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Development of predictive models to estimate the distribution and petrophysical properties of potential mudstone flow barriers can reduce risks inherent to exploration and exploitation programs. Such a predictive model, founded in sequence stratigraphy, requires calibration with outcrop and subsurface analogs. Detailed sedimentologic, petrophysical, and geochemical analyses of Lewis Shale (Lower Maastrichtian) samples from SE Wyoming reveal considerable variability in seismically significant rock properties. Lower Lewis strata represent late-stage transgressive deposits that include a distinctive condensed interval. The overlying progradational Lewis interval consists mostly of interstratified very silty shales and argillaceous siltstones. High-frequency sheet and lenticular sandstone bodies occur within the progradational Lewis package. Sealing capacity, as measured by mercury injection capillary pressure analysis (MICP), varies with fabric, texture, and compositional factors that are related to sequence stratigraphic position. Samples from the Lewis Shale transgressive interval have significantly greater MICP values (average 18,000 PSIA) and are markedly better seals relative to samples from the overlying Lewis Shale progradational package (average 3,000 PSIA). Transgressive shales with enhanced sealing capacity are characterized by higher total organic carbon and hydrogen index values, lower permeability, and less detrital silt content. These transgressive shales are enriched in iron-bearing clay minerals and authigenic pyrite. Greater shear wave velocities, larger shear moduli, and higher bulk density also characterize transgressive Lewis shales. The most promising seal horizons are laterally extensive, silt-poor, pyritic shales occurring in the uppermost transgressive systems tract. Stacking patterns of slow and fast shale horizons can yield seismic responses comparable to those interpreted as hydrocarbon-bearing reservoirs.