quantitative imaging analytics – the future of radiology

This article explores the area of quantitative imaging analytics in radiology, specifically as it applies to oncology applications such as lung cancer screening and tumor response. The number of images presented to a radiologist to read per patient continues to increase as scanner technology evolves. One solution is to reinterpret the pixel data as a set of quantitative metrics that can be assessed in conjunction with other information about the patient and even in comparison to metrics determined for other patients. Quantification and storage of image information allows radiologists to compare changes across many variables between prior and current imaging studies. With the ability to evaluate data derived across cohorts of patients in a database, each and every patient in their system becomes part of evidence-based analysis. Radiologists will be able to tap findings across all patients, rather than the 3% of cancer patients in clinical trials. Imaging analytics means radiologists can build on their own clinical expertise to make better, more insightful decisions in real-time.
The opportunity to participate in imaging analytics comes at a challenging time for radiologists. Among the potential challenges for radiologists in capturing quantitative data are time pressures. A recent study from the Mayo Clinic[1] suggests that radiologists there read an image every three to four seconds, which is up from three images per minute in 1999. The increase is due to a variety of factors, including a shift from radiographs to CT and MRI and new applications for imaging. Technology improvements have increased processing speeds as well as allowing for more images captured per exam. The number of images generated in an average CT exam rose from 82 to 679 between 1999 and 2010. Another Mayo Clinic study[2] notes that the number of images requiring interpretation per minute per radiologist increased from three in 1999 to 16 in 2010.

While their throughput is under pressure, radiologists are confronting a change from a fee-for-service payment model to a value-based model[3]. Radiologists have been an integral part of the clinical care team, aiding in the diagnosis of disease as well as evaluating the impact of treatment regimens. With a payment emphasis on value, the field of radiology has been looking for additional ways to convey the importance of their work, exemplified by the American College of Radiology’s Imaging 3.0 initiative[4].

While radiology is facing these challenges, there is significant opportunity to participate in the gathering momentum behind clinical analytics – the ability to customize prevention, diagnosis, and treatment based on an individual’s specific information, such as medical images, demographics and genomic information.
analytics opportunities

Analytics involves the discovery of relevant patterns in data. Healthcare analytics companies have generally developed with an operations emphasis, often combining Electronic Health Record (EHR) data with claims and/or practice management data to increase efficiency. More recently, companies have been pursuing the more clinical aspects of patient care, particularly in the relatively new field of genomics. In contrast to genomics, radiology has an established workflow for clinicians to work with images, the Picture Archiving and Communication System (PACS) as well as standards for the images themselves. Imaging analytics tools built into the PACS workflow will provide the most straightforward user experience for radiologists.

Advanced analytics can be used to help the radiologist with their image reads. One approach is machine learning, which involves an algorithm that will learn to identify clinically-significant patterns and anomalies in the images. Advanced statistical analysis can also be used to recognize correlations between image features and clinical conditions. If a given disease diagnosis is known to be associated with a particular set of imaging features then patient images can be examined for the existence of that “signature” appearance. This can help, for example, in determining whether a suspicious lung nodule seen on a CT scan is cancerous or whether coronary arteries on an angiogram harbor disease. In this highly-computerized process it is important to recognize the role of the physician in recognizing familiar patient symptoms and disease manifestations. Even in a machine learning context, physician judgment is a key element in “teaching” the computer.

Opportunities exist to move beyond single patient’s own data to include historical information from other patients, to yield not just information but knowledge. While electronic health records (EHRs), genomic profiling, and advanced medical images provide troves of health related information, extracting the most helpful insights out of the data is challenging and often resource intensive. Data mining, the discovery of patterns in the data using computers, can be applied to the care of future patients by the creation of research cohorts and exploration of their imaging data and health outcomes. The goal is predictive analytics, the ability to forecast outcomes from a set of parameters, from the reading room. Ideal candidates for analytics may be cancer screening and monitoring tumor response to therapy, as measurement of the size and change in size of a mass is inherently a quantitative process. In the future, more complex imaging features will be used in predicting outcomes.
Painting a higher resolution picture of a patient, including making meaningful, quantitative predictions, is one of the key challenges and opportunities in medical imaging. As radiologists strive to enhance value in the face of pressure to stem money spent on procedures such as CT, MRI and PET scans, extracting more meaning out of each exam will become paramount. With the ability to make more concrete conclusions via tools such as data mining, radiologists can provide not just a traditional exam read, but true exam analysis.

