***BURKS, ET AL. v. ALLEN, ET AL.*, No. 2361, September 2016 Term**

EXPERT TESTIMONY – GENERAL CAUSATION – *FRYE-REED* TEST – EVIDENTIARY HEARING – GENERAL ACCEPTANCE IN MEDICAL COMMUNITY.

Decedent was admitted to University of Maryland Medical Center (UMMC) with multi-system diagnoses, including renal and liver failure. When he experienced an episode of bradycardia, Dr. Burks treated him for presumed hyperkalemia, which was later confirmed. The treatment included Kayexalate given in a suspension with sorbitol and hemodialysis. Shortly thereafter decedent developed ischemic colitis which quickly progressed to necrosis of the colon. Surgical intervention failed and decedent died. Survival and wrongful death actions were brought alleging medical malpractice. The plaintiffs' expert witnesses theorized that the decedent's ischemic colitis was caused by the Kayexalate with sorbitol and opined that the standard of care required treatment with dialysis alone. Six weeks prior to trial, defense counsel filed a request for a *Frye-Reed* hearing, arguing that it was not generally accepted in the relevant medical community that Kayexalate with sorbitol, as given in this case, can cause ischemic colitis, and therefore plaintiffs' experts should be precluded from testifying on causation. The plaintiffs filed an opposition and supplements were filed. The assignment office did not schedule a hearing. The request was addressed on the morning of trial, by the judge who had just been assigned the case. The judge held a hearing on whether a *Frye-Reed* hearing should be held and ruled that the causation issue did not warrant a *Frye-Reed* hearing and, alternatively, if *Frye-Reed* was implicated, the *Frye-Reed* general acceptance test was satisfied. The case went to trial and the jury returned a verdict for the plaintiffs. Dr. Burks and UMMC appealed.

Held: Judgment affirmed. Ordinarily, when the admissibility of proposed expert testimony is challenged under *Frye-Reed*, and *Frye-Reed* is implicated, an evidentiary hearing should be held to decide whether the testimony satisfies the *Frye-Reed* test. The Court of Special Appeals assumed without deciding that *Frye-Reed* applied to the proposed expert testimony and affirmed the trial court's alternative ruling, made without holding an evidentiary hearing, that that testimony satisfied the *Frye-Reed* test. The materials submitted to the court in support of and opposition to the request for *Frye-Reed* hearing comprehensively addressed the substance of the *Frye-Reed* issue. They included medical and scientific articles, FDA warning labels, UMMC Guidelines for Treatment of Hyperkalemia, medical records of the decedent, and deposition testimony of the relevant experts. The arguments made in the written submissions and to the court on the first day of trial focused not on whether a hearing was needed but on the substance of the *Frye-Reed* issue. In fact, practically nothing was said about what a *Frye-Reed* hearing would include that was not already before the court to consider. In that circumstance, with the trial about to commence, the court did not err or abuse its discretion by deciding the *Frye-Reed* issue without holding an evidentiary hearing. On the merits, the evidence

before the trial court, in the request for *Frye-Reed* hearing and opposition, supported a legally correct conclusion that, although the causal connection between Kayexalate with sorbitol and ischemic colitis is not considered definitive, *i.e*., beyond question, Kayexalate with sorbitol is generally recognized by the relevant medical community as a cause of ischemic colitis in critically ill patients, such as the decedent.

Circuit Court for Baltimore City
Case No. 24-C-15-003384

REPORTED

IN THE COURT OF SPECIAL APPEALS

OF MARYLAND

No. 2361

September Term, 2016

ALLEN BURKS, ET AL.

v.

CYNTHIA ALLEN, ET AL.

Eyler, Deborah S.,
Wright,
Berger,

JJ.

Opinion by Eyler, Deborah S., J.

Filed: August 30, 2018

Arthur, Kevin F., J., did not participate in the Court's decision to report this opinion pursuant to Md. Rule 8-605.1.

In the Circuit Court for Baltimore City, Cynthia Allen, individually and as Personal Representative of the Estate of Dennis Allen ("the Estate"), and seven of her adult children, appellees/cross-appellants,[1] brought medical malpractice wrongful death and survival actions against Allen Burks, M.D., and the University of Maryland Medical Systems Corporation ("UMMS"), appellants/cross-appellees.[2] The allegations arose out of Dr. Burks's treatment of Mr. Allen in March 2013, when he was an inpatient at the University of Maryland Medical Center ("UMMC"). Specifically, the Allens alleged that Dr. Burks breached the standard of care by treating Mr. Allen's elevated potassium levels with a formulation of Kayexalate[3] combined with 35.8 percent sorbitol and by doing so without obtaining his informed consent; and that the medication caused him to develop ischemic colitis and ultimately to die. They alleged that UMMS was liable for Dr. Burks's negligence under the doctrine of *respondeat superior*.

Dr. Burks filed a pre-trial request for a *Frye-Reed* hearing, arguing that the Allens's theory that Kayexalate can cause ischemic colitis is not generally accepted in the

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[1] The adult children who are parties are Sara Allen, Ruth Allen, Dennis Allen, Jr., Daniel Allen, Sr., Donna Allen, Sherry Scipio, and Yolanda Allen. Cynthia's oldest daughter, Shelly Allen-Rainey, originally also was a plaintiff. She is not Mr. Allen's biological daughter. Mr. Allen treated Shelly as his daughter and she had her last name legally changed to reflect that she considered him her father. Shelly voluntarily dismissed her claims with prejudice on April 8, 2016. For ease of discussion, we shall refer to Cynthia and her children by their first names and collectively as "the Allens" or "the Allen family."

[2] For ease of discussion, we shall refer to the appellants/cross-appellees collectively as "Dr. Burks," except when necessary to distinguish between them.

[3] As we shall discuss, Kayexalate is the brand name for a drug that is now most often administered in its generic form.

relevant medical community, and therefore their expert witness testimony on that issue was not admissible. The Allens opposed the request. The court held a hearing and ruled that a *Frye-Reed* hearing was not required but, even if it was and the court applied the *Frye-Reed* test to the evidence provided in the motion and opposition, the challenged evidence was admissible.

After a ten-day trial, the jury returned a verdict in favor of the Allens, awarding $2,000,000 in non-economic damages to the Estate, and $1,000,000 in non-economic damages to Mr. Allen's wife and each of his seven children, for a total of $10,000,000 in damages.

Dr. Burks filed a motion for new trial or, in the alternative, for remittitur. The court did not grant a new trial but granted a remittitur, reducing the non-economic damages award to $906,250 pursuant to the cap on non-economic damages in Md. Code (1974, 2013 Repl. Vol.), section 3-2A-09 of the Courts and Judicial Proceedings Article ("CJP").

Dr. Burks noted an appeal, presenting three questions, which we have rephrased slightly:

> I. Did the trial court abuse its discretion by denying his motion for a pre-trial evidentiary *Frye-Reed* hearing on the Allens's causation theory?[4]
>
> II. Did the trial court err by denying his motion to exclude certain evidence on informed consent?

[4] Dr. Burks's first question presented also asks whether the court erred by not holding a hearing on admissibility of the Allens's causation evidence under Rule 5-702. There was no request below that the court do so, however.

III. Did the trial court err by permitting the Allens to introduce evidence about Dr. Burks's failure to order and administer calcium gluconate or calcium chloride and his failure to request a blood draw on the morning of March 18, 2013?

The Allens noted a cross-appeal, presenting one issue:

I. Does the cap on non-economic damages violate the equal protection clause of the 14th Amendment and Article 24 of the Maryland Declaration of Rights?

For the following reasons, we shall affirm the judgment of the circuit court.

FACTS AND PROCEEDINGS

Events of March 2013

On March 10, 2013, Dennis Allen, age 63, was transported by ambulance to Northwest Hospital Center in Randallstown for complaints of increasing "[w]eakness of the arms and legs." He was suffering from hepatitis C, cirrhosis of the liver, end stage liver disease, renal failure, and congestive heart failure, and already had been hospitalized twice in 2013—both times at UMMC—for a total of twenty-eight days. Blood tests performed at Northwest Hospital Center revealed that Mr. Allen also was suffering from acute rhabdomyolysis, a condition in which muscle fibers break down, releasing muscle proteins into the bloodstream. Rhabdomyolysis causes muscle weakness and pain, can lead to kidney failure if untreated, and can cause elevated potassium levels, especially for patients with renal insufficiency.

Mr. Allen was transferred from Northwest Hospital Center to UMMC the next day and was admitted to the intermediate care unit. Dr. Burks was the attending physician assigned to him. His primary admission diagnoses were rhabdomyolysis, chronic kidney

disease, and hepatitis C cirrhosis. Nephrology was consulted and from March 13 through 16, 2013, Mr. Allen underwent daily hemodialysis for his kidney failure. During that time, his bloodwork showed that his rhabdomyolysis was continuing to worsen. Mr. Allen did not receive dialysis on March 17, 2013.

On March 18, 2013, Dr. Burks arrived at UMMC sometime between 7 a.m. and 8 a.m. He had ordered routine laboratory tests for Mr. Allen to be performed in the early morning hours, but the results were not available.[5]

Shortly after noon, Mr. Allen experienced a precipitous drop in heart rate, setting off the heart monitor alarms. Dr. Burks ordered an immediate EKG, which was performed at 12:18 p.m. It showed bradycardia (an abnormally slow heart rhythm) and life-threatening heart rhythms. Dr. Burks made a preliminary diagnosis of hyperkalemia, *i.e.*, an elevated level of potassium in the blood. Hyperkalemia results when the kidneys are not able to excrete potassium in the urine. A potassium level over 5.5 mmol/L is hyperkalemic.[6] If left untreated, excess potassium can interfere with the electrical signals in the heart, causing a fatal cardiac arrhythmia.

At 12:25 p.m., Dr. Burks ordered a stat blood draw to evaluate Mr. Allen's potassium level. Given the emergency nature of the problem, he decided to begin the treatment protocol for hyperkalemia while awaiting the lab results.

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[5] As we shall discuss, Dr. Burks's failure to follow up on the absence of laboratory test results was a subject of some testimony and evidence at trial.

[6] Some witnesses testified that a potassium level over 5.1 mmol/L was hyperkalemic.

There are three phases to the hyperkalemia treatment protocol: stabilization, redistribution, and removal. The first phase addresses the danger of a fatal arrhythmia by stabilizing the heart muscle. Either calcium gluconate or calcium chloride is administered intravenously for this purpose and works within 2 to 3 minutes. In the redistribution phase, potassium in the blood stream is moved back into the cells to prevent it from interfering with the heart rhythm. Insulin, which works within 20 minutes, and sodium bicarbonate and albuterol, which work within 30 minutes, are prescribed in combination to achieve redistribution. Because insulin lowers blood sugar, dextrose is administered to counteract that effect. Insulin and dextrose are given intravenously; sodium bicarbonate is given orally; and albuterol is given through a nebulizer.

The third phase of the hyperkalemia treatment protocol is removal of the excess potassium from the body. There are three treatments by which potassium can be removed: diuretics, which cause the potassium to be excreted in the urine; hemodialysis, which removes the potassium directly from the bloodstream; and sodium polystyrene sulfonate ("SPS"), usually referred to by its brand name, Kayexalate,[7] which removes the potassium through the stool. Diuretics are not an option for a patient in renal failure, such as Mr. Allen. Dialysis begins to work within 30 minutes of being initiated and is

[7] Experts in the case at bar testified that although most physicians prescribe SPS in its generic form it is generally known as Kayexalate. For that reason, we shall use the brand name.

very effective to remove potassium from the body. The potassium stops being removed when the dialysis is stopped, however.

Kayexalate, approved by the FDA in 1958 to treat hyperkalemia, is an "ion-exchange resin" medication, also known as a "cation exchange resin." The resin contains sodium ions that are exchanged for potassium ions in the bloodstream in the colon. The potassium ions bind to the resin and then are excreted in the stool. Because Kayexalate produces constipation and sometimes fecal impaction, it usually is given in combination with sorbitol, an osmotic laxative. Osmotic laxatives increase the amount of water secreted into the bowels, which softens the stool, making it easier to pass. Kayexalate begins to work within 2 hours after it is administered. It reaches peak effectiveness approximately 4 to 6 hours after being administered and can continue to work for up to 24 hours. It can be administered either in an oral suspension formula or by enema.

