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Medical diagnosis – the promise

Abstract: The field of diagnosis is hardly static. Taking a step back, advances in diagnosis have been dramatic over the past few decades, and promise to accelerate going forward. Progress will be created through three main drivers: Continuing advances in the tools we use for diagnosis, adoption and use of electronic resources, and applying quality improvement strategies to reduce diagnostic error and variability.

Keywords: clinical decision support; diagnosis; diagnostic error; quality improvement.

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Introduction

Diagnosis – From ancient Greek, from διαγνώσκειν (*diagignóskein*, “to discern”), from διά (*diá*, “apart”)+γινώσκειν (*gignóskein*, “to learn”).

In the science fiction “Star Trek” series, Doctor “Bones” McCoy uses a small handheld device, the Tricorder, as his diagnostic tool of choice. Through the miracles of science in the 23rd century, the Tricorder’s medical attachment can noninvasively and instantaneously image internal organs for injury, perform sophisticated biochemical analyses and at the same time scan for alien life forms [1]. A quick wave over the body was usually sufficient to establish the diagnosis, at which point Bones would turn to Captain Kirk and exclaim: “It looks bad Jim, he’s got an advanced case of Anteres Fever.”

The natural question is “will we ever get there?” And the perhaps surprising answer is ... almost certainly yes. The advances in medical diagnostics over the past few centuries are nothing short of breathtaking, and there is no reason to believe that this progress will stop anytime soon. Three key factors are at work that will continue to drive progress in medical diagnostics:

1. Continuous innovation in every aspect of both clinical lab testing and diagnostic imaging
2. Advances in information sciences, improving access to data, knowledge and expertise

Figure 1 The original Tricorder model and probe used on the Star Trek television series, designed by Wah Ming Chang.

3. Using an organized approach to improving the quality and reliability of medical diagnosis.

Improvements in the clinical lab and diagnostic imaging

Diagnosis dates back thousands of years. How has it evolved over the past millennia, and where are we headed? Healers in the renaissance period had essentially no diagnostic tools. Diagnosis hinged primarily on the history and whatever physical findings were apparent to inspection and palpation. Other than a rudimentary examination of the urine (sometimes including a taste!), lab testing was nonexistent.

Modern lab testing and imaging were both developed over the last century, and for at least the first half of that century, much of the data varied widely in quality. Just

Figure 2 A medieval physician divining a patient's diagnosis from examination of the urine.

60 years ago, the Centers for Disease Control estimated that one lab test in four was unreliable [2].

Modern clinical laboratories offer literally thousands of tests of every imaginable type, and the reliability of these tests is exceptionally high. Although lab errors persist today, most of these now reflect problems in physician's ordering the right test or interpreting the results [3]. The error rate from the lab's testing process per se is ever smaller, in some cases <1 error per hundred thousand tests, thanks to advances in testing, guidelines from oversight groups, inspections with feedback, and participation in quality assurance and improvement programs.

Importantly, these advances do not always lead to increased costs, and in many cases produce substantial cost savings. For several decades, the most sensitive test to detect a myocardial infarction was a temporary spike in the serum levels of the cardiac isomer of creatine kinase (CPK-MB), an enzyme released from the injured heart cells. Not any more. Modern labs now measure troponin markers instead, another index of cell injury, but one that appears earlier, lasts longer, and offers both improved

sensitivity and specificity relative to CPK testing. It is a better test, at essentially no additional cost [4].

Every area of the lab has seen improvement. Routine chemical analyses have been replaced by ion-specific electrodes, atomic absorption spectrometry, and highly miniaturized and automated auto-analyzers. Immunological testing has expanded enormously, and antibody-based detection is now the standard for hundreds of tests detecting specific protein disease markers. Exotic new technologies seem to emerge on a regular basis. A recent announcement described a completely novel method of cancer detection using a small device interfaced with a smart phone. The system measures unique circulating cancer proteins and metabolites using magnetic nanoparticles [5]. Entirely new fields relevant to diagnosis have appeared just over the past decade or so: proteomics, oncoproteomics, metabolomics, biomarkers panels, and the list goes on.

Anatomic pathology, previously dominated by simple light microscopic examination, now relies extensively on imaging via electron microscopy and sophisticated immuno-histochemical and fluorescence imaging using highly specific antibody markers. Ever-more sophisticated microimaging capability is becoming available, some of it performed in situ, such as confocal microscopy and fluorescence microendoscopy.