The imaging data itself contains details buried within the pixel maps that may not be readily apparent to the human eye. For example, a tumor seen in an imaging exam is typically assessed on the basis of straightforward factors such as its size, location, and whether it has spread to nearby organs or lymph nodes. Patients are staged – assigned to a broad group and managed in a certain way – based on such factors. Current staging practices represent a low resolution picture of the patient, painted using broad brush strokes. In principle, higher resolution patient charting, and resulting gainful insights, are possible as more information becomes available. Precision medicine is indeed a key initiative in today’s health care environment. Often, what this amounts to is interpreting a large amount of available information, across many patient datasets, so as to be able to say “This current patient is similar to this group of previous patients whose outcomes we know.” Outcome could refer to factors such as survival time, whether or not a nodule in the lung is malignant or not, or tumor response to a particular therapy.

For precision medicine to become a reality, we must first determine a meaningful set of variables, or features, to describe the patient. That is, variables which have a correlation with a certain outcome. A simple example is that we know that tumor size on diagnosis is correlated with likelihood of surviving a certain time past diagnosis. In imaging for cancer screening, it is known that nodules which grow in size between exams are more likely to be malignant, and that tumors which shrink rapidly during therapy are associated with longer survival. Variables such as size and change in size, as well as more complex factors such as heterogeneity of a tumor, can be given a value or “score”.

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While electronic health records (EHRs), genomic profiling, and advanced medical images provide troves of health-related information, extracting the most helpful insights out of the data is challenging and often resource-intensive. Opportunities exist to move beyond single patient’s own data, to “Big Data”, including historical information from other patients, to yield not just information but knowledge.

Data mining, the discovery of patterns in the data using computers, can be applied to the care of future patients. Examples of such knowledge could include defining a subset of patients by blood test results to select an effective drug therapy, or more accurate cancer screening based on features of radiology images. Expectations of patients and payers are that diagnoses will be accurate and that the most appropriate and cost-effective care pathways will be followed.

The challenges in mining “Big Data” in healthcare include the increased need for information technology (IT) resources and know-how. Many academic medical centers have incorporated clinical informatics as part of their operational structure. Historically, the software responsible for handling data is different from one area of care to the next. For example, the EHR is used to capture the primary care visit information but imaging data is captured in a Picture Archiving and Communication System (PACS). To enable Big Data tools, these data need to be brought together for analysis.

Another challenge for data mining is that much of the available data is not in a format that is easily discoverable. Many reports, such as patient histories are unstructured text, meaning the data lack organization. Computers can more effectively analyze structured sequences with standardized labels and values. Medical images are pictures from which a radiologist has described his or her findings, typically as a narrative as with patient histories. There is therefore a push in medical informatics for reports that are in a structured format more suitable for data mining.
Ultimately, a score derived from a combination of features could be used to predict the likelihood of a given outcome using cohort analysis. For example, if the score for a current lung cancer screening patient with a suspicious nodule is in a certain range, it could be concluded that the probability, or risk, of the nodule being malignant is equal to the ratio of number of malignant nodules to the total number of nodules within the cohort of prior patients in that same score range. Scores need not be a result of only imaging features – factors from the EHR such as smoking history and age can also contribute to “filtering out” the most appropriate cohort of past patients, and enhancing the precision of any predictions.

Another possibility is analyzing various scores for a given patient in comparison to a selected cohort of previous patients. The selected cohort may be comprised of patients similar to the current patient – a similarity cohort – or simply one with which we wish to compare the current patient – a trial cohort. For example, a radiologist may wish to see whether the response of a patient’s tumor to chemotherapy is in the typical range for a trial cohort of patients who survived at least five years post treatment. This may then help the radiologist conclude and report that the patient is responding to therapy in a manner consistent with past patients who did well.