At 12:37 p.m., Dr. Burks used a UMMC electronic order set for hyperkalemia to order calcium gluconate stat, insulin stat, dextrose stat, sodium bicarbonate stat, and Kayexalate.[8] At 12:54 p.m., he ordered albuterol. At some time between 12:18 p.m. and 1:00 p.m., he also ordered a stat nephrology consult so hemodialysis could be started.

Dr. Burks was advised by a UMMC pharmacist that calcium gluconate was not available due to a nationwide shortage. As we shall discuss, there was conflicting evidence at trial as to whether Dr. Burks gave an oral order to substitute calcium chloride

[8] Dr. Burks testified that although the order stated that Kayexalate was to be administered on a routine basis he made clear that it was to be administered stat and that in fact happened.

for calcium gluconate. In any event, neither drug was administered. It is undisputed that the failure to administer those drugs did not cause any injury to Mr. Allen.

At 12:55 p.m., and continuing for 10 to 15 minutes, Mr. Allen received albuterol via a nebulizer. At 1:09 p.m., insulin and dextrose were administered intravenously. At 1:15 p.m., Mr. Allen was given sodium bicarbonate and 30 milligrams of Kayexalate orally. The Kayexalate was in a suspension solution containing 35.8 percent sorbitol. Dr. Burks did not inform Mr. Allen about the risks and benefits of Kayexalate prior to its being administered.

At 1:26 p.m., Mr. Allen's lab results were returned, revealing that his blood-potassium level was 7.3 mmol/L. That confirmed the diagnosis of hyperkalemia. A blood potassium level of 7.3 mmol/L is considered dangerously high and can quickly lead to a fatal arrhythmia. At 1:30 p.m., a nephrologist assessed Mr. Allen and ordered hemodialysis on a stat basis. Dialysis began at 2:45 p.m. and was completed at 5:45 p.m. Mr. Allen had two bowel movements during dialysis. After dialysis, Mr. Allen's potassium level was 4.5 mmol/L, which is within the normal range.

Dr. Burks left for the day around 8:00 p.m. Overnight, Mr. Allen had seven more bowel movements, several of them bloody, and began experiencing extreme abdominal pain. He told Cynthia he felt like he was "burning up inside."

At 3:00 a.m., on March 19, 2013, Mr. Allen's lab results showed that his potassium levels were slightly elevated again, at 5.7 mmol/L. At 6:12 a.m., the physician assigned to Mr. Allen overnight wrote a note in his chart that he had had "several episodes of stool mixed with blood overnight." When Dr. Burks returned to UMMC

around 7 a.m., he learned that Mr. Allen was experiencing "copious bloody bowel movements." Over the course of that morning, Mr. Allen's blood pressure dropped precipitously and could not be raised with fluid boluses.

Around noon, Mr. Allen was transferred to the intensive care unit ("ICU") to be prepped for exploratory surgery. Dr. Burks met with Cynthia and some of the Allen children. According to the family members, Dr. Burks told them he had "made a mistake" and was sorry. He said he had given Mr. Allen a drug that damaged his intestines, but that Mr. Allen was going to have surgery to correct it and everything would be all right. He estimated that the surgery would take 45 minutes to 2 hours.

After Mr. Allen was transferred to the ICU, Dr. Burks wrote a "discharge summary." In it, he noted that Mr. Allen's "differential diagnosis" included "intestinal ischemia due to hepatitis C related vasculitis versus intestinal ischemia due to concomitant Kayexalate and lactulose use versus hepatic decompensation with coagulopathy and lower GI bleed."[9] In other words, Dr. Burks listed Kayexalate use in the face of laxative use as a possible cause of Mr. Allen's intestinal ischemia, if that was what Mr. Allen was experiencing.

Mr. Allen's surgery lasted over six hours and confirmed the diagnosis of ischemic colitis. The exterior of his small intestine and colon (large intestine) appeared normal and there was a "palpable pulse" in the superior mesenteric artery, the largest artery

[9] Lactulose is a laxative that was being given to Mr. Allen to treat hepatic encephalopathy, *i.e.*, mental confusion caused by toxins in the colon entering the bloodstream due to liver failure.

supplying blood to the bowels. A colonoscopy performed during the surgery revealed "multiple areas of mucosal ischemia with ulceration and bleeding," however. The severe ischemic ulceration necessitated removal of almost all of Mr. Allen's colon. In his operative note, surgeon Ronald Tesoriero, M.D., wrote:

> [During the colonoscopy,] [w]e were able to advance the scope to the level of the transverse colon. There were multiple areas of mucosal ischemia with ulceration and bleeding in the colon. We were unable to pass beyond the transverse colon; however, *it was clear at this point that the patient had significant mucosal level ischemic colitis. Given the overall state of the patient's perfusion, this may have likely been induced by the Kayexalate.*[10]

(Emphasis added.)

Mr. Allen never regained consciousness. He died the next day, March 20, 2013. His death certificate records the cause of death as "ischemic colitis." On autopsy, his cause of death was determined to be "[m]ultiple complications in the setting of hepatitis C/cirrhosis." In the "Discussion" section, pathologist Rupal I. Mehta, M.D., noted:

> Ischemic necrosis [was] seen within [Mr. Allen's] residual small intestine, with scattered basophilic crystals, consistent with recent [K]ayexalate use. *The findings may be suggestive of [K]ayexalate colitis, which could have exacerbated the patient's underlying medical disease.*

(Emphasis added.) Because Mr. Allen's colon had been removed during surgery, it was not a part of the autopsy. Dr. Mehta noted, however, that the "[p]rior colectomy specimen showed extensive bowel necrosis and hemorrhage."

Lawsuit by the Allens

[10] The operative note does not bear a dictation date. It was signed by Dr. Tesoriero on March 23, 2013.

On June 25, 2015, the Allens filed suit against Dr. Burks and UMMS. Trial was scheduled to commence on September 7, 2016. On July 21, 2016, Dr. Burks filed a request for a *Frye-Reed* hearing, which was opposed. On the first day of trial, the court held a hearing and denied the request. We shall discuss that hearing and the court's ruling in detail below.

In their case-in-chief, the Allens called three expert witnesses: Richard Goldstein, M.D., a colorectal surgeon; James D. Leo, M.D., an internist; and Robert T. Odze, M.D., a pathologist. They also called thirteen fact witnesses: Siu Yan Amy Yeung, a clinical pharmacy specialist at UMMC; John Ashworth, III, the corporate designee for UMMS; Dr. Burks; Demetrius Jones, a phlebotomist at UMMC; Cynthia Allen; and all the Allen children. We summarize the pertinent testimony.

Ms. Yeung testified that in 2012 she served on the three-member UMMC team of pharmacists that developed internal guidelines for the treatment of hyperkalemia ("the UMMC Guidelines"). The UMMC Guidelines were reviewed by physicians in the nephrology department, the UMMC pharmacy committee, and the UMMC therapeutic committee. Upon approval, they were added to UMMC's internal computer database, which is accessible to doctors and nurses.

The UMMC Guidelines, entitled "Management of Hyperkalemia," contain a table listing each "Agent" used to manage hyperkalemia; the dose; the mechanism; how to administer it; how quickly it works; how long it works; how its effectiveness is monitored; and any "Comments" about the use of the agent. The table lists all the drugs and treatments we have discussed above, including Kayexalate. The "Comments"

column advises that the "[m]ajor complications" of Kayexalate are "intestinal necrosis and bowel perforation," and warns that Kayexalate "**[s]hould not** be used in patients with evidence of bowel obstruction, ileus or ischemia or to renal transplant patients in the early post operative phase." (Emphasis in original.) Ms. Yeung testified that these comments were included based on medical literature she had reviewed that reported the risk of intestinal necrosis and bowel perforation from Kayexalate to be between 0.27 percent and 1.8 percent. In a flow chart for the management of hyperkalemia that appears in the UMMC Guidelines, Kayexalate is listed as the third agent to be used to treat acute severe hyperkalemia, after the stabilization and redistribution agents have been administered and before hemodialysis. According to Ms. Yeung, the only preparation of Kayexalate available for use at UMMC was the oral suspension in 35.8 percent sorbitol that Mr. Allen received.

Dr. Goldstein explained that the submucosal layer of the colon, which is beneath the lining of the colon (the mucosa), is filled with thin-walled blood vessels that absorb most of the water in the digestive fluid flowing into the colon from the small intestine, leaving solid stool. The celiac, superior mesenteric, and inferior mesenteric arteries supply blood to these vessels and to the small intestine, liver, appendix, and other organs. Compromised blood flow, *i.e.*, ischemia, to the submucosal vessels cuts off the oxygen supply to the lining of the colon. That causes the tissue in the mucosal layer to break down, ulcers to form, and bacteria from the colon to enter the bloodstream, further breaking down the surrounding tissue. The loss of blood flow and the spread of bacteria throughout the submucosal layer of the colon causes necrosis, *i.e.*, tissue death. As the

volume of bacteria in the bloodstream increases, the body attempts to fight off the infection, causing the blood pressure to fall.

Dr. Goldstein opined that Mr. Allen died from intestinal necrosis caused by Kayexalate. In his view, the Kayexalate "cause[d] the[] blood vessels . . . under the lining of the colon [to] stop working." He could not say "how [K]ayexalate damages the lining of the intestine and produces intestinal ischemia," only that it has been "observed over and over and over again with the use of [K]ayexalate." Dr. Goldstein was questioned about the defense theory that Mr. Allen's necrosis-producing ischemic colitis was caused by several periods of generalized decreased blood flow to the colon due to low blood pressure during dialysis. He rejected that theory, explaining that the colon can sustain a 75 percent reduction in blood flow for up to 12 hours "without irreversible injury," and that the "very brief periods" of low blood pressure documented in Mr. Allen's chart would not have been sufficient to cause his severe necrosis. Moreover, Dr. Tesoriero's observation during surgery of a strong pulse and no clots in the superior mesenteric artery was inconsistent with generalized low blood flow having caused Mr. Allen's injury. Dr. Goldstein noted that other organs supplied by the same arteries—such as the appendix and the liver—were not necrotic, which was strong evidence of no general compromise of blood flow.

On cross-examination, Dr. Goldstein acknowledged that there are "multiple causes of ischemic colitis" and that "99 out of 100 times when a patient has ischemic colitis it's idiopathic[,]" meaning the cause is unknown. In reaching his opinion that Kayexalate caused Mr. Allen's ischemic colitis, Dr. Goldstein relied upon the medical literature, the

UMMC Guidelines, Dr. Burks's differential diagnosis in his discharge note, and Dr. Tesoriero's observations in his operative note. He also relied upon the "sequence of events," explaining that, until Mr. Allen was given Kayexalate, he did not have abdominal pain, diarrhea, or bloody stools. He viewed the timing of the onset of Mr. Allen's symptoms of ischemic colitis and the administration of Kayexalate as evidence of a causal link. Finally, Dr. Goldstein opined that although Mr. Allen was chronically ill none of his other health conditions was "imminently about to kill [him]."

Dr. Leo, an expert in emergency medicine, internal medicine, and critical care medicine, testified that the standard of care for treating Mr. Allen's acute hyperkalemia was to stabilize his heart immediately with calcium gluconate or calcium chloride; redistribute the potassium from his bloodstream into his cells by administering insulin (with dextrose), albuterol, and sodium carbonate; and remove the potassium by hemodialysis ordered urgently. Because Mr. Allen already had a catheter for dialysis in place and was being treated by UMMC's nephrology team, there was no risk of delay in starting dialysis; and, in fact, dialysis was started just over an hour after the nephrology consult. Dr. Leo opined that given the availability and superior effectiveness of dialysis Kayexalate was unnecessary, and therefore its use was not in accordance with the standard of care. According to Dr. Leo, the "infrequent" but very serious risk of ischemic colitis from Kayexalate was not outweighed by any potential benefit from its use, given that dialysis was available and more effective.