Advances in genetic testing are at the forefront of laboratory diagnostic innovation. The antenatal diagnosis of Down's syndrome is an illustrative example. The ability to perform amniocentesis and perform chromosome analysis was described decades ago, and offered the ability to diagnosis this condition early enough in the pregnancy to offer the option of abortion. Hailed as a breakthrough advance at the time, more remarkable is the recent announcement that the disease can be detected at even earlier dates, and without any of the risks of amniocentesis, using ultra-sensitive genetic amplification techniques to detect the genetic abnormality from the miniscule number of fetal cells that circulate in maternal blood [6]. These examples are just the small tip of a very large and growing iceberg: genetic markers have now been identified in hundreds if not thousands of disease states, and the potential for these markers to be useful in diagnosis will be an extremely active area of research.

The diagnosis of tuberculosis offers another remarkable story. Instead of waiting weeks for the bacillus to grow in culture, genetic testing, using the same technology for detecting anthrax in the mail, can diagnose active infection from a sputum sample. The test takes <2 h and has a sensitivity of over 95% in smear-positive patients and 75% in smear-negative patients who would otherwise have to wait 4–8 weeks for culture results [7].

Table 1 Recent Medical Subject Headings (MESH) added by the National Library of Medicine.

Costello syndrome	Congenital disorder with dysmorphic facies, musculoskeletal abnormalities and high prevalence of cancer, associated with mutations in H-ras gene
Cryoporin periodic syndromes	Autosomal dominant condition characterized by atypical hives and end-organ damage, not caused by autoantibodies
Yellow nail syndrome	Yellow nails, lymphedema, pleural effusions and respiratory tract involvement
Hereditary angioedema type IIIa	A hereditary angioedema restricted to women from mutations in factor XII gene, exacerbated by estrogen
Monilethrix	Autosomal dominant disorder causing abnormal hair and hair loss
Alien hand syndrome	Apraxic disorder perceived as being caused by an alien force
Donohue syndrome	Autosomal dominant disorder causing extreme insulin resistance due to mutations in the binding region of the insulin receptor

<ftp://nlmpubs.nlm.nih.gov/online/mesh/newterms/mshnew2010.txt>.

Non-invasive biochemical testing is quickly becoming a reality. Hemoglobin levels, oxygen saturation, and glucose can now be measured non-invasively, and more analytes are sure to follow. In 2015, the X-Prize Foundation will announce the winner of the first team (250 teams are competing for the ten million dollar prize) to develop a handheld device that will provide diagnostic data on 15 different parameters, non-invasively.

A host of new devices now provide bedside diagnostics by linkage to a smart phone, including electrocardiograms and ultrasound imaging. The market for these devices is estimated to two billion dollars in 2014. Point-of-care ultrasound units allow bedside detection of bladder distension, pleural effusions, and cardiomegaly, and significantly improve the detection of these problems compared to physical exam alone [8, 9]. The practice may actually save health care dollars compared to the time, expense, and professional fees associated with sending these patients for a similar examination in radiology. In patients with trauma, point-of-care ultrasonography takes <5 min and provides 90%–96% sensitivity for detecting significant intra-abdominal bleeding or organ injury. Initial studies using this approach have identified decreased need for CT scanning, reduced time to initiate treatment, lower costs, and improved mortality [8]. Comparable benefits are achieved using point-of-care ultrasonography to rule out hemothorax and pneumothorax, and this technique is twice as sensitive as physical examination in detecting pleural effusion, pulmonary consolidation, and interstitial lung disease. Developed for the military, a new handheld device can detect intracranial bleeding in the field in <10 min (<http://med-logic.us/infrascanner-handheld-brain-hematoma-screening-system/>).

If any doubt remains about progress in diagnosis, consider this: The number of distinguishable diseases continues to grow at an appreciable rate, averaging some 5% per year [10]. According to the MESH entries listed by the National Library of Medicine there are over 8000

diagnosable entities, (the World Health Organization's ICD-10 system lists over 12,000) and hundreds of new entries are added every year.

Advances in information sciences, improving access to data, knowledge and expertise

As modern medicine moves into the electronic age, the potential of this technology to improve the reliability of medical diagnosis is unprecedented. As computers, web access, and electronic medical records become the norm, a variety of functionalities come into play that favor accurate and timely diagnosis:

Improved access to data Modern diagnosis is critically dependent on data of all types, such as lab tests, imaging results, reports from consultants, and summaries of prior hospitalizations and clinic visits. By facilitating the storage, immediate retrieval, and filtering of this information, diagnosis is enhanced and greatly facilitated. Beyond just retrieving data, modern informatics system have the potential to enhance the clinicians ability to detect subtle abnormalities through the use of graphic displays, time trends, and trend lines that superimpose lab data with other information, such as medication start and stop dates and dosages.

Facilitated analysis Gordon Schiff and David Bates of Brigham and Women's Hospital recently reviewed the potential for electronic medical records to improve diagnosis, emphasizing the role EMRs can play in facilitating the synthetic process of diagnosis, "putting it all together" [11]. To begin with, EMRs save time in data retrieval, time that can be put to better use for analysis. The EMR also creates an environment that helps organize

and document thoughts and impressions. Prior notes can be easily retrieved, as well as the impressions of consultants and prior caregivers. Schiff and Bates identify several other capabilities of EMRs that will improve the speed and reliability of diagnosis, such as their potential ability to facilitate test tracking, ensure appropriate follow-up, enable Bayesian calculations of disease probabilities, and encourage second opinions and consultation.

