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ABSTRACT & COMMENTARY

More Is Not Better with Vitamin D Supplementation

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Dr. Scherger reports no financial relationships relevant to this field of study.

SYNOPSIS: Blood levels of vitamin D in the mid-normal range have been associated with several benefits, including healthy bones and better outcomes with COVID-19 infections. A recent study revealed vitamin D levels higher than normal from high-dose supplementation are harmful to bone health.

SOURCE: Billington EO, Burt LA, Rose MS, et al. Safety of high-dose vitamin D supplementation: Secondary analysis of a randomized controlled trial. *J Clin Endocrinol Metab* 2020;105:dgz212.

A randomized, controlled trial conducted at the University of Calgary, Alberta, Canada, included 373 healthy adults ages 55 to 70 years. Subjects received vitamin D supplements over three years. Participants were randomly assigned to taking vitamin D3 at 400 IU, 4,000 IU, or 10,000 IU. Researchers initiated calcium supplementation if the dietary calcium was less than 1,200 mg/day.

Each dose carried a similar safety profile. Those who took the higher dosages of vitamin D3 exhibited greater loss of total bone mineral density. Investigators observed this negative outcome started in participants who were taking daily doses of vitamin D3 of 4,000 IU and higher. Taking 10,000 IU of vitamin D3 was harmful to bone health.

■ COMMENTARY

Vitamin D is a prohormone that affects many areas of the body, including bone health, cell growth, neuromuscular and immune function, and inflammation severity.[1-3] Dietary sources of vitamin D are limited. Most of the vitamin is acquired through the skin by the interaction of ultraviolet light with cholesterol. Several factors result in humans absorbing less vitamin D than our evolutionary ancestors, including living indoors, sun protection, eating less organ meats, and living longer. The World Health Organization and others have

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cited a widespread deficiency in vitamin D.[4,5] Epidemiologic evidence suggests low vitamin D levels may cause premature aging, autoimmune disease, cancer, and cardiovascular disease.[2,3,6] In one study, the authors observed those with the lowest vitamin D levels died more often.[7] Recent evidence shows lower vitamin D levels are associated with a worse outcome from COVID-19 infection.[8] Evolution is based on the successful reproduction of the species. I tell seniors that evolution does not care how long humans live. Aging skin does not convert sunlight to vitamin D as well as younger skin.[9,10]

The paradox of vitamin D is that despite its many health benefits, randomized, controlled trials have failed to show a beneficial effect of testing for vitamin D levels and supplementation in the general population.[1,11-12] These have been single-variable studies and may fail to capture the benefit of vitamin D supplementation. Often unrealistic outcomes are tested for vitamin D supplementation (e.g., fracture prevention).

The "normal" range of vitamin D in the body is considered to be between 30 ng/mL and 100 ng/mL. Some suggest levels as low as 20 ng/mL are safe. The National Academy of Medicine recommends a daily intake of 600 IU for young adults and 800 IU for seniors.[1] The Endocrine Society suggests supplementation of 1,500 IU to 2,000 IU of vitamin D3 daily, which could result in optimal vitamin D levels in the blood (i.e., 40 ng/mL to 60 ng/mL).[13] This is what I recommend for adult patients, especially seniors.

New evidence for vitamin D and its importance seems to come out daily. I recommend keeping an eye out for more information about this important supplement, especially for older patients. ■

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ABSTRACT & COMMENTARY

Race Correction in Clinical Calculations: Is It Time to Reconsider?

By Mitchell Linder, MD

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Dr. Linder reports no financial relationships relevant to this field of study.

SYNOPSIS: Many clinical calculators use race as a predictive variable to assess risk for outcomes. Although most tools assume a genetic disposition for these outcomes, other factors, such as health disparities and other potential confounders, are more likely to be the underlying reasons for any race-related differences in outcomes.

SOURCE: Vyas DA, Eisenstein LG, Jones DS. Hidden in plain sight – reconsidering the use of race correction in clinical algorithms. *N Engl J Med* 2020;383:874-882.