Dr. Leo also testified that Dr. Burks breached the standard of care by not obtaining Mr. Allen's informed consent before giving him Kayexalate. After the stabilization and

redistribution drugs had been administered, which resolved the emergency, Dr. Burks should have informed Mr. Allen that Kayexalate works more slowly and less effectively than dialysis and that it has a "very infrequent but very dangerous side effect that it can cause [a] condition called ischemic colitis in which the large intestine can basically die because of loss of blood flow." Dr. Leo further opined that the Kayexalate caused Mr. Allen's ischemic colitis and death. Mr. Allen had lived with his chronic medical conditions for some time, but never had "manifested evidence of ischemic colitis." "He did not have any other reasonable causes for ischemic colitis to occur during [the March 2013] hospital admission." Like Dr. Goldstein, Dr. Leo rejected the defense theory that episodes of low blood pressure caused Mr. Allen's ischemic colitis, opining that those episodes were "too short a duration, too mild in degree and too far in time prior to the development of the ischemic colitis for those to have been connected."

Dr. Odze, an expert in pathology with a subspecialty in gastrointestinal and liver pathology, testified, based upon a review of Mr. Allen's pathology slides and medical records, that Mr. Allen's ischemic colitis and death were caused by Kayexalate or Kayexalate and sorbitol in combination. He explained that the "mechanism [of the bowel injury caused by Kayexalate and sorbitol] is poorly understood[, b]ut the consequence is very well understood." One theory is that sorbitol, a hyperosmotic agent, draws water out of the bloodstream and into the stool to counteract the constipating effects of Kayexalate and, in doing so, deprives the bowel tissue of oxygen. Dr. Odze did not "find any evidence in this case . . . that there was any other cause of ischemia in Mr. Allen's colon other than the ischemia caused by the Kayexalate." The "features in the tissue"

showed an "acute injury" and there was no "lack of blood flow" from outside the colon that contributed to or caused the ischemia. Had there been a generalized lack of blood flow, one would expect to see "widespread ischemic injury," including to the small intestine and appendix, which are more susceptible to ischemic injury than the colon is. The "pattern of destruction" in Mr. Allen's case was "inconsistent" with "an overall lack of blood flow." In the prior 25 years, Dr. Odze had conducted pathology reviews in "more than a dozen cases" in which a patient had "ingested Kayexalate Sorbitol mixture and then died." He saw Mr. Allen's case as a "classic example of Kayexalate induced ischemic necrosis of the bowel."

On cross-examination, in response to a series of questions about his understanding of the "mechanism" of injury caused by Kayexalate, Dr. Odze stated that it is not uncommon in medicine for the mechanism of a disease or condition to be poorly understood but for the "cause and effect" to be well understood. He opined that among gastrointestinal specialists, the causal connection between Kayexalate and ischemic colitis is well known. To the extent the defense experts would opine that there was insufficient evidence of a causal relationship, they were "[u]ninformed and incorrect."

Dr. Burks (called adversely) testified that when he treated Mr. Allen for hyperkalemia he was unaware of any reported association between Kayexalate with sorbitol and ischemic colitis. Ordinarily, he did not review UMMC Guidelines when considering treatment options for patients. Rather, he used "Up to Date," a peer-reviewed subscription website for physicians. Although an article about hyperkalemia on that website included information about the association between Kayexalate and ischemic

colitis, it was not "something that [Dr. Burks] paid particular attention to." Dr. Burks could not "disagree with [the] statement [in the UMMC Guidelines that a major complication of Kayexalate use is intestinal necrosis and bowel perforation] at this point[.]" In his view, it did not matter that he was unaware of the rare risk of ischemic colitis from Kayexalate use because that would not have changed the course of treatment. Even if he had known that dialysis could be started in 10 minutes, he still would have ordered Kayexalate, because Kayexalate continues to remove potassium from the bloodstream for up to 24 hours, whereas dialysis only works during the several hours in which it is being administered. After dialysis ends, the potassium levels can immediately begin to rise again.

Dr. Burks further testified that he discussed Mr. Allen's hyperkalemia with Mr. Allen and his wife after the cardiac event but before Kayexalate was administered. He did not discuss any risks of Kayexalate with Mr. Allen and did not offer him the option to have dialysis only, instead of in conjunction with Kayexalate. After Mr. Allen was transferred to the ICU, he met with members of the Allen family. He advised them that Mr. Allen had "developed injury to [his] intestines" and gave them an "incomplete list of possible reasons . . . [including] . . . Kayexalate." As of the time of trial, Dr. Burks's view remained that Kayexalate was a "possible but unlikely" cause of Mr. Allen's ischemic colitis.

On cross-examination, Dr. Burks elaborated that treating hyperkalemia with Kayexalate in conjunction with dialysis satisfied the standard of care. In his opinion, Mr. Allen's elevated potassium levels were caused by rhabdomyolysis, an ongoing condition

that warranted a multi-faceted approach to removing the excess potassium from his body. Dr. Burks emphasized that even with the Kayexalate and dialysis Mr. Allen's potassium levels rose to 5.7 mmol/L (above normal) by 3:00 a.m. on March 19, 2013. Because of the emergency nature of Mr. Allen's condition, Dr. Burks did not think he was required to obtain Mr. Allen's informed consent.

Shelly testified that she was present when Dr. Burks spoke to the Allen family. He told them that the surgery would last about 2 hours. Cynthia testified that she stayed with Mr. Allen overnight. She informed the nursing staff when she began observing blood in her husband's stool. He was screaming and crying in pain. Dennis, Jr., Daniel, and Sarah also were present in the hospital on the evening of March 18, 2013, and the next morning. They testified that they remembered their father being in severe pain and passing numerous bloody stools.

On March 19, 2013, Dennis, Jr., was in the waiting area when Dr. Burks came to speak to him and some of his siblings. Dr. Burks told them that he had "administered some medicine to [Mr. Allen] that began to attack his bowels," but if it was "caught early enough . . . he would be fine." He told them Mr. Allen would be having "routine surgery" lasting between "one to two hours."

At the close of the Allens' case, counsel for Dr. Burks moved for judgment. He argued with respect to all the claims that although the Allens had presented evidence that Kayexalate had caused Mr. Allen's ischemic colitis they had failed to present any evidence that he would have survived if the drug had not been given to him. With respect to the informed consent claim, he argued that the Allens had failed to present any

evidence that Mr. Allen would have declined to take Kayexalate had Dr. Burks advised him of the risk of ischemic colitis, and that the evidence showed that the emergency exception to the informed consent doctrine applied. The court denied the motion.

In his case, Dr. Burks called four expert witnesses: David Kaplan, M.D., an internist specializing in gastrointestinal and liver disease; Michael Schweitzer, M.D., a general surgeon; Michael Seneff, M.D., a critical care doctor; and Philip Buescher, M.D., an internist and critical care doctor.

Dr. Kaplan, an expert in internal medicine, gastroenterology, and hepatology, including liver diseases and liver transplant medicine, opined that Dr. Burks complied with the standard of care for the treatment of severe hyperkalemia, which is to give Kayexalate *and* to begin dialysis as soon as possible. According to Dr. Kaplan, Kayexalate is a "safe medication" that is "highly effective at removing potassium from the body." Dr. Burks was not required to obtain Mr. Allen's informed consent before administering Kayexalate as this was a cardiac emergency and there was no significant risk associated with the drug. In Dr. Kaplan's view, the medical literature does not support the premise that Kayexalate causes ischemic colitis and, to the extent it does, the risk is so small that it is not material. It would have been a breach of the standard of care for Dr. Burks to have delayed giving Mr. Allen Kayexalate to obtain informed consent.

Dr. Kaplan opined that Mr. Allen developed ischemic colitis from "multiple insults to the bowel" caused by repeated episodes of low blood pressure combined with his "overall clinical condition." He pointed to documented episodes of very low blood pressure during dialysis on March 13 and March 15, 2013, and noted that Mr. Allen may

have experienced other episodes of low blood pressure that were not reflected in his chart because he was not on a continuous blood pressure monitor. Dr. Kaplan testified that low blood pressure is "[t]he most common cause of ischemic colitis" and that low blood pressure lasting as little as 15 minutes can "lead to an episode of ischemic colitis . . . within 24, 48, even 72 hours [later.]" "Repeated bouts of low blood pressure can cause vasospasm meaning spasm of the small blood vessels that feed the colon and that spasm if it continues causes the . . . mucosa . . . to not have enough blood flow and the cells die . . . ." Mr. Allen's cirrhotic liver also could have been a contributing factor. The colon "drain[s] into the liver," so when the liver is "under high pressure that drainage from the colon is also under high pressure . . . [making the colon more sensitive] to changes in blood pressure." In Dr. Kaplan's opinion, there was not "sufficient evidence to claim that [K]ayexalate caused the injury" to Mr. Allen's colon. Mr. Allen was "predispose[d]" to ischemic colitis and the medical literature did not "substantiate[]" a causal relationship between Kayexalate and ischemic colitis. Moreover, Mr. Allen's medical prognosis at the time of his March 11, 2013 admission to UMMC was grim. His likelihood of dying within 90 days was 85 percent.

On cross-examination, Dr. Kaplan was asked whether he would have expected to see ischemic injury to the appendix if the cause was a vasospasm occasioned by generalized low blood pressure. He replied, "[n]ot necessarily," elaborating that vasospasm often affects the small blood vessels in a "patchy" way and that it would not be "surprising" to see a patient with ischemic colitis and a normal appendix.

Dr. Schweitzer, an expert in "general surgery including the care and treatment of ischemic colitis and multiple comorbidities that affect a patient's prognosis[,]" testified about causation. He had performed between 50 and 100 bowel surgeries for ischemic colitis. He opined that there are many known causes of ischemic colitis, including scar tissue, vascular problems causing clotting in the arteries that supply the colon, episodes of very low blood pressure during dialysis, and certain medications, such as estrogen and diuretics. In his opinion, Mr. Allen's ischemic colitis was caused by "end stage liver disease, renal failure, rhabdomyolysis, [and] congestive heart failure[.]" Dr. Schweitzer explained that with liver failure the pressure in the abdominal veins increases, causing blood to be "shunted to other areas and [not to] go through the organs like the small and large bowel very well." Mr. Allen's rhabdomyolysis could have contributed because the inflammation and pain associated with that condition can cause small blood vessels to constrict. Similarly, congestive heart failure can restrict blood flow. Dr. Schweitzer agreed with Dr. Kaplan that episodes of hypotension during dialysis could have been a contributing cause.

Dr. Schweitzer further opined that Kayexalate was *not* a cause of Mr. Allen's ischemic colitis. The medical literature establishes a "very rare association[], not necessarily a cause" between "[K]ayexalate with high sorbitol" and ischemic colitis. The cases where such an association has been seen were in patients whose "bowels aren't moving[.]" It is for that reason that Kayexalate is not recommended for patients who are post-operative or otherwise are experiencing constipation. Mr. Allen was not post-operative, did not have constipation, and did not have a bowel obstruction. Dr.

Schweitzer testified that he had treated five to ten patients who, like Mr. Allen, were not experiencing constipation (post-operative or otherwise) or an obstruction but were in renal failure, developed hyperkalemia, were treated with Kayexalate, and developed ischemic colitis. In his view, those patients did not develop ischemic colitis from Kayexalate.

Dr. Schweitzer testified that Mr. Allen was not going to survive his hospitalization under any circumstance. His rhabdomyolysis was worsening, he had end stage liver disease, and he was in stage four renal failure. In Dr. Schweitzer's view, Mr. Allen did not "have the reserve[s] to overcome" all those serious medical conditions.

On cross-examination, Dr. Schweitzer was asked about the lack of injury to the appendix. He replied that because the appendix is tiny, it "doesn't take much blood to fill [it]," whereas the colon requires much more blood flow.

Dr. Seneff was accepted as an expert in critical care medicine, including the "diagnosis, care and treatment of . . . liver disease, liver cirrhosis, kidney disease requiring dialysis, rhabdomyolysis, . . . severe hyperkalemia [and other conditions]." He opined that giving Kayexalate in conjunction with dialysis, as Dr. Burks did, is within the standard of care for the treatment of severe hyperkalemia. It is Dr. Seneff's practice to order Kayexalate for patients with severe hyperkalemia "even [while] in the process of getting dialysis." He noted that the UMMC Guidelines direct that Kayexalate be administered before starting dialysis, *i.e.*, that both are to be given.

