Staged testing as a solution to the challenges of testing lower risk patients

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INTRODUCTION

Several groups have published on the decreasing prevalence of reversible perfusion abnormalities in stress SPECT MPI populations, such that ischemia may be present in under 10% of tests among patients without established CAD.^{1,2} This trend is seen despite strong evidence that many patients with stable CAD can be managed safely and effectively with only medical therapy,^{3–5} prompting the question why are we testing lower and lower risk populations over time?

It is likely that many factors contribute including changing demographics, protocol driven care, malpractice concerns, and decreased continuity between inpatient and outpatient encounters. Regardless, the declining prevalence of ischemia is a major challenge for nuclear cardiology labs. Chief among these challenges is a marked decrease in positive predictive value with declining prevalence (Figure 1).

REVIEW OF TERMS

Although likely familiar to most of the readers of the *Journal of Nuclear Cardiology*, a brief review of terms is in order. The *pre-test risk* of the entire

population is equivalent to the *prevalence* in the population (pre-test probability estimates for individuals will vary around this). The *sensitivity* of a test is the proportion of those patients with disease who will be correctly identified as disease. Physicians worry about this parameter greatly out of concern for missing disease. Perhaps more critical in testing low risk populations is *specificity* which is defined as the proportion of non-diseased patients whom the test will correctly identified as non-diseased. It therefore follows that the proportion of non-diseased patients who are incorrectly identified as diseased is given by (1-specificity) (*false positives*).

In practice, the sensitivity and specificity are neither particularly intuitive nor useful for patients and clinicians. More practically useful are the *positive predictive value* (PPV) and *negative predictive value* (NPV). The PPV is defined as the proportion of all patients identified as abnormal by the test who are truly abnormal. When prevalence is moderate, PPV is principally affected by specificity with a very minor contribution from sensitivity. However, when prevalence drops, PPV declines precipitously, regardless of specificity (Figure 1A). Consequently, even very specific tests cannot overcome an adverse referral pattern in which low risk patients are referred for testing. Unfortunately, this implies that the proportion of patients with abnormal tests who are truly abnormal may be 50% or lower (false positive fraction = $1 - \text{PPV}$; Figure 1B). This, consequently, may lead to many unnecessary invasive angiograms.

Analogously to PPV, the NPV is the proportion of all patients identified as non-diseased who are truly non-diseased. Although sensitivity is a contributor to NPV, in modern testing populations, the low prevalence of disease is greater driver of NPV than sensitivity.

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Figure 1. The positive predictive value shown as a function of prevalence of ischemia (panel A) across a range of test specificities. Panel B shows the false positive fraction as a function of all positive tests (1—positive predictive value). In all cases, sensitivity was assumed at 0.90.

WHAT IS THE SOLUTION?

One solution to low PPV is to substitute to tests with greater specificity. Potential options include coronary CT angiography, attenuation corrected SPECT and PET MPI. While each has its partisans, all will fail to deliver high PPV in a low pre-test risk population. In order to maintain PPV > 50% in low pre-test risk populations, specificity of 99% or greater is necessary, a target that is unachievable by any coronary artery disease evaluation modality without severely compromising sensitivity.

The only solution to low pre-test risk is to address the pre-test risk itself. The ultimate solution is to educate referring physicians and to place greater emphasis on appropriate use. However, appropriate use criteria are complex, difficult to consistently interpret and have been challenging to implement on a large scale. An alternative approach is to layer testing so as to increase the pre-test risk population of those who ultimately undergo stress imaging.

In this issue of the *Journal* Smith and colleagues present the results of a study which supports one approach to layered testing which may improve the PPV of stress SPECT MPI. This work extends prior studies from Bourque^{6,7} and Duvall^{8,9} which showed that patients with excellent exercise capacity (≥ 10 METS) without concerning EKG changes or symptoms can safely omit radiotracer injection and imaging. The

present work shows that this strategy is probably safe even among older adults ≥ 65 years. While this approach is likely to help limit low-yield testing, it is unlikely to sufficiently increase pre-test risk as to entirely resolve the issue of suboptimal PPV. This is in part due to a concomitant decrease in rate of exercise testing and declining exercise capacity among SPECT-MPI referral populations.

LAYERED TESTING IS NOT A BAD WORD

Additional approaches to layered testing which could be helpful include use of calcium scoring together with stress SPECT or PET. Significant CAD is extremely uncommon among patients with no coronary calcium, particularly when symptoms are atypical, EKG changes are absent and risk factor burden is not very severe. This population describes a substantial proportion of patients referred for coronary imaging tests such as MPI and coronary CTA. The use of coronary artery calcium (CAC) as a gatekeeper for coronary CTA has been evaluated favorably in several prior studies.^{10,11} Similar proposals^{12,13} to use CAC as a gatekeeper for MPI are supported by large retrospective data sets from several nuclear laboratories showing a very low prevalence of ischemia and events in when CAC = 0.^{14–20}

In addition to significant value as a gatekeeper application with CAC = 0 used to limiting low-yield downstream testing, abnormal CAC testing provides additional value for a large majority of patients with normal MPI. Although expected to vary across populations, nearly one in four patients with normal MPI will have CAC > 0.²¹ These patients with normal MPI but coronary calcifications have worse prognosis^{16–18} and are likely to benefit from aggressive risk reduction strategies including medical therapy. Furthermore, emerging data suggest CAC scores improve diagnostic accuracy for obstructive CAD and increase diagnostic certainty of borderline or uncertain MPI results.^{22,23}

However, this strategy has only been evaluated retrospectively in the context of trials and observational studies conducted for other purposes. Many had significant exclusion criteria relevant to coronary CTA that limited applicability to other patient populations frequently referred for nuclear testing such as those with renal dysfunction, arrhythmias, established CAD, and elevated heart rates.²⁴ Furthermore, the relative value of a layered testing strategy using CAC compared to wider use of biomarkers of myonecrosis in stable chest pain²⁵ or using improved clinical risk assessment scores to improve patient selection^{26,27} remains largely unexplored.

Consequently, prospective randomized data evaluating whether layered testing can safely improve patient throughput and lower costs in patients referred for stress MPI is a significant unmet need. Until such data are available, it is likely that adoption of such strategies will remain limited.

CONCLUSIONS

Due to declining pre-test probability in nuclear stress testing populations, significant practice changes are needed to optimize resource utilization and maintain positive predictive value. The work by Smith et al. in this issue of the Journal supports not proceeding to tracer injection and imaging in patients with excellent exercise capacity who do not have concerning stress testing features. Although this represents a valuable first step, further measures are necessary to truly optimize resource utilization. Foremost among these is the use of coronary calcium scoring as a gatekeeper, which should be carefully investigated in prospective studies.

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