

Appendix 1

Explanation of the example estimate 12,000-data point calculation in an example clinical trial.

Assume the following:

A. 10 data points per lesion
B. 17 data points per CT exam required for organizational purposes
C. An average of 3 lesions per CT
D. With 5 CT exams (average) per subject in the study
E. With a total of 50 study subjects per trial

Thus:

(((17 data points per CT + (10 data points per lesion * 3 lesions per CT)) * 5 CT exams per patient) * 50 patients per study) = 11,750 data points per study

Appendix 2: Technical Details

In compliance with HIPAA, a single copy of ENABLE (the interface) is stored on a secure server accessible from workstations at the NIH CC. Patient bookmark lists are exported and stored on this server after being saved with the proper naming convention. Users can launch ENABLE from the server and input to its bookmark lists stored on the secure server. Outputs of the interface are stored in a common location on the server as well.

Appendix 3

The following outline reviews the steps taken from exporting the patient Bookmark List from PACS to generating and accessing the outputs produced by ENABLE. These instructions are specific to our PACS:

1. Exporting the PACS Bookmark List:
   a. Open PACS, open patient exam
      i. Could be current or not
   b. Open bookmark list (stored as a database in PACS, not yet DICOM structured)
   c. Right click: export visible columns
      i. Set baseline date
      ii. Select and verify target and non-target lesions
      iii. Verify follow-up sets to correspond correct lesions, especially for target/non-target lesions
      iv. Check "Study layout" box
      v. "Show only mine" box should not be checked
      vi. If patient has bookmarks in exams prior to baseline

1. These cannot be labeled as target or non-target even if the lesions were from before
    a. If this is the case, they need to be detached from the target/non-target follow-up set

vii. If patient has bookmarks in exams after patient is off study
1. These cannot be labeled as target or non-target even if these lesions are still present
    a. If this is the case, they need to be detached from the target/non-target follow-up set

viii. File is saved in a common location, to facilitate next/other file location
1. Verify that Medical Record Number is followed by protocol number in the file name as follows:
    a. MRN#1234567_01-C-2345

d. Open the interface (ENABLE)
i. Define output folder name
1. It is set as "Default"
2. Change it as desired, e.g., user's last name

ii. Select "Run"

iii. Select input folder
1. Within these, select single file or a group (as large as desired)

iv. After running, interface initial window will appear

v. Select "Show folder"
1. It will prompt you to output folder (common location called Master Folder"
    a. Within these, a folder named "Outputs" was created
        i. Within these, folders with "Default" or user's last name (as was set up in point d.i.1) was created
        ii. Inside these, folders with the date when interface was used
        iii. Then, the exact time when the interface run
        iv. Inside this, three folders named "Labmatrix," "Output Sheets," and "WordDocs"
            1. Within these, each file is named with the patient's name.

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