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Establishing benchmarks and metrics for disruptive technologies, inappropriate and obsolete tests in the clinical laboratory

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ABSTRACT

Benchmarks and metrics related to laboratory test utilization are based on evidence-based medical literature that may suffer from a positive publication bias. Guidelines are only as good as the data reviewed to create them. Disruptive technologies require time for appropriate use to be established before utilization review will be meaningful. Metrics include monitoring the use of obsolete tests and the inappropriate use of lab tests. Test utilization by clients in a hospital outreach program can be used to monitor the impact of new clients on lab workload. A multi-disciplinary laboratory utilization committee is the most effective tool for modifying bad habits, and reviewing and approving new tests for the lab formulary or by sending them out to a reference lab.

1. Introduction

Laboratory test overutilization is estimated to represent 2.9% to 56% of all laboratory tests internationally. Efforts have been made to reduce the demand for or utilization of these over utilized tests [1–6]. The most efficient outcomes have involved the formation of a laboratory utilization committee [2,6] or a laboratory formulary committee [5] based on the hospital pharmacy and therapeutics committee's organizational structure. This committee evaluates the clinical value of laboratory tests using an evidence-based review of the appropriate medical literature. This same literature is reviewed by numerous professional specialty medical organizations as well as healthcare insurance carriers to determine what tests or procedures should be performed and reimbursed. The conclusions based on these reviews need to be updated on a regular basis.

"The quality of guidelines is only as good as the published studies on which they are based" [7]. Often relevant studies evaluating laboratory tests demonstrate negative findings and are not published [7,8]. This phenomenon is referred to as positive publication bias or publication bias. Tzoulaki et al. [8] demonstrated publication bias during a review of reports evaluating emerging cardiovascular biomarkers. Therefore, misinterpretation is a potential impact of failing to publish studies with negative results during a review of evidence-based literature. Readers beware.

Tests may be obsolete and should be retired from clinical use, while others may be inappropriately used for specific disease categories. The playing field is not level. There are at least six newer game-changing disruptive technologies being evaluated [9–11] which will result in modifications of clinical practice and laboratory testing modalities. These newer disruptive technologies may replace obsolete or inappropriate tests. Lab utilization benchmarks and metrics are under continuous flux as a consequence. In the case of evolving newer technology, it is imperative to explore their impact early in their development to anticipate and monitor their impact on laboratory testing.

2. Approach

The three authors have reviewed the current literature related to laboratory test utilization with an emphasis on where do the definitions of obsolete or inappropriate test utilization originate. We evaluated whole genome sequencing, next generation sequencing and proteomics as examples of high impact disruptive technologies that generate large quantities of data that need software to reduce to clinically useful results. Practical examples of obsolete and inappropriate tests are reviewed as potential metrics to monitor improvement in test utilization. Another useful metric is test utilization by clients in a hospital outreach program which can be used to monitor the impact of new clients on laboratory workload. Finally, the result of published data from the work of laboratory utilization committees is summarized.

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3. Benchmarks and metrics for laboratory utilization

Benchmarks and metrics for laboratory utilization will be reviewed for three disruptive technologies as well as obsolete and inappropriately used tests.

3.1. Disruptive technologies

Medical practice as well as pathology is in the midst of the rapid development of at least six major game-changing disruptive technologies. They include genetics, proteomics, digital pathology, informatics, therapeutic pathology and *in vivo* diagnostics [9–11]. All six of these disruptive technologies share similar issues like resolution of best applications for routine clinical use, paucity of evidence-based outcome literature for review, education of practitioners and physician users of the clinical information generated and software to convert big databases the method generates into clinical useful information [9–11]. The utilization of these techniques will increase as these barriers or obstacles to clinical use are overcome.

3.1.1. Whole genome sequence

An example of a disruptive technology is next generation sequencing or massively parallel sequencing [12–14]. This technique is currently not cleared by the U.S. Food and Drug Administration [13]. It has been used to generate genome wide sequences and one of the authors (FLK) has had his genome sequenced at the CLIA approved laboratory at Illumina (San Diego, CA). The results revealed 3.23 million variants compared with the reference method and 20,426 of these variants were in the exome or in the coding elements.

The study interrogated 344 genes causally associated with 140 conditions as recommended by the American College of Medical Genetics. In that limited number of genes, 1,254 variants were detected and classified as clinically significant (0), carrier status (1), variants of unknown significance (255), likely benign variants (356) and benign variants (642). The definition of these variants calls and the failure of this technique to detect deletions, insertions, interspersed repeats and tandem repeats (repeats adjacent to each other like triplet repeats [15]) may lead to inappropriate interpretation of the results and expensive follow up clinical and laboratory evaluation. For example, a clinically significant pathogenic variant reported in at least 3 unrelated cases with control data may be found in additional genome studies in other populations [16] to be a benign variant that is also found with a new variant which contains the mutation that leads to the most significant deleterious effect on gene function. The software application for variant significance assignment, like DataGenno [17], will need to be up-to-date with the latest genotype/phenotype associations to prevent false positive findings and inappropriate follow-up testing.