Dr. Seneff was aware of case reports showing an association between Kayexalate and ischemic colitis. He opined that the association is "very rare[,] . . . [o]ne in 100,000,

maybe less than that." It "primarily [was] reported with the 70 percent sorbitol solution," which no longer is used. He opined that he would not give Kayexalate to a patient with a bowel obstruction but otherwise he "would never hesitate to give it." For the same reasons, there was no obligation to obtain informed consent prior to administering Kayexalate.

In Dr. Seneff's opinion, Mr. Allen's ischemic colitis could not have been caused by Kayexalate because he "already had the ischemic colitis before the [K]ayexalate was administered[.]" This opinion was based upon Mr. Allen's lab results from March 18, 2013. His blood was drawn at 12:57 p.m., before the Kayexalate was given. According to Dr. Seneff, the laboratory results from that blood draw showed that, over the preceding 30 hours, Mr. Allen's bicarbonate levels had dropped from a normal level of 24 to an abnormal level of 11. That change resulted from Mr. Allen's producing excess acid. Acid production rises when organs become ischemic. The change in Mr. Allen's acid production was an "om[ino]us sign" that the ischemic colitis already had begun. Dr. Seneff opined that Dr. Burks would not have been able to determine prospectively from those lab results that Mr. Allen was ischemic, however, and, even if he had recognized the lab results as a sign of ischemia, there was no way to know where in Mr. Allen's body the ischemia was occurring. Dr. Seneff agreed with Drs. Kaplan and Schweitzer that Mr. Allen's ischemic colitis was caused by episodes of hypotension coupled with increased venous pressure in his intestines.

Dr. Philip Buescher was accepted as an expert in internal medicine and critical care medicine, including, *inter alia*, the diagnosis and treatment of liver disease, kidney

disease, and hyperkalemia, and the prescription of Kayexalate. He opined that Dr. Burks did not breach the standard of care by ordering Kayexalate for Mr. Allen, even if dialysis was immediately available, and that Dr. Burks was not required to obtain informed consent before administering it. Dr. Buescher testified that he had ordered Kayexalate for patients with acute hyperkalemia at least 900 times in his career and had "not seen a single case of ischemic colitis" among his patients. He agreed with Dr. Seneff that Mr. Allen's ischemic colitis developed before the Kayexalate was administered to him, based upon his lab results showing low bicarbonate levels. He also agreed with Dr. Schweitzer that it was unlikely that Mr. Allen would have survived his hospitalization given his deteriorating condition overall. On cross-examination, Dr. Buescher acknowledged that he could not say whether the administration of Kayexalate to Mr. Allen accelerated and exacerbated the ischemic colitis that, in his view, already was developing. He reiterated, however, that Mr. Allen would have died during this hospitalization regardless of whether he had been given Kayexalate.

In their rebuttal case, the Allens played the video deposition of Carla Williams, the assistant director of UMMC's pharmacy clinical services. Her testimony, which we shall discuss in more detail, *infra*, was pertinent to the issue of the shortage of calcium gluconate.

At the close of all the evidence, Dr. Burks renewed his motion for judgment and the court denied it.

On September 22, 2013, the case was sent to the jury on a special verdict. The jury returned a verdict that same day. It found that Dr. Burks had breached the standard

of care by treating Mr. Allen with "Kayexalate Sorbitol mixture"; that that breach was a cause of injury to Mr. Allen and was the cause of Mr. Allen's death; that Dr. Burks had a duty to obtain informed consent before treating Mr. Allen with Kayexalate; that a "reasonably prudent person in [Mr.] Allen's position would have withheld his consent" to that course of treatment had he been informed of the risks; and that the failure to obtain informed consent also was a cause of Mr. Allen's injury and was the cause of his death.

As noted previously, the jury awarded the Estate $2 million in non-economic damages and awarded Cynthia and Mr. Allen's seven biological children $1 million each in non-economic damages; and the court later reduced the damages award in accordance with the statutory cap on non-economic damages. The reduced damages award totaled $906,250 and was apportioned as follows: $181,250 to the Estate and $90,625 to Cynthia and to each of the seven children plaintiffs.

This timely appeal followed.

DISCUSSION

APPEAL

I.

Frye-Reed

(a)

As mentioned, Kayexalate first was approved by the FDA in 1958 as a treatment for hyperkalemia. It was marketed in powder form. Shortly after it was introduced, physicians found that Kayexalate frequently caused severe constipation that could result in life threatening intestinal impaction. That problem could be avoided by mixing the

powder with sorbitol. As a result, the FDA approved labeling for Kayexalate powder encouraging it to be administered with sorbitol. In 1982, a premade suspension of Kayexalate in 33-36 percent sorbitol was approved for distribution. The availability of the premade formulation contributed to an increase in the use of Kayexalate. Sometime thereafter, the FDA approved a premade suspension of Kayexalate in 70 percent sorbitol.

Some of the history that followed is recounted in a 2010 "Clinical Commentary" published in the Journal of the American Society of Nephrology by Richard Sterns, M.D., *et al*., titled *Ion-Exchange Resins for the Treatment of Hyperkalemia: Are They Safe and Effective?* (hereinafter *Sterns*). The *Sterns* commentary was cited by Dr. Burks in his motion for *Frye-Reed* hearing and by the Allens in their opposition. By 2005, the FDA had received 35 adverse event reports of serious bowel injuries following oral and rectal administration of Kayexalate in sorbitol. That year, the FDA removed the recommendation for concomitant use of sorbitol from the label for the powdered form of Kayexalate. In 2006, the largest manufacturer of the premixed oral suspensions met with the FDA and was permitted to continue manufacturing the 33-36 percent sorbitol and Kayexalate combination because, since 1982, it had not received any adverse reports of colonic necrosis with administration of that suspension; the only adverse reports concerned the 70 percent sorbitol suspension. In September 2007, the FDA asked all manufacturers of the 70 percent suspension to reformulate their products. The 70 percent suspension has not been manufactured since.

In 2009, the FDA issued a "black box" warning for Kayexalate powder, as follows:

> Cases of colonic necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use. The majority of these cases reported the concomitant use of sorbitol. Risk factors for gastrointestinal adverse events were present in many of the cases including prematurity, history of intestinal disease or surgery, hypovolemia, and renal insufficiency and failure. Concomitant administration of sorbitol is not recommended.

According to Dr. Sterns, that same year, an article was published reporting 11 new cases of colonic necrosis over a nine-year period in a single clinical center, four of them fatal, several in patients without end stage renal disease, and some in patients with noncritical illnesses. Some of the fatalities were in patients given the Kayexalate oral suspension with 33-36 percent sorbitol. Dr. Sterns recommended: "Clinicians must weigh uncontrolled studies showing benefit against uncontrolled studies showing harm. It would be wise to exhaust other alternatives for managing hyperkalemia before turning to these largely unproven and potentially harmful therapies." *Sterns*, at 3.

In 2011, the FDA revised its "black box" warning for powdered Kayexalate to state:

> **WARNINGS**
>
> **Colonic Necrosis**
> - *Cases of intestinal necrosis, which may be fatal, and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use.*
> - Do not use in patients who do not have normal bowel function. This includes postoperative patients who have not had a bowel movement post surgery.
> - Do not use in patients who are at risk for developing constipation or impaction (including those with a history of impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction).

- Discontinue use in patients who develop constipation. Do not administer repeated doses in patients who have not passed a bowel movement.

PRECAUTIONS

- *Concomitant use of Sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal.*

(Bold in original.) (Italics added.)

In the case at bar, on July 21, 2016, Dr. Burks filed a request for a *Frye-Reed* hearing, memorandum in support, and numerous exhibits. He sought to preclude the Allens from introducing their proposed expert medical causation testimony, which was based on the premise that Kayexalate can cause ischemic colitis. He argued that although it is generally accepted in the relevant medical community that Kayexalate, in combination with sorbitol, has been *associated* with a small number of cases of ischemic colitis it is not generally accepted that Kayexalate, sorbitol, or some combination of the two actually *cause* ischemic colitis. Rather, there is considerable controversy over that general causation question. Moreover, they asserted that most of the adverse events reported in the medical literature involve a different formulation of Kayexalate (powder versus liquid suspension), a different concentration of sorbitol (70 percent versus 33-36 percent), and a different mode of administration (enema versus oral). Thus, even to the extent the medical literature supports a causal connection between that formulation of Kayexalate and ischemic colitis, that formulation was not used to treat Mr. Allen and therefore could not serve as the basis for the Allens' medical experts to opine that the Kayexalate in sorbitol administered to Mr. Allen caused his ischemic colitis.

Dr. Burks's exhibits included several articles and studies, the earliest of which was an experiment on rats published in 1987 in Surgery by Keith D. Lillemoe, M.D., *et al*., *Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: Clinical and experimental support for the hypothesis* (hereinafter *Lillemoe*). That study was performed after five patients suffered necrosis of the colon (four fatal) after receiving Kayexalate with sorbitol enemas. In the study, some of the rats were given Kayexalate with sorbitol, some were given sorbitol alone, and some were given Kayexalate alone. The mode of administration was enema for all of them. Seven out of ten of the rats who received sorbitol alone developed colonic necrosis, and six of the ten rats who received Kayexalate with sorbitol developed colonic necrosis. None of the rats who received Kayexalate alone developed colonic necrosis.

Also appended were articles by Maura Watson, D.O., *et al.*, in 2012, published in the American Journal of Kidney Disease, and Ziv Harel, M.D., *et al*., in 2013, published in the American Journal of Medicine. *See Association of Prescription of Oral Sodium Polystyrene Sulfonate With Sorbitol in an Inpatient Setting With Colonic Necrosis: A Retrospective Cohort Study* (hereinafter *Watson*); *Gastrointestinal Adverse Events with Sodium Polystyrene Sulfonate (Kayexalate) Use: A Systematic Review* (hereinafter *Harel*).

Dr. Watson described colonic necrosis as a "rare but potentially fatal event" that has been reported after Kayexalate use, "most often in postoperative or intensive care settings and most frequently with rectal [Kayexalate]/sorbitol (particularly 70% sorbitol), rather than [Kayexalate] alone." *Watson*, at 409. The estimated frequency among

hospitalized patients is 0.27% in all cases occurring after surgery. *Id*. Because it is so rare, a very large population would be required to assess the risk factors and show an association between colonic necrosis and Kayexalate. Dr. Watson concluded that there is not enough evidence to show an association between colonic necrosis and exposure to Kayexalate. The precise mechanism of injury is unknown. She observed that use of Kayexalate may be associated with serious gastrointestinal adverse events, but a controlled trial is needed to make that determination.

Dr. Harel conducted a literature review to "identify eligible reports of adverse gastrointestinal events associated with [Kayexalate] use" and then applied the World Health Organization ("WHO") causality assessment system to those reports to determine inclusion in the review. *Harel*, at 264.e9. Ultimately, out of 553 articles describing adverse events, 30 articles describing 58 cases were included because they "satisf[ied] at a minimum a possible level of certainty [under the WHO system]." *Id*. at 264.e10-e11. The study found evidence that Kayexalate, not sorbitol, might be the pathogenic agent causing adverse gastrointestinal events, but emphasized that the literature review could not "ensure that the relationship between [Kayexalate] and the described gastrointestinal adverse events is certain." *Id*. at 264.e14. Moreover, the authors could not calculate the risk of such an association because they lacked data on the prevalence of Kayexalate use. *Id*.

Dr. Burks also cited a 2015 rat experiment study by Isabelle Ayoub, published in PLOS One, that, unlike *Lillemoe*, showed that Kayexalate, not sorbitol, "is the main culprit for colon necrosis[.]" *See Colon Necrosis Due to Sodium Polystyrene Sulfonate*

with and without Sorbitol: An Experimental Study in Rats, at 7. Dr. Burks argued that these contradictory studies show that the data is insufficient to support a generally accepted theory that the oral suspension of Kayexalate with 33-36 percent sorbitol is causally connected to ischemic colitis that produces necrosis of the colon.