This was a theoretical analysis of multiple existing diagnostic algorithms and clinical prediction guidelines and their use of race or ethnicity categories as inputs for calculation. Vyas et al identified 13 prominent tests and calculators in wide use today that each include race/ethnicity in their formulas. Studies they identified include pulmonary function testing, the Fracture Risk Assessment tool (FRAX), the Simplified Calculated Osteoporosis Risk Estimation (SCORE), the Breast Cancer Surveillance Consortium Risk Calculator, the National Cancer Institute Breast Cancer Risk Assessment Tool, the Rectal Cancer Survival Calculator, the pediatric urinary tract infection calculator (UTICalc), the STONE score (used for prediction of possible kidney stones), the Vaginal Birth After Cesarean (VBAC) risk calculator, the Kidney Donor Risk Index, the estimated glomerular filtration rate (eGFR) calculator, The Society of Thoracic Surgeons Short-Term Risk Calculator, and The American Heart Association's Get with the Guidelines — Heart Failure. They noted this list is not all-inclusive but includes readily available examples about how pervasive the use of race/ethnicity is in medical decision-making tools.

The authors examined the tools by specialty to show how each equation uses "race-correction" and how each race adjustment could negatively affect Black patients. In cardiology, the heart failure score predicts lower risks for Black patients (without providing any rationale). Vyas et al noted this could cause clinicians and hospitals to devote fewer resources to these patients, since they are deemed lower risk. For nephrology, the authors specifically noted how calculators overestimate kidney function based on assumptions about race-related differences in creatinine and overestimate the potential for kidney transplant failure involving kidneys from Black donors.

The STONE score also assigns lower scores to Black patients, thereby potentially guiding clinicians away from a possible diagnosis. The VBAC calculator predicts a lower chance of success for African American and Hispanic patients. This lower predicted success rate might discourage these patients from an attempt at a trial of labor and, thus, exacerbate the disproportionately high rate of cesarean delivery that minorities experience already.

Vyas et al urged institutions, medical societies, and individual clinicians to thoroughly review existing tools. To do this properly, clinicians must re-evaluate how they conceptualize race and apply it to the care they provide.

■ COMMENTARY

Systemic racism abounds in the medical field, with clinical calculators as just one example where it can be seen. Past research has shown that commonly employed commercial prediction algorithms used to allocate healthcare also include underlying racial bias.[1] Unfortunately, we cannot look under the hood to see the inner workings of the tools we often use.

How can clinicians make evidence-based decisions that incorporate guideline-supported rationale? Vyas et al suggested clinicians ask three questions: Is the need for race correction based on robust evidence and statistical analyses (e.g., with consideration of internal and external validity, potential confounders, and bias)? Is there a plausible causal mechanism for the racial difference that justifies the race correction? Would implementing this race correction relieve or exacerbate health inequities?

Asking these questions could help identify inherent bias and systemic racism that could harm patients. It is the responsibility of every practitioner to provide unbiased and appropriate care for patients. Ensuring clinical tools are based on these same principles is a good start. For example, as of June 1, 2020, the University of Washington labs have transitioned from using the eGFR formula to using one that excludes race as a variable.[2-4]

The inclusion of the VBAC calculator on this list is especially concerning. An analysis of this calculator has shown most of the race-related statistics that underpin the algorithm likely are related to social advantage or disadvantage, as opposed to the result of any specific race.[5] Considering these known assumptions built into the VBAC calculator, using the tool becomes more dangerous. It could serve to perpetuate health disparities by needlessly steering patients to repeat cesarean delivery solely because of their race.

With the higher rate of maternal morbidity and mortality that minorities sustain in the United States and the world, it is our duty to look at the tools we use to determine what potential conflicts or biases are included and whether that opinion is valid and applicable to patients.[6] Of course, that one step will not reverse entrenched biases everywhere nor eliminate systemic racism in one sweep, but every act to combat inequalities is a worthwhile one to undertake. ■

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ABSTRACT & COMMENTARY

A Novel Rifabutin-Containing Combination Regimen Eradicates *H. pylori* Infection

By Richard R. Watkins, MD, MS, FACP, FIDSA, FISAC

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Dr. Watkins reports no financial relationships relevant to this field of study.