Promising recent research has looked at correlations between how “textured” a tumor looks on an image and the prognosis of the patient. A more textured, or heterogeneous, appearance has been shown to infer a worse prognosis in a recent article in Nature Communications[5]. Prognostic features such as this are sometimes called imaging biomarkers. There are many features that describe things like texture of a tumor in a grey scale map, or irregularity of tumor edges. In computerized analysis, it is useful to look at many features and determine which provide the best correlations with outcome, or to combine such features in order to obtain a more robust correlation that is not overly dependent on any one feature. In combining features, it is important to avoid choosing multiple highly-correlated features as these do not provide independent evidence that a certain outcome is likely. Chosen features should also be reliably obtained for all patients and have variation among patients over time that is truly due to differences in morphology, rather than differences in image acquisition or display. A combination of features is sometimes called a “signature” within the emerging field of radiomics.
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**longitudinal insights**

In another form of analytics, a “longitudinal” timeline representation can be used to provide clear visual insights into the patient’s continuum of care. The timeline may include graphical representations of laboratory tests, imaging procedures, disease diagnosis and courses of therapy, along with quantitative values and plots from imaging and non-image-based analyses. An example of a longitudinal representation could be examining a plot of tumor size relative to the duration of a course of radiotherapy. Along with the plot could be icons situated at the dates of follow-up CT scans from which tumor size was determined. Scans could then be examined by clicking on the icon and opening a viewer. At the time a radiologist sits down to read an exam, a longitudinal view would be a useful snapshot of the patient’s care up to that point. Quantities already represented in the timeline can be re-evaluated using the current image set and the timeline updated.

As well as making use of a longitudinal view for a current patient, radiologists may want to examine the timelines of patients within a similarity cohort. This would allow, for example, an examination of the response or progression of tumors harbored by these patients after administration of a certain drug, helping predict the likely drug response for the current patient. Alternatively, longitudinal features such as response or progression could be used to define patient cohorts. This would allow, for example, the longer term survival data for patients responding quickly to a drug to be examined.

**practicality via automation**

A caveat to introducing analysis based on information such as the imaging features of other patients is that this cannot create a workflow bottleneck. As much as possible, information processing should be done in the background and be ready for consumption by the radiologist at the time of exam reading. One key element of feature extraction from large numbers of datasets is automated delineation, or segmentation, of volumes such as tumors and selected healthy organs. Time consuming manual segmentation is not an option when searching for patterns among large numbers of patients in a database. However reliable automated segmentation can be difficult because of factors such as uncertainty in the boundary between the object of interest and adjacent tissue. For example the border between a lung nodule and the mediastinum, chest wall, or a blood vessel can be challenging to delineate.

Intelligence needs to be built into the segmentation algorithm so that it is not solely reliant on the grey scale map. For example, having automatically detected the lung-chest wall boundary prior to segmentation of a nodule can provide a known outer bound for the nodule. Attempts have been made at fully-automated nodule detection, but such techniques typically result in the need for time-consuming manual addition or rejection of delineated nodules. A promising middle ground is manual identification of nodules with subsequent automatic segmentation, sometimes called a “click and grow” scenario. This approach takes advantage of the skill of a radiologist in identifying suspicious nodules and the ability of computers to quickly find boundaries.
medical informatics at the forefront

To keep pace with the changing world of medical imaging, many radiologists are becoming medical informatics experts, working alongside IT professionals to help facilitate the necessary exchange of information. The goals of these groups are to make more data available to themselves while making their findings readily available to all stakeholders. The intent is that in addition to the radiologist more readily accessing patient data, the radiologist’s detailed findings and predictive analytic results will inhabit a space within the EHR framework alongside more traditional EHR information. Because many EHR systems have patient portals already, their use as the information hub brings a more patient-centric nature to all elements of care including radiology exams. Making this information available from within the EHR is in line with Meaningful Use mandates in the United States.

