IMPACT OF TESTS ON DIAGNOSTIC THINKING AND CLINICAL DECISIONS

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Phased evaluation of medical tests:
Diagnostic thinking efficacy

Proposals for a Phased Evaluation of Medical Tests

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Med Decis Making 2009
Why does it matter?

- Why order tests if the results do not make any difference to clinical/treatment decisions? [“intention to test is intention to treat”]

- Test results will have an impact on patient outcomes, provided they correctly guide clinical and treatment decisions made by physicians.
  - Not easy to study: if all doctors followed sound evidence-based guidelines on disease management, then testing MUST clearly influence treatment decisions and there is no need to study it!

- Reality: “empiric” management of syndromes in the absence of any diagnostic confirmation.
  - If medical practice is mostly non-evidence based, then there can be no real connection between testing and outcomes!
Fig 2 Simplified test-treatment pathway showing each component of a patient’s management that can affect health outcomes


“The principal way in which testing leads to changes in a patient’s health is through changes in clinical decision making and management, guided by these test results. The latter includes selecting, starting, stopping, or modifying treatment; ordering more tests; or watchful waiting.” [Bossuyt et al. Med Desic Making 2009]
Change in physician’s decisions or behavior is an intermediate step for improvement in patient outcomes.
Example: influenza RIDTs

Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza

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Background: Rapid influenza testing decreases antibiotic and ancillary test use in febrile children, yet its effect on the care of hospitalized adults is unexplored. We compared the clinical management of patients with influenza whose rapid antigen test result was positive (Ag+) with the management of those whose rapid antigen test result was negative or the test was not performed (Ag0).

Methods: Medical record review was performed on patients with influenza hospitalized during 4 winters (1999-2003). Hospital policy mandated influenza testing (antigen or culture) for all patients with acute cardiopulmonary diseases admitted from November 15 through April 15. A subset of patients participated in an epidemiological study and had reverse-transcriptase polymerase chain reaction or serologic testing performed. Clinical data from Ag+ and Ag0 patients were compared.

Results: Of 166 patients with available records, 86 were Ag+ and 80 were Ag0. Antibiotic use (74% [86%] of 86 patients vs 79% [99%] of 80 patients; P=.002) was less and antibiotic discontinuance (12% [14%] of 86 patients vs 2% [8%] of 80 patients; P=.01) was greater in Ag+ compared with Ag0 patients. No significant differences in antibiotic days, length of hospital stay, or antibiotic complications were noted. Antiviral use (63% [73%] of 86 patients vs 6% [8%] of 80 patients; P<.001) was greater in Ag+ than Ag0 patients. Antigen status was independently associated with withholding or discontinuing antibiotics in multivariate analysis. Of 44 Ag+ patients deemed low risk for bacterial infection, 27 continued to receive antibiotics despite positive influenza test results. These patients more commonly had pulmonary disease and had significantly more abnormal lung examination results (P=.005) compared with those in whom antibiotics were withheld or discontinued.

Conclusions: Rapid influenza testing leads to reductions in antibiotic use in hospitalized adults. Better tools to rule out concomitant bacterial infection are needed to optimize the impact of viral testing.

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Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda

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Abstract

Background: Early and accurate diagnosis of malaria followed by prompt treatment reduces the risk of severe disease in malaria endemic regions. Presumptive treatment of malaria is widely practised where microscopy or rapid diagnostic tests (RDTs) are not readily available. With the introduction of artemisinin-based combination therapy (ACT) for treatment of malaria in many low-resource settings, there is need to target treatment to patients with parasitologically confirmed malaria in order to improve quality of care, reduce over consumption of anti-malarials, reduce drug pressure and in turn delay development and spread of drug resistance. This study evaluated the effect of malaria RDTs on health workers’ anti-malarial drug (AMD) prescriptions among outpatients at low level health care facilities (LLHCF) within different malaria epidemiological settings in Uganda.