SYNOPSIS: Researchers found a significantly higher eradication rate for *H. pylori* with a 14-day regimen of rifabutin, amoxicillin, and omeprazole compared to 14 days of amoxicillin and omeprazole.

SOURCE: Graham DY, Canaan Y, Maher J, et al. Rifabutin-based triple therapy (RHB-105) for *Helicobacter pylori* eradication: A double-blind, randomized, controlled trial. *Ann Intern Med* 2020;172:795-802.

The treatment of *Helicobacter pylori*, the most common cause of peptic ulcers and gastric cancer, has become more challenging because of the spread of antibiotic resistance. Several antibiotics that were used empirically, such as clarithromycin, metronidazole, and levofloxacin, are no longer effective in many cases. Previous studies have shown rifabutin is active in vitro against *H. pylori*, and resistance is slow to develop. After promising results from a pilot study, Graham et al conducted a clinical trial to compare a treatment regimen that contained rifabutin to a standard combination for eradicating *H. pylori*.

The authors conducted a Phase III, double-blind, randomized, controlled clinical trial, enrolling adults with dyspepsia and confirmed *H. pylori* infection. Patients were randomly assigned in a 1:1 ratio to receive a fixed-dose combination of 3 g amoxicillin, 120 mg omeprazole, and 150 mg rifabutin (AOR) or amoxicillin plus omeprazole (AO), four capsules every eight hours for 14 days. Researchers performed a follow-up 13C urea breath at the test-of-cure visit (conducted between days 43 and 71 after initiation of treatment) to determine *H. pylori* eradication. The authors measured plasma concentrations of the drugs at baseline and at day 13 visits. Also, investigators conducted pharmacogenetic testing at baseline to assess the status of CYP 2C19, the liver enzyme that metabolizes omeprazole. Exclusion criteria included prior *H. pylori* treatment; alarm symptoms (e.g., anemia, melena, weight loss, or dysphagia); more than two active gastric or duodenal ulcers; a history of esophageal or gastric surgery; previous gastric cancer; and recent receipt of antibiotics, a proton-pump inhibitor, or a bismuth-containing medication. Also, persons of Asian descent were excluded because of concerns about polymorphisms in cytochrome P450 genes that can affect omeprazole metabolism.

Two hundred twenty-eight patients received AOR and 227 received AO. The treatment groups were well-balanced in terms of demographic characteristics. The mean age was 46.5 years (standard deviation [SD], 13 years), 62.2% were women, and 60.0% were Hispanic. At baseline, 22 patients were infected with amoxicillin-resistant *H. pylori* strains. No isolates were resistant to rifabutin. The mean adherence rate, determined by pill counts, was 97.5% (SD, 14.2%) in the AOR group and 97.9% (SD, 13.1%) in the AO group.

The eradication rate was higher in the AOR group compared to the AO group (83.8%; 95% CI, 78.4% to 88.0% vs. 57.7% [95% CI, 51.2% to 64.0%], respectively; $P < 0.001$). Interestingly, the eradication rate with the AOR regimen was high even for strains that were resistant to amoxicillin (80%), but predictably was much worse for the AO regimen (25%). The rates of adverse events were similar between the two groups, with diarrhea and headache more common in the AOR group vs. the AO group (10.1% and 7.5% vs. 7.9% and 7.0%, respectively), while nausea, abdominal pain, and dizziness were more frequent in the AO group. More rashes were seen with AOR (1.3%) than with AO (0). Finally, no adverse events were found to be related to the CYP 2C19 genotype.