3.1.2. Tumor genome sequence

In 2009 the highest rate of reported cancers was prostate, lung and bronchus and colon and rectum for men with female breast replacing prostate for women in the U.S. [18]. The annual incidence rate was 459 cases per 100,000 individuals. Comprehensive sequencing of numerous human cancers have revealed driver genes, 2 to 8 such genes per tumor, which alter intracellular signal transduction pathways related to the cells future death or survival and/or genome maintenance [19,20]. There are at least 10 FDA approved cancer therapies based on the inhibition of these tumor-activated intracellular pathways [19]. For example, the BRAF kinase inhibitor, Vemurafenib, has shown a response rate in 50% of patients with metastatic melanoma that have the BRAF valine to glutamic acid mutation at codon 600 (V600E) [21]. This V600E mutation is associated with aggressive clinical course in patients with thyroid papillary microcarcinoma [22]. In one study of a hybrid score composed of one molecular diagnostic (V600E) and 3 histopathologic parameters were used to predict this tumor's clinical course with a sensitivity of 96% and specificity of 80% [22].

The selection of the correct molecular diagnostic tests for specific tumors is aided by published guidelines. Immunohistochemistry detection of estrogen and progesterone receptors in breast cancer from American Society of Clinical Oncology and College of American Pathologists [23] and selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors from the International Association for Study of Lung Cancer, Association for Molecular Pathology and College of American Pathologists [24].

Whole genome sequencing of a tumor will provide access to all known and unknown variants related to the tumor's survival skills [25]. The development of software [26] which will convert the patient's raw genome sequence into a medically relevant assessment of therapeutic targets and drug metabolism based on the tumor's body site will be very useful. From this genome analysis, the clinician wants to know what anticancer drug or drugs will this patient respond to as well as the dose.

3.1.3. MALDI-TOF

MALDI-TOF (Matrix Assisted Laser Desorption Ionization-Time of Flight) spectroscopy is a relatively new technology to the Clinical Microbiology laboratory. Pathogen identification has always relied on visual and biochemical interrogation where the summary of results may point to a specific identification (genus and species) or sometimes to at least the genus level. Visual and biochemical results can sometimes yield variable results meaning in some cases the ID may change depending on the result. The use of MALDI-TOF allows the clinical microbiology laboratory to identify bacteria once an isolate has been cultured potentially without performing any biochemical testing [11,27,28]. The implications are quicker pathogen identifications to clinicians and the potential to affect antibiotic treatment before susceptibility results are available. The ability to obtain a quicker answer will disrupt the testing workflow and require a re-evaluation of that workflow to optimize the use of MALDI-TOF and antibiotic susceptibility testing [11,27,28].

3.2. Professional subspecialty medical organizations

Benchmarks and subsequent metrics for monitoring laboratory test utilization have been developed by professional subspecialty medical organizations in the format of recommendations and guidelines [29]. Examples include guidelines for hypothyroidism in adults from the American Association of Clinical Endocrinologists and the American Thyroid Association [30], definition of myocardial infarction from the American College of Cardiology Foundation and American Heart Association [31], definition of diabetes mellitus from the American Diabetes Association [32], pharmacogenetics as well as follow-up testing for metabolic diseases identified by expanded newborn screening using tandem mass spectrometry from the National Academy of Clinical Biochemistry [33,34], and use of bone metabolic markers from the Japan Osteoporosis Society [35].

Thirty-five of these specialty societies have joined the Choosing Wisely project organized by the American Board of Internal Medicine. Societies are asked to provide five specific, evidence-based recommendations on when tests and procedures may be appropriate or inappropriate for patient care (www.choosingwisely.org).

A review of the lists from 26 specialty societies revealed 135 recommendations. Laboratory tests were referenced in 25 items or 18.5% of the total. Only one organization, American Society of Clinical Pathology, had a list of 5 laboratory test-related recommendations [36]. Kale et al. [37] reviewed the national annual savings if outpatient visits to the primary care physicians did not include unnecessary or inappropriate laboratory tests including CBC ($32.7 million), urinalysis ($3.3 million) and basic metabolic panel ($10.1 million). Those three procedures yield an annual cost savings of $46.1 million compared to the elimination of inappropriate Pap tests at an annual savings of $47.8 million. These figures illustrate the magnitude of healthcare savings by implementing simple laboratory test ordering practices which reduce duplication and/or inappropriate testing. Collaboration by subspecialty medical societies in disruptive technology development and improvements in routine clinical laboratory test