While imaging is a cornerstone of modern medical practice, the value of an image is amplified by association with EHR information. The challenge is that EHR systems are more adept at consuming and storing data than disseminating information. In particular, making more of the patient’s pre-imaging history at the time of image reading gives the radiologist context to provide additional insights in their conclusions. Radiologists are also then better equipped to help the referring clinician in determining whether the ordered exam is appropriate in the first place, thus playing a role in patient care as well as cost savings. Most of all, the radiologist’s “customer” (i.e. referring clinician) needs concise, concrete conclusions to make decisions on patient management, and such conclusions are best made with complete sets of information.
Radiology findings can be stored in the EHR and thus linked to a patient’s health record. Findings typically include narrative exam read summaries, along with structured, quantitative data such as tumor sizes and growth, as well as annotated key images that illustrate the findings. After reading the exam, information gathered during the reading process needs to be available throughout the healthcare enterprise and even to patients. Interoperability of the EHR with image-centric systems such as PACS and other image viewing applications is evolving with customer demand.

One of the key elements in improving the usefulness of radiology reports both within and outside of the radiology department is increased use of structured reports. Traditional narrated reports are mostly unstructured, in the sense that they are in sentences rather than in the form of specific elements with corresponding values. Unstructured sections of a report will always be valuable because they provide opportunities for humans to communicate in a natural way, often referring to relationships between different observations and between observations and the patient’s medical history. However, structured data is better for data mining and research, such as in plotting tumor progression and response. Creation of patient similarity cohorts and of quantitative, longitudinal views of patient care are examples of where structured reports are essential.

Industry efforts such as the RSNA radiology reporting initiative[6] are aimed at accelerating the use of structured radiology reports. Templates have been created for many different exam types by expert subcommittees, in an effort to standardize format, content and structure of reports. These templates are available for use as a starting point by IT staff and vendors in implantation of structured reporting systems.

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**better biomarkers needed for cancer screening**

Cancer screening is an established though often controversial practice. When false positive rates in cancer screening are high, more people who do not have cancer are flagged as “positive” during the screening program and therefore subjected to additional tests. This experience can be dangerous, in the case of biopsies, as well as financially and emotionally challenging as a patient confronts an expensive, life changing diagnosis.

Recently, lung cancer screening using low dose CT (LDCT) for a selected high risk group has been approved for Medicare reimbursement in the US. This change is largely due to the results of the National Lung Screening Trial (NLST), which compared survival rates between people randomly assigned to either a chest x-ray or LDCT group. Results are reported in the Journal of Clinical Oncology[7]. Each group received three annual screening exams. Results showed a 15-20% relative reduction in deaths in the LDCT group, amounting to an additional three lives being saved per 1000 people enrolled in the CT group over the seven year study period (17.6 deaths per 1000 versus 20.7 deaths per 1,000). However, over the three screening exams, the false positive rate in the LDCT group (based on size of a nodule being at least 4mm or the presence of other abnormalities suspicious for lung cancer) was 24.2% versus 6.9% in the chest x-ray group. Of all the positive LDCT screens, only 3.6% were ultimately associated with a confirmed lung cancer. Clearly, lives saved comes at a high cost of false alarms, and there is a pressing need to reduce the false positive rate in LDCT-based lung cancer screening.

False positives can be reduced by making a screening test more specific, which generally implies that the test is less sensitive. In this case, fewer people who do not have cancer will be flagged as positive but more people who do have cancer will be missed. The trade-off can be best mitigated with a better test for determining the likelihood that a visible nodule is cancerous. The use of imaging biomarkers may significantly reduce the specificity-sensitivity trade-off. A well-known biomarker for malignancy is growth of a nodule between scans, however this of course requires waiting until the next scan before the growth metric can be calculated. A biomarker with high specificity and sensitivity that is based on the radiological appearance of a nodule in an isolated exam is therefore appealing and is a topic of interest in radiomics research.

A promising approach to improving the ratio of true positives to false positives in lung cancer screening is the ACR’s Lung Imaging Reporting and Data System (Lung-RADS”). This tool is designed to standardize reporting and management recommendations in CT-based lung cancer screening and outcome monitoring. Lung-RADS is a form of radiomics that uses a decision process to place lung nodules into risk categories according to size, opacity (solid, part solid, non-solid) and growth between screening exams. The classification of a nodule as “positive” using Lung-RADS is more specific than the simple size criteria used in the NLST trial and as such a smaller false positive rate is expected. In particular, size thresholds are larger, and growth between screening exams is required for a nodule to be classified, or remain classified, as positive.

