Benefits and drawbacks of multiplex panels for the identification of pathogens in clinical specimens

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Declaration of conflict of interest

- My diagnostic laboratory uses commercial multiplex PCR panels for the diagnosis of respiratory, gastrointestinal and viral herpetic infections

Resolution

- Be it resolved that molecular multiplex panels for infectious agents should be used to simplify laboratory workflow, improve patient management and decrease overall health system costs.

- AGAINST

Rationale “FOR”

- Multiple targets in one test
  - Detect all diagnosable causes of the syndrome
  - Increase sensitivity of detection
  - Decrease TAT to result reporting
  - Support cohorting of patients
  - Improve laboratory workflow
- Positively influence clinical care
  - Enable appropriate and timely therapy
  - Shorten illness duration and time away from work/school
  - Decrease morbidity and mortality
  - Avoid unnecessary investigation and Rx (antibiotics, X-rays)
  - Decrease ED and admission LOS
  - Enable outbreak investigation and control
- Reduce overall health care costs

Multiplex detects all diagnosable causes of respiratory virus infection– do we need to?

- Up to 20 or so pathogens per test
  - Influenza A/B, RSV, rhino/enterovirus, parainfluenza viruses, human metapneumovirus, adenovirs, coronaviruses, human bocavirus
  - *+/- Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bordetella pertussis/parapertussis*

- *Treatable causes of infection?*
  - Influenza A/B
  - RSV in rare situations
  - Bacteria
    - Clinical presentation more likely to be different from viral RTI
    - Better tested as discrete less expensive tests?

Indications for influenza Rx

- High risk clinical settings (CPS 2018, U Allen et al)
  - Asthma, chronic pulmonary disease
  - Cardiovascular disease
  - Malignancy
  - Chronic renal and liver disease
  - Sickle cell disease
  - Immune suppression
  - Children <5 years
  - Rheumatological disorders, chronic ASA Rx
  - Neurological impairment
  - Pregnant women
  - Obesity
  - Aboriginal populations
  - Children in chronic care
- Hospitalization with severe clinical presentation
- Symptom onset <48 h and preferably <12 h
- Generally not indicated for otherwise healthy non-hospitalized patients

Influenza

- *Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments* (43 trials)
  - Jefferson et al. BMJ 2014;348:g2545
- Main findings (treatment)
  - Modest benefit on symptom duration (17 h)
    - Children with asthma no effect
  - No significant effect on hospitalization or serious complications
  - Significant incidence of adverse effects
    - Nausea, vomiting, headache, renal, psychiatric
- Are we over-treating influenza?
- What about those other viruses?

Multiplex increases sensitivity of viral detection

Method*	Multiplex higher sensitivity?	Sensitivity	Specificity
Viral culture	Yes	44-80%	100%
Rapid antigen	Yes	65-75%	96%
DFA	Yes	50-80%	99%
POC molecular	Yes/No	76-98%	99%
Single-plex PCR	No	100%	(100%)
Multiplex PCR**		85-100%	98%

Multiplex has the advantage over multiple single-plex conventional PCRs wrt cost, lab efficiency, TAT, but not sensitivity (influenza A and B, adenovirus)**

Highly sensitive POC tests for influenza/RSV have clear advantage over multiplex tests wrt cost, lab efficiency, TAT, sensitivity

*Gill PJ et al. JAMA Pediatrics 2017, 171(8):1-7; **Popowitch EB et al. JCM 2013, 51(5): 1528-1533

Which test is best?

- If we have only one test for all respiratory viruses, and our main diagnostic focus is influenza, we are using a sledge hammer to kill a flee
  - Not cost-effective, esp. in ED, sensitivity for influenza may not be optimal, and it is more difficult to rapidly change molecular targets in a multiplex panel from a regulatory standpoint

- Consider a point of care rapid influenza molecular test instead (not EIA/IC-LF assay)
  - 15-30 minutes TAT
  - Can inform investigation and treatment while patient in ED
  - Sensitivity approaching single-plex or multiplex PCR
  - Cost-effective compared to multiplex panel
  - Easier to alter target in response to changes in circulating viruses

- Asymptomatic children frequently test positive for respiratory viruses, esp. entero/rhinoviruses, bocavirus
  - 30% of children in day care (Moe et al, PLOS ONE July 19, 2016)

- *Why do we need to know all those other viruses in the ED or on the wards for otherwise healthy individuals?*
- *In children a positive test may not correlate with causality*
- *Decision to admit depends on clinical criteria, not a positive viral respiratory test.*

Multiplex decreases TAT to result reporting

Method	TAT hands on (batch)
Viral culture	2-10 d
Rapid antigen	10-30 min
DFA	4-5 h (5-24 h batch)
POC molecular	15-30 min
Single-plex	4-5 h (5-24 h batch)
Multiplex	45 min-5 h (1-24 h)

Some multiplex assays achieve TATs that can influence patient management in the ED, most do not, and in the ED we really only need to know about influenza +/- RSV within 48 h of symptom onset
More support for molecular POC assays