■ COMMENTARY

The dwindling number of effective drugs to treat *H. pylori* infection is an increasing concern. In the United States, the FDA has not approved a new therapy to treat *H. pylori* since 1997. Therefore, the study by Graham et al is welcome since it provides evidence for the effectiveness of a novel, fixed-combination regimen. Another highlight was that the adherence rate, tolerability, and adverse event profile of the three-drug regimen compared favorably to the two-drug regimen. Moving forward, it will be important to see how much the novel regimen will cost and if the rate of adverse events will remain low once it becomes widely prescribed. Moreover, although none of the *H. pylori* strains demonstrated rifabutin resistance, this undoubtedly will occur with increasing use. Clinical microbiology laboratories will need to recognize and monitor these patterns.

Despite the robust design, there were a few limitations to the study. First, since the investigators excluded people of Asian descent, it is unclear if the drug will be safe and effective for this group. Second, there were limited data on the clinical breakpoints for the amoxicillin-resistant strains. Third, quadruple therapy that includes bismuth is the regimen prescribed most frequently for *H. pylori* in the United States. How AOR would compare to this regimen is unknown. Finally, all clinical sites were in the United States, so the results might not be applicable to other geographic areas.

A new combination treatment option for *H. pylori* infection appears to be on the horizon. Although it is a cause for optimism, whether these results will hold up in real-world settings remains to be elucidated. Further studies that compare AOR to current first-line regimens also seem warranted. ■

ABSTRACT & COMMENTARY

Possible Aerosol Spread of SARS-CoV-2 in an Apartment Building

By Stan Deresinski, MD, FACP, FIDSA

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Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Although not definitive, evidence is consistent with aerosol spread of SARS-CoV-2 in an apartment building as a result of transport through the drainage system to apartments directly above.

SOURCE: Kang M, Wei J, Yuan J, et al. Probable evidence of fecal aerosol transmission of SARS-CoV-2 in a high-rise building. *Ann Intern Med* 2020; Sept. 1. doi:10.7326/M20-0928. [Online ahead of print].

After visiting Wuhan, China, all five members of a family living in a 15th floor apartment in Guangzhou, China, developed COVID-19 in late January 2020. Days later, couples living directly above them in apartments on the 25th and 27th floors became ill. A review of surveillance videos in the building showed no evidence of contact between any of the three clusters, and no one among the two couples had traveled or knew of coming in contact with anyone with COVID-19. However, the three apartments shared the same waste pipes.

Among many air and surface samples collected from within the apartment tower, the only ones in which SARS-CoV-2 was recovered were in the implicated 15th floor apartment as well as from a vacant bathroom on the 16th floor directly above. The investigators released a tracer gas into the floor drainpipe of the 15th floor apartment, and the gas was detected in the bathrooms of the implicated apartments on the 25th and 27th floors. The investigators concluded this event was the result of aerosolization of fecal material containing SARS-CoV-2 within the drainage plumbing system of the Guangzhou apartment.

■ COMMENTARY

In 2003, SARS-CoV caused an outbreak in the Amoy Gardens housing complex in Hong Kong, affecting 321 individuals, 42 of whom died. Apartments in China commonly include floor drains with underlying U-shaped traps that are water-filled. Yu et al reported the Amoy Gardens outbreak was the result of the traps in the index apartment drying out and, thus, allowing aerosolization of virus particles upward, possibly abetted by an exhaust fan, through the air shaft into apartments above.[1] Flushing toilets has been demonstrated to generate aerosols.

Kang et al concluded the Guangzhou event spread similarly. However, since the bathroom floor traps had been cleaned in the interval, they could not determine if the traps had lost their protective water. Nonetheless, the authors proposed the "bioaerosolization of wastewater mixed with urine, feces, and exhaled mucus

originating from index patients is suggested to be the source of infectious bioaerosols in this outbreak."

Although the role of aerosols in transmission of SARS-CoV-2 has been disputed, the accumulated evidence indicates this is an important mode of infection spread. The degree to which this is a risk at a distance remains somewhat uncertain but undoubtedly is a function of the density of aerosol particles and the duration of exposure. Also disputed is the role of the high SARS-CoV-2 RNA loads in the feces of COVID-19 patients since the detection of transmissible virus (as opposed to just residual RNA fragments) has been a rarity.