In a study published in the Annals of Internal Medicine[8], where the NLST data was reevaluated using Lung-RADS criteria, the false positive rate at the time of baseline scan was more than halved and in follow-up scans was reduced four-fold. The particularly large reduction in follow-up scans is due to the requirement for growth by Lung-RADS. At the same time, use of Lung-RADS criteria did reduce sensitivity, by approximately 9% and 15% at baseline and follow-up, respectively. The implication is that the cost for subjecting fewer cancer-free patients to follow-up procedures is missing cancers during the screening period. This trade-off will have to be further evaluated, ideally via a prospective study where Lung-RADS categorization is used throughout the trial and the overall impact on survival compared to use of other classifiers determined.
productizing analytics

Analytics-focused applications are beginning to emerge in the marketplace, aimed at both operational and clinical aspects of patient care. This is clearly an evolving field, capturing the interest of very large companies like IBM. Smaller vendors, including startup companies dedicated to analytics, have also recognized the demand for solutions enabling higher value and efficiency in healthcare. In radiology, analytics tools will be used in conjunction with traditional PACS systems, as well as increasingly making use of data source combinations from central image archives and EHRs. Applications like cancer screening, and monitoring tumor therapy response, are inherently quantitative by nature and are therefore ideal candidates for analytics. Radiomics potentially adds dozens or even hundreds of parameters beyond simple size-based metrics to be measured, analyzed, tracked and distributed to stakeholders. However, as with many good ideas and new introductions, the key to adoption is likely to be ease of use and efficiency. Automation and background processing, while maintaining transparency and trust in how results were obtained, will pose a challenge to vendors.
HealthMyne is an early stage healthcare informatics company with a focus on imaging analytics enhanced by EHR integration. The company is committed to providing tools that are aligned with the needs of radiology practices in the new value-based healthcare system. Forward-thinking initiatives such as the American College of Radiology’s Imaging 3.0 vision are guiding principles in software development. High priority is being given to the development of specific capabilities such as automated determination of Lung-RADS categories for lung cancer screening and assembly of structured reports under the guidance of the RSNA reporting initiative.

HealthMyne understands that for radiologists to provide the best value to their referrers, organization and patients, they must have easy access to complete information about the patient. Furthermore, comprehensive datasets for entire cohorts of patients, will be useful in predictive analytics. This need has been the driver behind clinical collaborations focused on automatically retrieving information from the EHR along with receipt of imaging studies.

In keeping with cutting-edge research, HealthMyne has a collaborative effort underway to make its system the first commercial platform for radiomics-based analytics. The platform is designed to extract radiomic features for external use in development of predictive models. The aim is for the system to seamlessly incorporate these models into a clinical predictive analytics tool that can readily, and practically, be used to guide the care of individual patients.

The HealthMyne system includes a PACS-like interface with a worklist and configurable viewports. A client-server architecture allows tasks such as automatic retrieval of image and EHR data to occur in the background, along with automatic image registration, segmentation and analysis such as calculation of feature scores and Lung-RADS categories. The user interacts with the client side of the software, performing tasks such as cohort creation and examination of cohort-based and longitudinal analytics results.

In line with the trend toward “Deconstructed PACS” environments, the HealthMyne system is intended to act as a diagnostic imaging application, interconnecting with third-party vendor neutral archives (VNAs) and primary PACS systems. In one intended scenario, the HealthMyne software will open from within the primary PACS. Structured reports created via image analytics will be stored as DICOM objects for later examination and data mining.

To summarize, HealthMyne is committed to providing radiologists, and the involved patient care team, with an imaging Informatics platform that enables disparate data aggregation, advanced data mining analytics, and seamless evidence-based reporting.

Please see HealthMyne.com for more information.

An example of automatic segmentation of thoracic structures along with a single-click lung nodule segmentation using the HealthMyne system.
references

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