Dr. Burks's exhibits also included his expert witness designations; the deposition of Dr. Sterns, who had been identified as an expert by the Allens (but was not called to testify at trial); and the depositions of Drs. Leo, Goldstein, Buescher, Seneff, and Schweitzer.

The Allens filed an opposition to the request for a *Frye-Reed* hearing, in which they argued that the medical literature establishes a general causal link between Kayexalate, given in conjunction with sorbitol, and ischemic colitis. They pointed to the 2009 and 2011 FDA "black box" warnings, and in particular to the 2011 warning, which states, "**PRECAUTIONS** Concomitant use of Sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal." (Emphasis in original.) The Allens maintained that, used in that context, "implicated" means causally connected, *i.e.*, that there is a cause and effect relationship between Kayexalate with sorbitol, given orally, and necrosis of the colon. The Allens provided as an exhibit the FDA "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products - - Content and Format," October 2011 ("FDA Guidance"), which states, in part, at page 3:

> The WARNINGS AND PRECAUTIONS section [of the label] is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically*

> *significant* because they have implications for prescribing decisions or for patient management. **To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.**

(italics in original) (bold added) (footnote omitted).

The Allens also relied upon the UMMC Guidelines, which, as noted, identify ischemic colitis as a "major complication" associated with Kayexalate, and the UMMC medical records for Mr. Allen, reflecting that Drs. Burks, Tesoriero, and Mehta all expressed the view that Mr. Allen's ischemic colitis may have been caused by Kayexalate. They attached the autopsy report as an exhibit.

The Allens argued that the medical literature cited by Dr. Burks in his request for a *Frye-Reed* hearing did not show the absence of a causal relationship but only showed that some researchers think there is a need for further study to quantify more precisely the risk of colonic necrosis from Kayexalate administered in sorbitol. They attached as exhibits medical literature supporting a cause and effect relationship, including:

- A 2001 article by Susan Abraham, M.D., published in the American Journal of Surgical Pathology, studying 11 patients who were given Kayexalate and were found to have Kayexalate crystals on biopsy, which concluded that "Kayexalate in sorbitol can result in injury to the upper gastrointestinal tract *in addition to the more commonly appreciated risk of colonic necrosis*." *Upper Gastrointestinal Tract Injury in Patients Receiving Kayexalate ([SPS]) in Sorbitol*, at 643 (emphasis added). The article, citing a 1997 study by Rashid and Hamilton, states: "Kayexalate . . . in sorbitol has been demonstrated to cause colonic necrosis in a subset of uremic[11] patients who are administered the cation exchange resin for hyperkalemia." *Id*. at 637.

[11] "Uremia" is the "entire constellation of signs and symptoms of chronic renal failure[.]" *Dorlands Illustrated Medical Dictionary*, at 2006 (32nd ed. 2012). As

Continued…

- A 2008 article by Lawrence Weisberg, M.D., in Critical Care Medicine, reviewing the medical literature pertinent to management of hyperkalemia and stating, with citations:

> There are numerous case reports of patients who have developed intestinal necrosis after exposure to [Kayexalate] in sorbitol as an enema, and as an oral agent. A retrospective study estimated the prevalence of colonic necrosis to be 1.8% among postoperative patients receiving [Kayexalate]. Thus, the slow onset of action and serious, albeit infrequent, toxicity make [Kayexalate] a poor choice for the treatment of urgent hyperkalemia.

Management of severe hyperkalemia, at 3249 (citations omitted).

- A 2009 article by C.E. McGowan, M.D., in the Southern Medical Journal, studying pathology records of 29 patients who received oral Kayexalate. Eleven patients had confirmed intestinal necrosis and four died. The article concluded:

> [Kayexalate] in sorbitol has been implicated in the development of intestinal necrosis, primarily mediated by the sorbitol component. Previous studies documented these findings almost exclusively in postoperative, renal transplant, and critically ill patients. Our study highlights that all patients are potentially susceptible, including those without previously described comorbidities. The indications for [Kayexalate] use, as well as alternate vehicles for its delivery, should be re-evaluated. [Kayexalate]-induced ischemia remains an under recognized, easily avoided complication, associated with significant morbidity and mortality. Physicians who routinely use this agent in sorbitol should be aware of its life-threatening complications.

Intestinal Necrosis due to Sodium Polystyrene Sulfonate (Kayexalate) in Sorbitol, at 497.

…cont'd
discussed above, Mr. Allen was suffering from renal failure, which is why he had been undergoing hemodialysis.

- A 2010 case study by Mohamad Erfani, in Practical Gastroenterology, documenting colonic necrosis in a patient who received oral Kayexalate in sorbitol for hyperkalemia. *Sodium Polystyrene Sulfonate (SPS): Sorbitol-induced Colonic Necrosis*. The study concluded:

> Intestinal necrosis following [Kayexalate]-sorbitol administration is a rare clinical condition that may have significant morbidity and mortality. [Kayexalate]-sorbitol should be used with caution, especially in the postoperative setting, in uremic or ill patients . . . When clinically indicated other measures to treat hyperkalemia should be considered instead of [Kayexalate]-sorbitol. Physicians need to be aware of [Kayexalate]-sorbitol GI side effects while managing hyperkalemia.

  Id. at 49.

- A 2015 "Up to Date" article by David Mount, M.D. (and edited by Dr. Sterns), generally reviewing the treatment and prevention of hyperkalemia in adults, and stating: "A major concern with [Kayexalate] in sorbitol is the development of intestinal necrosis, usually involving the colon and ileum, which is frequently a fatal complication." *Treatment and prevention of hyperkalemia in adults*, at 8 (citations omitted).

In addition, the Allens attached as exhibits to their opposition deposition transcripts of Mrs. Allen and Drs. Sterns, Kaplan, Goldstein, and Odze.

In a reply memorandum, Dr. Burks argued that the conflicting medical opinions in the literature cited by the Allens and the literature he cited showed that there is disagreement about whether Kayexalate can cause intestinal necrosis; therefore, that proposition is not generally accepted in the relevant medical field, and expert testimony should not be permitted, under *Frye-Reed*. He argued further that the UMMC Guidelines do not establish a causal relationship either, as they are based on the same disputed literature, and his statement to the Allens about Mr. Allen's differential diagnosis and what might have caused his bowel problem merely was a repetition of what the medical

community has not reached an agreement about. Nor, he argued, are the FDA "black box" warnings evidence of general acceptance by the medical community.

In a supplement, the Allens attached deposition testimony by Ms. Yeung, in which she stated that the UMMC Guidelines, listing intestinal necrosis as a major complication of Kayexalate use, were based on the FDA "black box" warnings.

This case was not specially assigned, and the assignment office did not schedule a pre-trial hearing on Dr. Burks's request for a *Frye-Reed* hearing. Consequently, the request was taken up by the court at the outset of the first day of trial. The trial judge, who only was assigned the case that morning, first saw the request, opposition, and appended materials then. Nevertheless, she held a comprehensive hearing for approximately one hour and fifteen minutes, during which she queried counsel about the medicine and the *Frye-Reed* cases. At one point, she remarked about the important distinction between a controversy over the means by which an agent causes a particular harm and a controversy over whether the agent can cause the harm at all. After counsel finished their arguments, the judge took a twenty-minute recess to further review the materials provided, denied the request for a *Frye-Reed* hearing, and explained the reasons for her ruling.

The ruling was made in the alternative. First, relying primarily upon this Court's decisions in *Myers v. Celotex Corporation*, 88 Md. App. 442 (1991), *cert. denied*, 325 Md. 249 (1992), and *CSX Transportation, Inc. v. Miller*, 159 Md. App. 123 (2004), *cert. granted*, 384 Md. 581, *cert. dismissed*, 387 Md. 351 (2005), the judge concluded that the medical causation opinions being offered by the Allens' expert witnesses were not of the

type requiring a *Frye-Reed* analysis. The judge emphasized that the Allens' experts were not using new or novel scientific techniques but were using the accepted differential diagnosis method to reach a conclusion about the etiology of Mr. Allen's ischemic colitis. The judge also distinguished cases such as *Blackwell v. Wyeth*, 408 Md. 575 (2009), which applied *Frye-Reed* to medical causation opinions, because, unlike in those cases, here there was no discernible "analytical gap" between the underlying science and the ultimate conclusions reached by the experts.

Second, and alternatively, the judge concluded that if the proffered medical causation opinions of the Allens's expert witnesses were subject to the *Frye-Reed* general acceptance test, they satisfied it. The judge stressed that the 2009 and 2011 FDA "black box" warnings were based on there being a "causal association" between Kayexalate and ischemic colitis and that the use of the word "implicated" in the 2011 warning supported the conclusion that acceptance of a causal connection between Kayexalate with sorbitol and necrosis of the colon is not novel or new. The judge also found persuasive the fact that the UMMC Guidelines themselves "demonstrate[] that there is some acknowledgement on the part of at least one Defendant that there is an associative causative link." The judge ruled that as the *Frye-Reed* test was satisfied, there was no need for a *Frye-Reed* hearing.

We note at this point that the oral argument before the trial court focused almost exclusively on the substance of the *Frye-Reed* dispute—whether there is general acceptance in the relevant medical community of a causal link between Kayexalate with sorbitol and ischemic colitis and necrosis—and not on whether an evidentiary hearing

was needed for the court to make that determination. At the beginning of the hearing, the court correctly described it as not being a *Frye-Reed* hearing, but a hearing on whether to hold a *Frye-Reed* hearing. However, counsel on both sides did not direct their arguments to why an evidentiary hearing was necessary, instead providing reasons why the court should find that the general acceptance test applied and was not met (the defense) or that the general acceptance test did not apply or was satisfied in any event (the plaintiffs). Except for one brief remark by defense counsel at the very close of the argument, there was no proffer as to who the defense (or the plaintiffs) would call to testify at an evidentiary hearing on *Frye-Reed* and what information would be provided to the court at such a hearing beyond what already had been provided in the articles and deposition transcripts submitted as exhibits. Defense counsel's single remark was that if Matthew Weir, M.D., the Chief of Nephrology at UMMC, "can find a time that he's available," the defense would call him to testify "that there is no definitive evidence that [K]ayexalate causes bowel ischemia." An article by Dr. Weir that did not concern Kayexalate was one of the exhibits to the Allens's opposition to the *Frye-Reed* hearing request.[12] Otherwise, Dr. Weir had no connection to the case and had not been identified as an expert witness by any party.

[12] The 2015 article published in the New England Journal of Medicine by Dr. Weir concerned a study on the use of patiromer, a slow-acting potassium binding resin medication recently approved by the FDA for treatment of non-urgent hyperkalemia. Matthew R. Weir, George L. Bakris, David A. Bushinsky, et al., *Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors*, N Engl J Med 2015; 372:211–221.

(b)

On appeal, Dr. Burks contends the circuit court erred by denying his pre-trial request for a *Frye-Reed* hearing on the general causation question whether Kayexalate (either with or without sorbitol) can cause ischemic colitis. He focuses on the causation question itself, arguing that a cause and effect relationship between Kayexalate and ischemic colitis is "not generally accepted in the medical community and is unsupported by the medical literature" and therefore does not satisfy *Frye-Reed*. He asserts that in ruling on the admissibility of a medical expert's opinion the court must assess whether the data on which the opinion is based is supported by the underlying science.[13] That test was not met here, according to Dr. Burks, because the medical literature the Allens's experts relied upon merely established an association, not a causal connection, between Kayexalate (given in sorbitol) and ischemic colitis and the preparation of Kayexalate administered to Mr. Allen differed from the preparations associated with virtually all the adverse events reported in the literature. In one paragraph of his opening brief, Dr. Burks argues that given the "widespread dispute" over whether Kayexalate causes ischemic colitis, evidence bearing on the admissibility of the Allens's causation theory should have

[13] Dr. Burks also argues that recent case law makes clear that there is a significant overlap between *Frye-Reed* and Rule 5-702(3) and suggests that the court's ruling violated that rule. In this case, there was no motion *in limine* filed under Rule 5-702, and no objection to the expert testimony based on that rule, and so whether the requirements of the rule were satisfied was neither raised nor decided below. Accordingly, the sole issue before us concerns the request for a *Frye-Reed* hearing. *See Alford v. State*, 236 Md. App. 57, 72 (2018) (holding that appellate court will not uphold, under Rule 5-702, trial court's decision to exclude expert witness's proffered testimony when the issue whether that testimony satisfied Rule 5-702 was not raised or decided below).

been presented to the trial court before it ruled on admissibility. He does not say what that evidence would have been. He asks this Court to vacate the judgment and remand for a new trial.