Methods: All health workers (HWs) in 21 selected intervention (where RDTs were deployed) LLHCF were invited for training on the use RDTs. All HWs were trained to use RDTs for parasitological diagnosis of all suspected malaria cases irrespective of age. Five LLHCFs with clinical diagnosis (CD only) were included for comparison. Subsequently AMD prescriptions were compared using both a ‘pre - post’ and ‘intervention - control’ analysis designs. In-depth interviews of the HWs were conducted to explore any factors that influence AMD prescription practices.

Results: A total of 166,131 out-patient attendances (OPD) were evaluated at 21 intervention LLHCFs. Overall use of RDTs resulted in a 38% point reduction in AMD prescriptions. There was a two-fold reduction (RR 0.62, 95% CI 0.55-0.70) in AMD prescription with the greatest reduction in the hypo-endemic setting (RR 0.46 95% CI 0.51-0.53) but no significant change in the urban setting (RR1.01, p-value = 0.820). Over 90% of all eligible OPD patients were offered a test. An average of 30% (range 25%-35%) of the RDT-negative fever patients received AMD prescriptions. When the test result was negative, children under five years of age were two to three times more likely (OR 2.6 p-value <0.001) to receive anti-malarial prescriptions relative to older age group. Of the 63 HWs interviewed 92% believed that a positive RDT result confirmed malaria, while only 40% believed that a negative RDT result excluded malaria infection.

Conclusion: Use of RDTs resulted in a 2-fold reduction in anti-malarial drug prescription at LLHCFs. The study demonstrated that RDT use is feasible at LLHCFs, and can lead to better targeting of malaria treatment. Nationwide deployment of RDTs in a systematic manner should be prioritised in order to improve fever case management. The process should include plans to educate HWs about the utility of RDTs in order to maximize acceptance and uptake of the diagnostic tools and thereby leading to the benefits of parasitological diagnosis of malaria.
Does solid culture for tuberculosis influence clinical decision making in India?


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**SUMMARY**

**SETTING:** Medical units at an academic tertiary referral hospital in Southern India.

**OBJECTIVE:** To investigate the impact of solid culture on Löwenstein-Jensen medium on clinical decision making.

**DESIGN:** In a retrospective review of 150 culture-positive and 150 culture-negative consecutively sampled tuberculosis (TB) suspects, treatment decisions were analysed at presentation, after the availability of culture detection results and after the availability of drug susceptibility testing (DST) culture results.

**RESULTS:** A total of 124 (82.7%) culture-positive patients and 35 (23.3%) culture-negative patients started anti-tuberculosis treatment prior to receiving their culture results; 101 patients (33.7%) returned for their results; two (1.3%) initiated treatment based on positive culture and no culture-negative patients discontinued treatment. DST was performed on 119 (79.3%) positive cultures: 30 (25.2%) showed any resistance, eight (6.7%) showed multidrug resistance and one (0.84%) showed extensively drug-resistant TB. Twenty-eight patients (23.5%) returned for their DST results. Based on DST, treatment was modified in four patients (3.4%).

**CONCLUSION:** Using solid culture, 150 cultures need to be tested for one treatment modification and 30 for DST. The cost of the widespread application of culture will need to be balanced against its impact on treatment decisions in India.

**KEY WORDS:** tuberculosis; culture; decision making
Does an interferon-gamma release assay change practice in possible latent tuberculosis?

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Summary

**Background and Aims:** Suspected latent tuberculosis infection (LTBI) is a common reason for referral to TB clinics. Interferon-gamma release assays (IGRAs) are more specific than tuberculin skin tests (TSTs) for diagnosing LTBI. The aim of this study is to determine if IGRA changes practice in the management of cases referred to a TB clinic for possible LTBI.

**Design and Methods:** A prospective study was performed over 29 months. All adult patients who had TST, CXR & IGRA were included. The original decision regarding TB chemoprophylaxis was made by TB team consensus, based on clinical history and TST. Cases were then analysed with the addition of IGRA to determine if this had altered management. An independent physician subsequently reviewed the cases.