Although bathroom drain traps are rare in the United States, other bathroom drains may include U-shaped traps. These traps should not be allowed to dry out (such dry out is possible if these traps are meant to drain sinks or bathtubs that go unused). Also, maintain bathroom hygiene and ventilation. Surfaces in toilet areas used by COVID-19 patients can be contaminated with SARS-CoV-2. At one Wuhan hospital, aerosol samples were more highly contaminated in a small, poorly ventilated patient toilet room than were patient care areas.[2] ■

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BRIEF REPORT

Can Chopsticks Carry SARS-CoV-2?

By Carol A. Kemper, MD, FACP

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Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Lui G, Lai CKC, Chen Z, et al. SARS-CoV-2 RNA detection on disposable wooden chopsticks, Hong Kong. *Emerg Infect Dis* 2020;26:2274-2276.

Although some may feel threatened by the possible presence of SARS-CoV-2 virus on their cereal box, Lui et al added a twist to the tale of surface contamination. Using real-time PCR (RT-PCR), they examined the risk of viral contamination of chopsticks used by patients with COVID-19 infection.

Five patients hospitalized for COVID-19 infection were recruited for this study, including one patient who remained asymptomatic, two whose symptoms had resolved, and two with active infection with moderate to severe COVID pneumonia. Patients received a set of plain, unvarnished, wooden chopsticks in a sealed plastic bag for meals. The chopsticks were collected, dipped in a buffered solution, and shaken for 30 seconds. SARS-CoV-2 RNA was detected using RT-PCR and compared with the results of serial sputum samples and nasopharyngeal (NP) and throat swabs.

Chopsticks from all five patients were positive at various points, similar to the results of sputum and NP/throat swabs, including those from the asymptomatic patient. This patient had been exposed to a known infected patient and, although she remained asymptomatic, she was hospitalized for isolation. On day 2 of her hospitalization (12 days after exposure), her throat and sputum samples tested positive for SARS-CoV-2, along with a pair of chopsticks. Although she was described as asymptomatic, a high-resolution chest CT showed patchy bilateral ground glass infiltrates and small areas of consolidation. Chopsticks from two other patients were positive for up to two to three days post-resolution of symptoms, although viral RNA could be detected in sputum specimens for up to eight days. Multiple sets of chopsticks were positive during the acute phase of illness in the remaining two patients (at days 5-7 in one patient with pneumonia and respiratory failure, and at days 7-8 in the final patient with fever and pneumonia).

This small study suggests salivary contamination of utensils with SARS-CoV-2 virus can occur. Sharing food and utensils, or using communal food bowls, which is common throughout Asia, probably is not a good idea if one is trying to avoid COVID-19. The Chinese government had been pushing to change the age-old practice of sharing morsels of food with children and partners using your own chopsticks as a demonstration of love and respect or even intimacy. Several restaurants have changed their practices by adding "serving chopsticks" to communal food bowls, but the practice remains limited, and many families have been resistant to this change.[1] ■

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PHARMACOLOGY UPDATE

Remdesivir Injection (Veklury)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

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Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved remdesivir, the first treatment for COVID-19. This comes about six months after the agency granted an Emergency Use Authorization (EUA) in May 2020. Remdesivir is an antiviral acting as a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor. It is distributed as Veklury.

INDICATIONS

Remdesivir should be prescribed to treat COVID-19 in adults and pediatric patients ≥ 12 years of age and weighing at least 40 kg who need hospitalization.[1] The agent should be used in a hospital or an equivalent inpatient care setting.

DOSAGE

The recommended dose is a 200-mg single loading dose on day 1 delivered through intravenous infusion (30 minutes to 120 minutes).[1] From day 2 on, follow a once-a-day maintenance dose of 100 mg. The recommended duration is five days if extracorporeal membrane oxygenation and/or invasive mechanical ventilation is not required. If clinical improvement is not achieved, duration may be extended to 10 days. For those requiring invasive mechanical ventilation, remdesivir should be given for 10 days. Because of the risk of reduced antiviral activity, co-administration with chloroquine or hydroxychloroquine is not recommended.[1] Remdesivir is available as a 100-mg, single-dose vial.