The Allens respond that there was no need for a *Frye-Reed* hearing on the general causation question whether Kayexalate in sorbitol "may cause intestinal necrosis (ischemic colitis)" because the medical literature, the FDA "black box" warnings, and the UMMC Guidelines show a general level of acceptance of that theory of causation within the relevant medical community. Furthermore, the observations by Drs. Burks and Tesoriero in their medical and operative notes provide further support for a cause and effect relationship between Kayexalate in sorbitol and ischemic colitis.

(c)

In *Frye v. United States*, 293 F.1013 (D.C. Cir. 1923), the District of Columbia Court of Appeals held that for expert testimony predicated on a novel scientific principle or discovery to be admissible, the principle or discovery must be generally accepted in the relevant scientific field. When the Court of Appeals adopted the *Frye* general acceptance test in *Reed v. State*, 283 Md. 374 (1978), it explained that the test governs the admissibility of novel scientific evidence. Until the 2000s, the *Frye-Reed* test was not applied outside that context. In the meantime, in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the United States Supreme Court held that Federal Rule of Evidence 702 had superseded *Frye* and established, in its place, a non-exclusive list of factors, including general acceptance, for federal district courts to consider in ruling on the admissibility of scientific expert testimony. A few years later,

in *General Electric Co. v. Joiner*, 522 U.S. 136, 146 (1997), the Supreme Court upheld the exclusion of expert testimony that PCBs caused a plaintiff's lung cancer because there was "too great an analytical gap between the data and the opinion proffered."

In the mid-2000s, the Court of Appeals expanded the *Frye-Reed* general acceptance test to include techniques that are not novel and also to include scientific conclusions, as well as techniques. *See Montgomery Mutual Ins. Co. v. Chesson*, 399 Md. 314 (2007) ("*Chesson I*"); *Blackwell*, 408 Md. at 575; and *Chesson v. Montgomery Mut. Ins. Co.*, 434 Md. 346 (2013) ("*Chesson II*"). Indeed, in *Blackwell*, the Court approved the "analytical gap" concept articulated by the Supreme Court in *Joiner*. Now, under *Frye-Reed*, the admissibility issue is whether "the expert[s] bridged the 'analytical gap' between accepted science and [their] ultimate conclusions in [this] particular case." *Savage v. State*, 455 Md. 138, 160 (2017).

In *Chesson I*, which marked the first "drift" by the Court of Appeals toward adopting the *Daubert* "analytical gap" concept, *see Savage*, 455 Md. at 187 (Adkins, J., concurring, joined by Barbera, C.J., and McDonald, J.) (discussing the "jurisprudential drift" towards *Daubert*), the Court held that a circuit court abused its discretion by not holding a *Frye-Reed* hearing to consider the admissibility of testimony by a medical doctor on behalf of plaintiff workers that they were suffering from "sick building syndrome" from mold in the building where they worked. The employer had requested a *Frye-Reed* hearing, arguing that it was not generally accepted in the medical community that "sick building syndrome" is a recognized disease and that the protocol the expert had

devised to make that diagnosis and form his causation opinions was not generally accepted.

The Court of Appeals remanded the case for a *Frye-Reed* hearing. It held that the circuit court should have "determine[d] whether the medical community generally accepts the theory that mold exposure causes the illnesses that [the workers] claimed to have suffered, and the propriety of the tests [their expert] employed to reach his medical conclusions." *Chesson I*, 399 Md. at 328. In other words, the *Frye-Reed* test applied not only to the expert's own novel diagnostic testing methods but also to the analysis he had employed in concluding that there was a causal relationship between mold exposure and the cluster of symptoms he had dubbed "sick building syndrome." The Court rejected the workers' argument that under *Myers*, 88 Md. App. at 442 (medical doctor opining that lung cancer was caused by asbestos fibers), and *CSX Transportation, Inc. v. Miller*, 159 Md. App. at 123 (medical doctor opining that arthritis was caused by years of walking on ballast), *Frye-Reed* did not apply because their expert merely was making a medical diagnosis of an illness. The Court commented that the case "involve[d] more than a generally accepted medical opinion and diagnosis. [The workers' expert] employ[ed] medical tests to reach a conclusion that is not so widely accepted as to be subject to judicial notice of reliability." *Chesson I*, 399 Md. at 332. The Court also stated that "novel medical theories regarding the causes of medical conditions have been subject to *Frye* analysis. *Reed*, 283 Md. at 383 . . . (noting that the *Frye* test has been applied to 'medical testimony regarding the cause of birth defects')." *Chesson I*, 399 Md. at 333.

The Court disposed of the appeal by means of a limited remand for the circuit court to hold a *Frye-Reed* hearing.[14]

In our recent review of the evolution of *Frye-Reed* in *Sissoko v. State*, 236 Md. App. 676 (2018), *cert. denied* __ Md. __ (July 12, 2018), we discussed the *Myers* and *CSX* cases. *CSX*, the more recent of the two, having been decided in 2004, stated that the *Frye-Reed* general acceptance test only applied to "new and novel scientific techniques[,]" and that "[a] doctor's opinion as to the etiology of his patient's arthritis is simply not the type of thing contemplated by the phrase 'new and novel scientific technique.'" *Id.* at 186–87 (quoting *Reed v. State*, 283 Md. at 380). Rather,

> [w]hat is contemplated are new, and arguably questionable, techniques such as lie detectors tests, breathalyzer tests, paraffin tests, DNA identification, voiceprint identification, as in the *Reed* case itself, and the use of polarized light microscopy to identify asbestos fibers, as in *Keene Corporation v. Hall*, 96 Md. App. 644, . . . (1993).

Id. at 187. In *Sissoko*, where, after a *Frye-Reed* hearing, the circuit court ruled that the State's expert testimony about abusive head trauma, formerly known as shaken baby syndrome, was admissible, we explained that *Myers* and *CSX* did not support one of the State's arguments, that *Frye-Reed* had no application at all:

> These cases are not helpful to the State's position because they were decided before the Court of Appeals extended the reach of *Frye-Reed* beyond the bounds of novel scientific tests and techniques. We do not

[14] The limited remand in *Chesson I* resulted in the circuit court's holding a *Frye-Reed* hearing and ruling that the workers' expert witness's opinions were admissible. In a second appeal, *Chesson II*, the Court of Appeals reversed, holding that the evidence adduced at the *Frye-Reed* hearing and the Court's own research showed that the expert's opinions were the product of a flawed methodology and his theory of general causation was not generally accepted in the medical community.

> mean to suggest that if they were decided today their outcomes would differ, only that the analysis employed necessarily would be more expansive.

236 Md. App. at 715.[15]

In the case at bar, the trial court cited *Myers* and *CSX* in making its first alternative ruling, that whether Kayexalate with sorbitol as administered to Mr. Allen can cause ischemic colitis was not subject to a *Frye-Reed* analysis to be admissible. We conclude that it is not necessary in this appeal to decide whether that ruling was legally correct. Assuming without deciding that the Allens's proposed expert witness testimony that medical causation exists in fact was subject to a *Frye-Reed* analysis to be admissible, we nevertheless hold that the trial court did not abuse its discretion by deciding the *Frye-Reed* issue without an evidentiary hearing and in ruling that *Frye-Reed* was satisfied.

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[15]As noted in *Chesson I*, the *Reed* Court cited a case in which *Frye* was applied to the issue of the cause of a birth defect. That case—*Puhl v. Milwaukee Automobile Ins. Co*., 99 N.W.2d 163 (Wis. 1959)—clearly would not warrant a *Frye-Reed* hearing today, or in 1983, when *Reed* was decided. The plaintiff alleged that injuries she sustained in an automobile accident, when she was 12 weeks pregnant, caused the baby she was carrying to be born with Down syndrome. At trial, the plaintiff's medical expert, who was not an expert in Down syndrome, testified, based on literature he had read, that Down syndrome can be caused by lack of oxygen to a fetus and that the plaintiff's placenta may have been partially torn during the accident, causing such a lack of oxygen. The defendant's expert testified that the cause of Down syndrome was not known but that it might be a defect in the sperm or egg. There was no pretrial hearing based on *Frye*. The jury found in favor of the plaintiff.

On appeal, the Supreme Court of Wisconsin held that the evidence of a causal connection between lack of oxygen and Down syndrome was legally insufficient, as it established nothing more than an unproven, speculative hypothesis by an expert who was not qualified in the field of Down syndrome.

The Wisconsin Supreme Court's opinion was reported ten months after publication of the discovery that Down syndrome is caused by a chromosomal defect. *See* Gautier, Marthe & Harper, Peter, *Fiftieth anniversary of trisomy 21: returning to a discovery (*available at https://perma.cc/D46J-97AV). The opinion does not mention that.

(d)

In *Clemons v. State*, 392 Md. 339 (2006), the Court of Appeals held that Comparative Bullet Lead Analysis ("CBLA"), a scientific test that had been generally accepted as a forensic tool for decades, was no longer generally accepted in the relevant scientific community and therefore was not admissible in evidence under *Frye-Reed*. In the circuit court, the defendant filed a pre-trial motion *in limine* to exclude the State's CBLA evidence. At the suggestion of the court, the parties deferred a ruling on the motion until trial. When the State's CBLA expert took the stand, *voir dire* was conducted first by the prosecutor and then by the defense, in the presence of the jury. Those examinations explored whether CBLA remained a generally accepted forensic tool. The court ruled that the expert could give his CBLA opinions, thereby denying the motion *in limine*.

Before the Court of Appeals, that ruling was challenged under *Frye-Reed*. The Court addressed the challenge, even though no *Frye-Reed* hearing had been held. Admonishing that "*Frye-Reed* examinations are better conducted in pre-trial hearings" outside the hearing of a jury, *id*. at 347 n. 6, the Court went on to state:

> If the issue is to be dealt with at trial, it should be addressed, in its entirety, as a preliminary matter prior to admission of the challenged evidence, not, as here, by having the challenge made only to [the expert's] status as an expert during the [proponent party's] case and then receiving most of the evidence bearing on whether the inferences to be drawn from the [scientific evidence] are generally accepted in the relevant scientific community during the [opponent party's] case, after the challenged inferences have already been admitted. If a party raises a *Frye-Reed* objection, all evidence bearing on admissibility of the challenged evidence should be presented and considered *before* a ruling is made on the challenge.

Id. (emphasis in original). As noted, however, notwithstanding the absence of a *Frye-Reed* hearing, the Court reviewed the question whether the expert opinion on CBLA should have been excluded as not satisfying *Frye-Reed*.

Clearly, when a motion has been filed in which a party seeks to preclude the admission of scientific evidence based on *Frye-Reed*, it is preferable for the court to schedule a pre-trial hearing at which evidence may be taken, to the extent the court agrees that *Frye-Reed* applies. As *Clemons* demonstrates, however, that is not an ironclad requirement. In the case at bar, Dr. Burks filed his request for a *Frye-Reed* hearing, accompanied by a request for a hearing on that request, approximately six weeks before trial, and the Allens filed their opposition on August 8, 2016. The case had not been specially assigned, and the assignment office did not schedule any hearing date before trial. For that reason, the *Frye-Reed* matter was not taken up until the first day of trial. Therefore, through no one's fault, least of all the fault of the judge who was assigned the case the morning of trial, the question whether the Allens's expert witnesses would be precluded from testifying because their opinions did not satisfy *Frye-Reed* first came to the court's attention on the day of trial.