**Results:** Of 204 patients studied, 68 were immunocompromised. 120 patients had positive TSTs. Of these, 36 (30%) had a positive QFT and 84 (70%) had a negative QFT. Practice changed in 78 (63%) cases with positive TST, all avoiding TB chemoprophylaxis due to QFT. Of the immunocompromised patients, 17 (25%) underwent change of practice. No cases of active TB have developed.

**Conclusions:** This study demonstrates a significant change of clinical practice due to IGRA use. Our findings support the NICE 2011 recommendations.
Evaluation of the Impact of Interferon-Gamma Release Assays on the Management of Childhood Tuberculosis

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Background: Interferon-gamma release assays are increasingly being used in low-incidence settings, but there is little information on whether test results influence clinical decisions in children.

Methods: In June 2009, the Montreal Children’s Hospital began implementing the QuantiFERON-TB Gold In-Tube (QFT) as a follow-up test to the tuberculin skin test (TST). Pediatric respirologists were asked to document how the QFT result changed their initial clinical management based on the TST.

Results: During a 2-year period, 399 children with TST and QFT results were recruited prospectively. The median age was 13 years. In the cohort, 83% were foreign-born and 82% were Bacille Calmette–Guerin vaccinated. The QFT was negative in 5 of 11 (45.5%) children diagnosed with active tuberculosis (TB). Among 55 TST+/QFT– children evaluated as TB contacts, the negative QFT changed the treatment decision in only 3 (5.5%), and isoniazid was prescribed to the remainder. In 201 TST+/QFT– children from targeted school and immigrant screening programs, a negative QFT result was used to withhold isoniazid in 145 (72.1%) children. These children were followed for 1 year, during which no TB cases occurred. In a multivariable analysis, history of TB contact and TST induration ≥ 20 mm were associated with fewer changes in clinical decisions.

Conclusions: Our cohort study showed that pediatric respirologists used negative QFT results to withhold isoniazid in most low-risk children who were referred for a positive TST found through targeted screening programs. In contrast, in almost all TST-positive children who were evaluated as TB contacts, negative QFT results did not change clinical management.

Interferon-gamma release assays (IGRAs) are blood-based tests that have been developed to replace the tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection (LTBI). Meta-analyses of IGRA performance in children show that they have increased specificity and similar sensitivity compared to the TST, although the IGRA sensitivity may be lower in high-incidence versus low-incidence settings.1,2 Many national guidelines in low-incidence countries recommend the use of IGRAs in conjunction with the TST in children.3

In Canada, the Canadian tuberculosis (TB) Committee has published an advisory statement on the use of IGRAs in children, allowing for their use as an adjunct diagnostic tool for ruling in suspected active TB, investigating contacts of TB cases, confirming a positive TST in children with low probability of LTBI, confirming a negative TST in immunocompromised children, and targeted screening of recent immigrants.4,6 Although the use of IGRAs is steadily expanding, there is little evidence on how exactly IGRA results impact clinical management, especially in children. In children, the high specificity of IGRAs may prove to be useful in immigrant children from TB endemic settings, where the TST specificity is compromised by Bacille Calmette–Guerin (BCG) vaccination after infancy, multiple BCG vaccinations or boosting by multiple TSTs.