Improved access to knowledge EMRs enable the application of ever-more sophisticated decision support resources to aid with diagnosis. These tools can link clinicians to specific knowledge relevant to a diagnosis being considered, such as the “Infobutton” functionality invented by James Cimino [12]. Decision support tools to assist with formulating a differential diagnosis, such as DXplain and Isabel, can analyze the key findings in a given case to suggest a range of possible diagnoses. Programming IBM’s “Watson” supercomputer to assist with diagnosis will be the next advance in this progression [13]. Larry and Lincoln Weed and others have argued that the finite range of human knowledge and the shortcomings of cognition are limiting factors for diagnostic accuracy; health information technology offers the attractive opportunity to surpass our selves by taking advantage of these advances [14].

Improved access to expertise A final opportunity presented by modern informatics is to link patients and clinicians with experts. Telemedicine is in its infancy, but enables ophthalmologists specializing in retinal disease to see the fundus of a patient hundreds of miles away. Telephonic communication between patient and doctor is already yielding way to video communications, and holographic techniques are already in advanced stages of testing [USA Today Feb 24 2011]. E-consults are another new tool that works to the advantage of diagnosis. Instead of the traditional visit to the physician, many specific patient problems can be analyzed by subspecialists just from the EMR. A front line clinician can request an Endocrinologist’s consideration of abnormal thyroid tests, for example, or a Nephrologist’s review of an electrolyte abnormality. This saves time for patients and physicians alike, and is a cost-saver besides.

Improving diagnosis by applying principles of quality improvement

Performance improvement is the third area that will drive diagnosis forward. The clinical laboratory, already achieving 4 and 5 sigma levels of performance through quality improvement, provides an ideal model to emulate. The

science of quality improvement is built on measurement. The principles are simple enough – we start at point “x”, we aspire to be at point “y”, and through measurement and intervention we improve performance and minimize variation. Every healthcare organization has applied these basic concepts to literally hundreds of projects over the past decade. Except in the area of diagnosis. For almost every aspect of diagnosis, we have no baseline, we have no idea how much variation exists in practice, and we have no goal. What percentage of medical diagnosis is correct? What is the rate of diagnostic error in practice? How long should it take to diagnosis asthma, or anemia, or cancer? What is an acceptable rate of error? We really have no idea.

The reason is simple: we do not know how to measure diagnostic errors. If we ever hope to improve the reliability of diagnosis, we need measurement and we need a goal. If the diagnostic error rate is now 10%, can we make it to 5%? Only through accurate measurement can we identify the gaps and focus attention on the opportunities. Although the current tools healthcare organizations use to detect adverse medical events are insensitive to diagnostic error, new tools are coming online that will hopefully meet this need. Patients are probably our best option to report diagnostic errors, physician reports will increase as the culture of safety matures, and novel “trigger tools” will identify patients at highest risk for diagnostic errors.

Measurement will enable, at last, trials of the many interventions already identified that have potential to address the system-based and cognitive shortcomings that culminate in diagnostic error. Second opinions, decision support, better electronic medical records, the use of checklists, training on reflective practice, and many other creative ideas are all ripe for clinical trials, as soon as measurement techniques have been established.

An added benefit of measurement is that it would permit feedback. Feedback is critical to developing expertise and maintaining it, and lack of feedback leads to overconfidence and complacency, factors that promote diagnostic error [15]. In the absence of autopsies, a system of ongoing surveillance and measurement of diagnostic accuracy and error would go a long way towards restoring an effective feedback process. Feedback, coupled with performance improvement efforts coupled with electronic decision support are also the essential ingredients for reducing variability in clinical performance.

In summary, although diagnosis seems like a static field at any one point in time, a broader view reveals a dramatic story of improvement, the pace of which seems to be accelerating. The first factor pushing the field forward is the ongoing progress in diagnostic testing, especially advances in genetic testing and imaging. The second

factor is the ability that medical informatics provides to make diagnosis easier, less variable, and more accurate and timely by facilitating access to knowledge, data and expertise. The final innovation, hopefully just around the corner, is the ability to apply principles of performance improvement to the status quo, and trial the many system-based and cognitive interventions already suggested.

Diagnosis is the most ancient of the medical arts, and some would say the most critical. The future of the diagnostic sciences will be bright indeed to the extent that

we can leverage and supplement the inevitable advances that arise from creative endeavor with the miracles of the information age, and focus this work through the lens of applied quality improvement methodology. The Tricorder will be here before we know it.

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