The request, opposition, reply, and supplement were all-encompassing on the issue of whether the expert opinion evidence in question was admissible under *Frye-Reed*. In addition to thorough discussions of the law, they attached deposition transcripts of the expert witness testimony in question and of the contrary expert witness testimony; the relevant hospital and medical records, such as the UMMC Guidelines; the FDA "black box" warnings; and published medical literature on the causal connection, if any, between

Kayexalate, with and without sorbitol, and ischemic colitis/intestinal necrosis. The request did not identify any witnesses that Dr. Burks intended to call in an evidentiary *Frye-Reed* hearing, nor did it proffer the substance of any such witness's testimony. As noted above, the only mention by Dr. Burks of a witness who might be called was the remark at the conclusion of the hearing on the first day of trial, referencing, tentatively, Dr. Weir.

In his brief in this Court, Dr. Burks focuses his argument on the trial court's alternative ruling, that the proffered testimony of the Allens' expert witnesses on medical causation satisfied *Frye-Reed*, saying almost nothing about the court's ruling against holding a *Frye-Reed* hearing. As mentioned earlier, in one paragraph of his opening brief Dr. Burks states, in general terms, that because there is "widespread dispute" over whether Kayexalate causes ischemic colitis evidence bearing on the admissibility of the Allens's experts' opinions should have been presented to the trial court. Beyond that, he says nothing about what that evidence should have been or, significantly, what difference having an evidentiary hearing rather than a hearing on a comprehensive record, such as took place, would have made.

We see nothing in this record to support a conclusion that the absence of an *evidentiary Frye-Reed* hearing was prejudicial to Dr. Burks. To be sure, as we have explained and as *Clemons* made clear, there is a strong preference in favor of *Frye-Reed* issues being decided after a hearing at which evidence may be presented. Given the particular circumstances and procedural posture in this case, however, we hold that there

was no harm to Dr. Burks from the trial judge ruling on the *Frye-Reed* question after holding a hearing at which substantial evidence, but no live evidence, was presented.

(e)

The final *Frye-Reed* appellate issue is whether the trial court was legally correct in ruling that the proffered medical causation testimony by the Allens's expert witnesses satisfied the *Frye-Reed* test. Our standard of review is *de novo*. *Sissoko*, 236 Md. App. at 711.

In a nutshell, the *Frye-Reed* issue in this case is whether it is generally accepted in the relevant medical community that the drug Kayexalate, given orally in a formulation with 35.8% sorbitol, can cause ischemic colitis in a patient such as Mr. Allen. As the Court of Appeals has explained, "[g]eneral acceptance [under *Frye-Reed*] does not equate to unanimity of opinion within a scientific community, nor universality, and is not subject to a quantum analysis." *Chesson II*, 434 Md. at 356; *see also U.S. Gypsum v. Baltimore*, 336 Md. 145, 183 (1994) (holding that without being directed to any information indicating "that the divergence of opinion over the use of [surface dust sampling for asbestos] amounts to the type of 'fundamental division in the scientific community' which necessitates the exclusion of such testimony[,]" the dust sampling evidence was admissible) (quoting *Reed*, 283 Md. at 392)). Although there have been changes in the scope of the *Frye-Reed* test over the past decade, this principle has remained.

In addition to the cases discussed above, the Court of Appeals's decision in *Rochkind v. Stevenson*, 454 Md. 277 (2017), although made under Rule 5-702, is helpful to our analysis. Stevenson brought a lead paint case, claiming she developed Attention

Deficit Hyperactivity Disorder ("ADHD") from exposure to lead paint as a young child. The Court of Appeals addressed the question whether the trial court abused its discretion, under Rule 5-702(3), by admitting Stevenson's expert's testimony of general causation between lead paint exposure and ADHD. That rule requires, among other things, that there be a sufficient factual basis for the expert's opinion; and that cannot be shown unless the opinion is based on an "adequate supply of data[.]" 454 Md. at 287. The expert, a pediatrician, based her general causation opinion on an EPA epidemiological paper that concluded, from a compendium of studies, that there is an association between childhood lead exposure and ADHD.

The Court of Appeals held that the EPA paper did not supply adequate data to support the expert's opinion. Because the paper did not properly account for various potential confounding factors, such as parental education level, socio-economic status, parental caregiving quality, and the strong familial component to ADHD, it did not show a causal connection between childhood exposure to lead and ADHD. Moreover, in offering her opinion, the expert failed to differentiate between the specific symptoms of ADHD and the general symptoms of attention deficits, did not factor in that many symptoms of ADHD are symptoms of other disorders and learning disabilities, and overstated the known effects of lead exposure. In the Court's view, the expert's opinion merely was conjecture and speculation.[16]

[16] Because the Court concluded that the expert's opinion was not based on an adequate supply of data, it did not assess whether she used a reliable methodology in reaching her opinion. Also, because it held that the expert's opinion should have been

Continued…

More recently, in *Sugarman v. Liles*, __ Md. __, No. 80, Sept. Term 2017 (filed July 31, 2018), the Court of Appeals revisited the same EPA epidemiological paper discussed in *Rochkind*, holding that it supplied a sufficient factual basis under Rule 5-702(3) for a pediatrician's general causation opinion that elevated blood lead levels can cause deficits in auditory encoding and processing speed. In so holding, the Court discussed cases from other jurisdictions addressing the "analytical gap" concept, including *King v. Burlington North Santa Fe Railroad Co.*, 762 N.W.2d 24 (Neb. 2009). In that case, the Supreme Court of Nebraska reversed a trial court order excluding an expert's opinion that exposure to diesel exhaust fumes had caused the plaintiff's late husband to develop multiple myeloma, a form of blood cancer, because the expert relied upon epidemiological studies that did not "draw definitive conclusions on causation." 762 N.W.2d at 48. In *Liles*, the Court of Appeals cited *King* with approval, explaining that an expert may rely on scientific studies that do not make "definite conclusions of a causal relationship," so long as they are "qualified to interpret and extrapolate from the relevant studies." *Liles*, slip. op. at 30. Thus, the pediatrician expert witness was permitted to extrapolate from the EPA epidemiological paper's finding that exposure to lead can cause attention decrements to opine that it also could cause slower processing speed and auditory encoding deficits, which were "factors of attention." *Id*. at 31.

…cont'd
excluded under Rule 5-702, the Court did not address whether the circuit court abused its discretion by not holding a *Frye-Reed* hearing.

We return to this case and the question whether the trial court erred in its ruling. The uncontroverted facts that were disclosed to the court in support of and in opposition to the request for a *Frye-Reed* hearing, and as further developed at trial, show that Mr. Allen developed ischemic colitis, which led to necrosis of the tissue in his colon and death. In plain language, lack of oxygen to his large intestine caused the tissue to break down and die, which killed him. Ischemic colitis is a well-recognized and established medical condition with a clearly defined reason behind it: reduced or absent blood flow that deprives cells in the colon of oxygen, damaging the tissue. The dispute in this case was not over the existence or nature of that medical condition or its immediate cause—deprivation of oxygen to the colon. Rather, the dispute was over how Mr. Allen's colon came to be oxygen deprived.

Although not essential to our decision, we note that this case is very different from virtually all the general medical causation cases in Maryland in which expert witness testimony has been found to be subject to *Frye-Reed*. "Sick building syndrome" (*Chesson I* and *Chesson II*) is not even a recognized syndrome (a group of symptoms consistently appearing together) or medical condition. The claimed injury in the other cases was a syndrome or generally described condition without a clearly identified or understood cause, or at least where the cause was an ongoing topic of widespread debate: *Wilson v. State*, 370 Md. 191 (2002) (sudden infant death syndrome), *Blackwell* (autism), *Sissoko* (abusive head trauma/shaken baby syndrome), and, although decided under Rule 5-702, *Rochkind* (ADHD). Here, we have an established, acute medical condition in which the colon is deprived of oxygen and the question whether Kayexalate in sorbitol,

administered orally, can cause a decrease in oxygen to the colon to bring about that condition.

There was substantial evidence offered by the Allens in opposition to Dr. Burks's motion that strongly supports a finding that, while there may be some disagreement among experts in the field, there is not a "'fundamental division in the scientific community'" that necessitated exclusion of the Allens's expert witness testimony. First, several pieces of evidence showed that UMMC, Dr. Burks, and other UMMC health care providers involved in Mr. Allen's care already had accepted the proposition that Kayexalate with sorbitol is causally connected to ischemic colitis. The UMMC Guidelines, in effect since 2012, and made available to guide doctors at that institution in the treatment of hyperkalemia, expressly identify "intestinal necrosis," *i.e.*, death of intestinal tissue, as a "[m]ajor complication" of Kayexalate administration. In the differential diagnosis Dr. Burks gave in his discharge summary, upon Mr. Allen's transfer to the ICU for surgery, he included "intestinal ischemia *due to* concomitant Kayexalate and lactulose use." (Emphasis added.) So, before Mr. Allen even was operated on, Dr. Burks thought that he could have intestinal ischemia brought on by the treatment with Kayexalate in combination with the laxative Mr. Allen was being given to address his liver problems. (And at trial, Dr. Burks acknowledged that the Kayexalate given to Mr. Burks was a possible cause of his ischemic colitis.) Thus, it was never Dr. Burks's position that the Kayexalate given to Mr. Allen could not have caused his ischemic colitis. Likewise, in his operative note, Dr. Tesoriero said Mr. Allen's ischemic colitis "may have likely been induced by Kayexalate"; and, in his pathology note, Dr.

Mehta commented that the ischemic necrosis and crystals in Mr. Allen's small intestine "may be suggestive of kayexalate colitis . . . ."

In addition, the FDA "black box" warnings for Kayexalate, and for the generic SPS suspension (which also was provided in the papers in support of and opposition to the request for a *Frye-Reed* hearing), support a finding that there is a cause and effect relationship between Kayexalate given with sorbitol, as Mr. Allen received, and ischemic colitis. Both the 2009 and 2011 Kayexalate warnings state that cases of necrosis of the colon "have been reported in association with Kayexalate use." The 2009 warning includes in the risk factors for adverse gastrointestinal events, such as ischemic colitis, "renal insufficiency and failure. Concomitant administration of sorbitol is not recommended." The 2011 warning goes further, stating, "Concomitant use of Sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal." The FDA label for the suspension of SPS in sorbitol likewise warns that intestinal necrosis has been reported in association with SPS use and that risk factors include renal insufficiency and failure. And in the drug interaction section, it too states that "Concomitant use of sorbitol with [Kayexalate] has been implicated in cases of intestinal necrosis, which may be fatal."

The FDA Guidance explains that "[t]o include an adverse event in the [warnings] section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been *definitively* established." FDA Guidance at 3 (footnote omitted) (emphasis added). Thus, as used in an FDA drug warning, "association" means something more than a mere coincidental occurrence but

less than a "definitive" causal connection and therefore reasonably can include likely cause and effect relationships. *See Liles*, slip. op. at 31 (experts may extrapolate from scientific data that show less than a "definite conclusions of a causal relationship"). In addition, we agree with the Allens and the trial court that the word "implicated" carries a causal meaning, *i.e.*, that the use of Kayexalate with sorbitol is involved in causing colonic necrosis. Given that there is a specific warning for the powder form of Kayexalate about its being given with sorbitol, there is no reason to think that, because the warning is for the powder, it is irrelevant to Kayexalate given in a suspension made from a combination of Kayexalate and sorbitol.

The medical articles furnished by the Allens in opposition to the motion for *Frye-Reed* hearing lend further support to the proposition that within the relevant medical community, a cause and effect relationship between Kayexalate, in the formulation given to Mr. Allen, and ischemic colitis is generally accepted. As early as 2001, Dr. Abraham wrote that colonic necrosis was a "commonly appreciated risk" of Kayexalate with sorbitol and that Kayexalate with sorbitol had been "demonstrated to cause" colonic necrosis in patients with kidney failure. One of Mr. Allen's multiple system problems was kidney failure. Dr. Weisberg's 2008 medical literature review commented on the many case reports of patients developing intestinal necrosis after being given Kayexalate with sorbitol, both by enema and orally, and warned that Kayexalate was a "poor choice" for treatment of hyperkalemia for that reason. Dr. McGowan's 2009 article studied pathology records of patients receiving Kayexalate and observed that "[Kayexalate]-induced ischemia remains an under recognized, easily avoided complication" when used

with sorbitol, especially in certain populations, including the "critically ill," which Mr. Allen certainly was. The articles by Erfani, in 2010, and Mount, in 2015, likewise supported a causal link, and warned against using Kayexalate with sorbitol, especially in patients with kidney failure. The articles submitted by Dr. Burks did not offer any reason to contradict a cause and effect relationship when Kayexalate is administered in conjunction with sorbitol but took the position that more studies should be done to investigate the causal connection between Kayexalate with sorbitol and colonic necrosis. The studies offered to the court weighed in the direction of the medical community generally recognizing a cause and effect relationship especially in the population of critically ill patients experiencing renal failure, such as Mr. Allen.