In 2009, the Montreal Children’s Hospital (MCH), a tertiary-care university teaching hospital, began implementing the QuantiFERON-TB Gold In-Tube (QFT; Cellestis Ltd., Victoria, Australia) as a routine clinical test for children with specific indications. The TB Clinic at the MCH sees a substantial number of immigrant children and a majority of them are BCG vaccinated. Using a more specific
Impact on clinical decisions are important but not easy to study

- How doctors act on tests will be influenced/confounded by:
  - Their practice environment (evidence-based/protocol-driven or not; public vs. private; HMO vs. not, developed vs. developing country, etc.)
  - Even within a health system, MDs may vary in their behaviours for the same condition (“variation in practice quality”)
  - How quickly test results get fed back to the doctors who need them
    - POC tests should have a bigger impact on clinical decisions than regular tests
  - Hard to study if a test is not approved for clinical use (will need to estimate hypothetical impact)
Impact of GeneXpert MTB/RIF on Patients and Tuberculosis Programs in a Low-Burden Setting
A Hypothetical Trial

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Abstract

Rationale: Guidelines recommend routine nucleic-acid amplification testing in patients with presumed tuberculosis (TB), but these tests have not been widely adopted. GeneXpert MTB/RIF (Xpert), a novel, semiautomated TB nucleic-acid amplification test, has renewed interest in this technology, but data from low-burden countries are limited.

Objectives: We sought to estimate Xpert’s potential clinical and public health impact on empiric treatment, contact investigation, and housing in patients undergoing TB evaluation.

Methods: We performed a prospective, cross-sectional study with 2-month follow-up comparing Xpert with standard strategies for evaluating outpatients for active pulmonary TB at the San Francisco Department of Public Health TB Clinic between May 2010 and June 2011. We calculated the diagnostic accuracy of standard algorithms for initial empiric TB treatment, contact investigation, and housing in reference to three Mycobacterium tuberculosis sputum cultures, as compared with that of a single sputum Xpert test. We estimated the incremental diagnostic value of Xpert, and the hypothetical reductions in unnecessary treatment, contact investigation, and housing if Xpert were adopted to guide management decisions.

Measurements and Main Results: A total of 156 patients underwent Xpert testing. Fifty-nine (38%) received empiric TB treatment. Thirteen (8%) had culture-positive TB. Xpert-guided management would have hypothetically decreased overtreatment by 94%, eliminating a median of 44 overtreatment days (interquartile range, 43–47) per patient and 2,169 total overtreatment days (95% confidence interval, 1,938–2,400) annually, without reducing early detection of TB patients. We projected similar benefits for contact investigation and housing.

Conclusions: Xpert could greatly reduce the frequency and impact of unnecessary empiric treatment, contact investigation, and housing, providing substantial patient and programmatic benefits if used in management decisions.

Keywords: tuberculosis; diagnosis; health care quality assurance; operations research; public health
Impact on clinical decisions are important but not easy to study

- **Study design options:**
  - Retrospective audits can be misleading — one can never quite tell if the change in management was definitely because of the test result — unless MDs explicitly recorded the rationale for the change (quality of medical records)
  - Prospective studies are better but the study itself can potentially influence the MDs to alter their behaviours (“Hawthorne effect”)
  - If empiricism is widespread, it is hard to tease out what role, if any, a test is playing
  - Change in behaviour is only a “surrogate” for downstream patient outcomes:
    - Behaviour might change, but outcomes may not!
    - If we can directly measure outcomes, do we still need to study change in behaviours??
Using patient management as a surrogate for patient health outcomes in diagnostic test evaluation

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Some generic principles for this design

- Studies of patient management must provide a clear description of the role and position of a test in the clinical pathway; potential consequences of a positive and negative test result on patient management need to be pre-specified and the potential patient benefits of these management changes clearly stated.

- A detailed description of the study design is crucial to understand how the authors attempted to minimise bias.

- Need to report information on how the data were collected for a study (actual management, dedicated case report forms or only assumed from charts?)

- Estimates of changes in management must be reported contingent on test results; otherwise it is not possible to conclude to what extent management changes are dependent on the test.

- Patient management studies are easiest to interpret if it can be assumed that clinicians use all test information appropriately in a standard way, so that a change in patient management can be attributed to the test itself rather than to variations in behaviour.

- If variations between clinicians are anticipated, for e.g. due to differences in preference or experience, these factors can also be measured to assist interpretation of the results.

Staub et al. BMC Res Meth 2012