Multiplex important to support cohorting of admitted patients

- In hospitals with multiple bed rooms (most adult), cohorting for RSV and influenza is common
  - Not enough rooms to cohort for every known virus on a multiplex panel, as multiple circulating viruses at any one time
  - “Respiratory room” compromise
- Not cohorting for other viruses may inadvertently expose patients to additional respiratory viruses that could worsen clinical status and increase LOS
- Therefore, this is not a good reason to do the multiplex test over other tests, if results do not influence management

Multiplex testing can improve lab workflow

- Yes, by streamlining workflow into one testing modality
- No, if it would be better to decant a significant percentage of testing to a sensitive influenza POC molecular test instead of multiplex, or to do no testing at all in many situations (non-admitted outpatients)

Multiplex tests positively influence patient care

- Enable appropriate and timely therapy
  - Only for influenza, and not as quickly as POC molecular
- Shorten illness duration (influenza) and therefore time away from work/school
  - Effect modest in adults (17 h reduction in symptoms) (Jefferson et al)
  - No effect in children with asthma (Jefferson et al)
- Decrease morbidity and mortality for influenza
  - No solid evidence (Jefferson et al)

Multiplex tests positively influence patient care

- Avoid unnecessary investigation and Rx (antibiotics, X-rays)
  - Multiplex panel (12 viruses, LDT, adults, TAT 9-15 h, Semret et al, Montreal)
    - Positive influenza result
      - 10x increased likelihood of starting or continuing oseltamivir
      - No significant effect on discontinuing antibiotics
    - Antibiotic use
      - Positively correlated with radiological evidence of pneumonia
      - De-escalation of antibiotics not significantly correlated with negative multiplex test result for any virus because of concern regarding viral/bacterial co-infection
      - Consider effect of combining viral pathogen testing with procalcitonin
  - Multiplex panel [FilmArray Respiratory panel (Biofire Dx) vs. conventional dx, children, TAT 3 h, Subramony et al)
    - Decreased antibiotics (median 4 vs. 5 d)
    - Fewer CXRs (60 vs. 80%)
    - Longer isolation (20 vs. 0 h)
- Evidence not strong for effect on investigation and Rx

Multiplex tests positively influence patient care

- Decrease ED and admission LOS
  - Multiple studies fail to demonstrate decreased LOS in ED or for admitted children linked to viral testing (Doan et al, Cochrane Database Systematic Review 2014, Wishaupt et al, Pediatrics 2011, Stollar et al, Eur J Peds 2014)
  - In adults, a theoretical possible benefit
- Enable outbreak investigation and control
  - Yes, identification of non-conventional viral respiratory pathogens can be aided by multiplex PCR testing, but do we really know whether they are the same strain of virus?

Multiplex testing can reduce overall health care costs

- Silo'ed budgets within hospital
  - Difficult to assess overall impact of a new test
  - Healthcare utilization/cost effectiveness studies expensive and time-consuming
  - Most have been done with older suboptimal assays
- Direct one-for-one test substitution (e.g. multiplex PCR for DFA) rarely supportable within laboratory budget alone
  - Usually requires reduction of volume of testing and introduction of targeted sensitive POC assays
    - Best achieved by utilization initiatives
  - Need to engage various clinical stakeholders to support initiative, provide input on judicious use of a new expensive test, and sometimes provide financial support, if aligned with program needs
- Multiplex testing should reduce overall health care costs, but it is difficult to prove and hard to obtain financial support from other programs to effect this change
- Need to utilize decision support tools provided by your HIS

Rationale "FOR" and "AGAINST"

- Multiple targets in one test
  - Detect all diagnosable causes of the syndrome (only need POC influenza +/- RSV most of the time)
  - Increase sensitivity of detection (not compared to single-plex PCR tests)
  - Decrease TAT to result reporting (not compared to POCT influenza/RSV molecular)
  - Support cohorting of patients (but not possible to do properly, so why bother?)
  - Improve laboratory workflow (agree but not good enough reason on its own)
- Positively influence clinical care
  - Enable appropriate and timely therapy (influenza molecular POCT is better, cheaper, faster for this purpose and should we be treating as much as we do?)
  - Shorten illness duration and time away from work/school (modest reduction only)
  - Decrease morbidity and mortality (unproven)
  - Avoid unnecessary investigation and Rx (antibiotics, X-rays) (limited evidence)
  - Decrease ED and admission LOS (limited evidence)
  - Enable outbreak investigation and control (I'll give you that)
- Reduce overall health care costs (it should if used with discretion, but no solid evidence)

Multiplex respiratory panels

- Not a good option as a single test for a hospital serving patients with mild to severe illness
- Limit use to hospitalized patients with significant underlying disease or severe clinical presentation
- Add in a sensitive molecular POC test for influenza virus +/- RSV to properly identify patients needing prompt treatment
- Then fund and carry out proper healthcare utilization studies for today's generation of assays