POTENTIAL ADVANTAGES

Remdesivir is the only drug and only antiviral agent approved for COVID-19.

POTENTIAL DISADVANTAGES

Remdesivir has not been proven to reduce overall mortality caused by COVID-19. Hypersensitivity reactions, including anaphylactic reactions, have been observed during and following administration.[1] Increased risks of transaminase elevations also have been reported.[1]

COMMENTS

Remdesivir's approval was based on data from three randomized trials.[1] The first, performed by the National Institute of Allergy and Infectious Diseases (NIAID), included hospitalized subjects with mild/moderate and severe COVID-19 and evidence of lower respiratory tract infection.[1,2] The May 2020 EUA was based on an interim analysis of this study.[3] A total of 541 subjects were randomized to remdesivir and 521 to placebo for 10 days. Subjects were stratified into four ordinal hospitalized severity categories (requiring any oxygen, requiring ongoing medical care, requiring use of high-flow oxygen device or requiring noninvasive ventilation, and extracorporeal membrane oxygenation or invasive ventilation). The primary outcome measure was time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. The authors watched for patients who reached one of these ordinal improvements: not hospitalized, and no limitation of activities; not hospitalized, limitation on activities, requiring home oxygen, or both; or hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care. The overall median time to recovery was 10 days on remdesivir vs. 15 days for placebo. In those with severe disease, the median recovery time was 11 days vs. 18 days. Those requiring supplemental oxygen were 45% more likely to benefit from remdesivir. Secondary endpoints were mortality and improvement of one or two categories on the 7-point ordinal severity scale. Mortality rates were not statistically different over the study period. Remdesivir-treated subjects were 50% more likely to improve in ordinal categories.

In an open-label, non-placebo-controlled, study of 397 severe COVID-19 subjects (evidence of pneumonia, oxygen saturation [SpO_2] ≤ 94%, or receiving supplemental oxygen at screening), remdesivir (five-day course) showed no difference in improvement in clinical status on day 14 or time to clinical improvement compared to a 10-day course.[1,4] There also was no significant difference in all-cause mortality. In another randomized, open-label, three-arm (five-day, 10-day, or standard of care) study of 584 subjects with moderate disease (evidence of pneumonia, SpO_2 > 94%), a five-day treatment was better than standard of care in terms of improvement in clinical status on day 11.[1] However, no difference was observed for the 10-day course vs. standard of care.[1] All-cause mortality at day 28 was ≤ 2% in all groups. The cost for a five-day course of treatment is $3,120.

CLINICAL IMPLICATIONS

Remdesivir's benefit appears to be modest, but may be better for those receiving low-flow oxygen. No mortality benefit has been demonstrated. The World Health

Organization conducted an open-label, randomized trial on the effect of four drugs on in-hospital mortality as well as initiation of ventilation or hospitalization duration in more than 11,000 subjects in 30 countries.[5] Investigators concluded remdesivir, hydroxychloroquine, lopinavir, or interferon produced little or no benefit. The study has neither been peer reviewed nor published. It has been criticized for its open-label design and for lacking the same level of scientific rigor as the NIAID study.[6] Regardless, remdesivir is expected to be used extensively until other therapeutics are available. ■

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5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME QUESTIONS

1. Using race as a data point in clinical algorithms:
a. leads to better outcomes for all patients.
b. should be looked upon warily, since most often there are underlying causes that contributed to the outcomes used in the creation of the algorithms, not patient race itself.
c. is always important.
d. is appropriate if the data used to create the algorithm showed race as a contributing factor to the outcome.

2. Which was the threshold where excessive vitamin D supplementation results in thinner bone density?
a. 1,000 IU
b. 2,000 IU
c. 4,000 IU
d. 10,000 IU

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.