To be sure, neither the medical literature nor the expert testimony by Drs. Leo and Odze, whose depositions were submitted to the court in support and opposition to the *Frye-Reed* motion, delved deeply into the reason, or reasons, for the causal relationship. Dr. Goldstein theorized that Kayexalate affects the lining of the colon such that the web of thin-walled blood vessels that absorb most of the water in the digestive fluid entering the colon stop working. That in turn decreases oxygenation to the lining of the colon. Although Dr. Odze's theory focused on the sorbitol that is combined with the Kayexalate, it was similar to the theory espoused by Dr. Goldstein: the sorbitol, acting as a hyperosmotic, draws water from the web of blood vessels in the lining of the colon, thereby depriving the bowel tissue of oxygen. These experts rejected the causation theory offered by Dr. Burks's experts—that there was a generalized decrease in oxygenation to the colon caused by episodes of low blood pressure during dialysis—

explaining that there would have been damage to other organs, not just the colon, if that were the case. They acknowledged that there are cases of ischemic colitis in which the cause is unknown, but made clear that administering Kayexalate with sorbitol, especially in a patient with Mr. Allen's conditions, is a recognized cause of ischemic colitis.

The evidence before the circuit court on the request for a *Frye-Reed* hearing and opposition was sufficient to support a legal finding that, although there is not universal acceptance in the medical community that Kayexalate with sorbitol can cause ischemic colitis, that proposition is generally accepted, and that the risk of ischemic colitis from Kayexalate with sorbitol is "commonly appreciated." Accordingly, the court's ruling was not in error.

II.

Denial of Motion to Exclude Certain Evidence on Informed Consent

After the court denied Dr. Burks's motion to preclude expert witness testimony under *Frye-Reed*, Dr. Burks moved *in limine* to exclude the same testimony for purposes of informed consent. Dr. Burks's reasoning was that the court had ruled in favor of the Allens on the *Frye-Reed* issue because there was some association, although not a causal connection, between Kayexalate as given to Mr. Allen and ischemic colitis, and if there is not an actual causal connection then the risk of experiencing ischemic colitis in conjunction with administration of Kayexalate with sorbitol is fortuitous and therefore not material. The court rejected that argument. Dr. Burks makes the same argument on appeal.

For the same reasons we have explained in addressing the first question presented, this contention lacks merit. The trial court found, on several bases, that there was general acceptance in the relevant medical community of a causal connection between Kayexalate as given to Mr. Allen and ischemic colitis. Therefore, the contention rests on a faulty premise. Neither at trial nor on appeal does Dr. Burks make any other argument that there was insufficient evidence that the risk of developing ischemic colitis from the Kayexalate and sorbitol as given was not a material risk.

III.

Admission of Evidence about Calcium Gluconate and Calcium Chloride and about Blood Draw

(a)

As mentioned above, the UMMC Guidelines for treatment of hyperkalemia call for calcium gluconate or calcium chloride to be given in the first phase to protect the patient from a heart attack due to dangerous arrhythmias. Dr. Burks ordered calcium gluconate stat. In his deposition, Dr. Burks testified that the pharmacy informed him that calcium gluconate was not available, due to a nationwide shortage, and that he gave an oral order to the nurse assigned to Mr. Allen (Nurse Michelle Frock) to substitute calcium chloride in place of calcium gluconate. UMMC protocol requires that a nurse receiving an oral order document it in the patient's chart within 48 hours and that the notation be signed by the physician who gave the order. An oral order was not documented in Mr. Allen's chart, however, and the calcium chloride never was administered. In her

deposition testimony, Nurse Frock said she did not recall Dr. Burks giving an oral order and if one had been given, she would have documented it in Mr. Allen's chart.[17]

Before trial, Dr. Burks filed a motion to preclude the Allens from introducing evidence that he failed "to administer calcium gluconate or calcium chloride." He argued that the only possible relevance of the evidence was to the standard of care, but because it was undisputed that Mr. Allen did not suffer any injury from the failure to administer calcium gluconate and/or calcium chloride, the evidence of a breach in the standard of care had no causal significance and therefore was irrelevant. The court granted the motion.

At the beginning of the second day of trial, before Dr. Leo, the Allens's sole standard of care expert, took the stand, counsel for the Allens asked the court to revisit that ruling. He argued that the evidence was admissible to challenge the veracity of the defense theory that, when confronted with Mr. Allen's severe, life-threatening case of hyperkalemia, Dr. Burks did everything in his power to treat it. Counsel for the Allens maintained that evidence that Dr. Burks did not give either calcium gluconate or calcium chloride to Mr. Allen to treat the most dangerous aspect of the hyperkalemia cast doubt on the credibility of Dr. Burks's defense that he used every available tool to treat the emergency. Dr. Burks's counsel responded that the evidence was not relevant to the standard of care and any bearing on credibility it might have was outweighed by the confusion it would cause, as the jury would have to make sense out of the collateral

[17] Nurse Frock did not testify at the trial.

dispute over whether Dr. Burks did or did not give an oral order for calcium chloride. The court agreed with the Allens that the evidence was admissible for credibility purposes and reversed its earlier ruling.

Dr. Leo testified that the UMMC Guidelines stated that calcium—in either of its two forms—be administered as the first line drug to counteract hyperkalemia; that it was "the most important and most urgent medication that Mr. Allen needed"; and that the hospital records reflect that calcium gluconate was unavailable and that calcium chloride was never ordered for or administered to Mr. Allen. As discussed, Dr. Leo opined that Dr. Burks breached the standard of care by administering Kayexalate because dialysis was a safer and readily available alternative. Relatedly, he opined that Dr. Burks could have administered repeated doses of calcium gluconate or calcium chloride to stabilize Mr. Allen's heart muscle and to "buy . . . more time" pending the initiation of dialysis.

When Dr. Burks testified at trial (as an adverse witness called by the Allens), he stated that after he ordered calcium gluconate, he received a call from the UMMC pharmacy advising him that calcium gluconate was not available due to a nationwide shortage. He further testified that he believed that he gave a verbal order to Nurse Frock and he thought, from not being told anything to the contrary, that his order was followed and that Mr. Allen was given calcium chloride. He also testified that it was possible that the UMMC pharmacy advised him that there was a hospital-wide shortage of calcium chloride and, if that were the case, he would not have given an oral order to Nurse Frock to administer it. He could not recall with any confidence which of those scenarios had

occurred, however. He agreed that Mr. Allen's medical record did not reflect that calcium chloride ever was administered.

During the defense case, Dr. Kaplan testified on cross-examination that the standard of care required Dr. Burks to order calcium gluconate (which he did), but that he did not breach the standard of care by not administering that drug because he was advised that it was unavailable. Dr. Kaplan then was shown UMMC records reflecting that calcium gluconate was administered to another patient at the hospital on March 18, 2013. Dr. Kaplan responded that he could not speak to whether there were limited supplies of calcium gluconate available at UMMC on March 18, 2013. Dr. Kaplan further opined that calcium chloride was not an appropriate substitute in Mr. Allen's case because he did not have a central IV line in place and the drug could not be safely administered through a peripheral IV line.

Dr. Seneff also was cross-examined on this issue. He testified that calcium was the "first" drug a physician would want to administer during a hyperkalemic emergency but disagreed that it was the "most important." In his view, all the drugs in the three-phases, in combination, were equally important.

On rebuttal, the Allens played the videotaped deposition of Carla Williams, the assistant director of UMMC's Pharmacy Clinical Services division. She testified that when there is a shortage of a drug the UMMC pharmacy pulls the supply of those drugs from the "Omnicells," which are the secure drug storage facilities available to doctors and nurses on each unit in the hospital, and instead stores the drug at the central pharmacy location. In March 2013, there was a shortage of both calcium gluconate and

calcium chloride, and both had been pulled from the "Omnicells" as a result. A small supply of the drugs would have been available in the emergency department and operating room Omnicells, however, and in crash carts on each unit, unless it had already been used. There was no way for Ms. Williams to determine from the UMMC records the actual quantities of calcium gluconate and calcium chloride available at UMMC on March 18, 2013.

On appeal, Dr. Burks challenges the court's ruling admitting the evidence that Mr. Allen was not given calcium gluconate or calcium chloride.[18] He contends the evidence was not relevant, as it had no tendency to prove a breach in the standard of care that caused injury to Mr. Allen, and should not have been admitted for credibility as it was extrinsic evidence on a collateral matter.

The Allens respond that the evidence properly was admitted because it was relevant to "undermine the credibility of the defense[, *i.e.*,] . . . [that] Dr. Burks did everything he could in order to respond to Mr. Allen's medical emergency." They maintain that evidence that Dr. Burks failed to ensure that Mr. Allen received either one of the two drugs that were, according to all of the experts, most crucial to prevent him from suffering a fatal heart arrhythmia had a tendency to show that Dr. Burks was not

[18] In his reply brief, Dr. Burks argues for the first time that the court also erred by improperly admitting into evidence three exhibits relative to the calcium gluconate/calcium chloride issue: a printout of the Omnicell records from March 13, 2013; a billing record for Mr. Allen that reflected he never was charged for calcium chloride; and a print-out showing medications stocked in the UMMC crash carts. "[A]ppellate courts ordinarily do not consider issues that are raised for the first time in a party's reply brief" and we decline to address the admission of these exhibits. *Gazunis v. Foster*, 400 Md. 541, 554 (2007).

meticulous in his treatment of Mr. Allen, which made it more probable that he (Dr. Burks) did not carefully assess whether Kayexalate was necessary or appropriate as a treatment for Mr. Allen's hyperkalemia. We agree.

Evidence is relevant if it has "any tendency to make the existence of any fact that is of consequence to the determination of the action more probable or less probable than it would be without the evidence." Md. Rule 5-401. A court "does not have discretion to admit irrelevant evidence[.]" *Ruffin Hotel Corp. of Md., Inc. v. Gasper*, 418 Md. 594, 620 (2011); *see also* Md. Rule 5-402 ("Evidence that is not relevant is not admissible.").

In his opening statement, Dr. Burks's attorney told the jury that all of the actions his client took on March 18, 2013, were aimed at preventing Mr. Allen from "suffering an immediate, life-threatening emergency that would have stopped his heart"; that Dr. Burks's treatment of Mr. Allen "prevented [him] from dying from a heart arrhythmia"; and that when faced with "a patient [who] could die . . . in front of him[, Dr. Burks] used every avenue possible to stop that from happening." During defense counsel's examination of Dr. Burks, who, as mentioned, was called adversely by the Allens, he affirmed that Mr. Allen was experiencing an "immediately life threatening emergency" around noon on March 18, 2013; that Dr. Burks took "prompt and urgent action to respond to that life threatening emergency"; that he ordered a "cocktail" of drugs, including calcium gluconate, to avert the emergency; and that absent that treatment, Mr. Allen was "certain to die from the elevated potassium level." The defense experts testified, likewise, that Mr. Allen was in danger of dying of a fatal heart arrhythmia and that Dr. Burks's treatment prevented that outcome. Thus, the defense theory was not

simply that the administration of Kayexalate was within the standard of care (and, in any event, did not cause Mr. Allen's ischemic colitis), but that Dr. Burks responded to a cardiac emergency and prevented him from dying from a hyperkalemic arrhythmia.

Evidence that Dr. Burks did not ensure that Mr. Allen received calcium chloride after he learned from the UMMC pharmacy that calcium gluconate was unavailable was relevant to the overall credibility of Dr. Burks's defense. Dr. Burks's alleged carelessness in providing a drug crucial to treating Mr. Allen's life threatening emergency had a tendency to make it more probable that he also was careless in his decision to prescribe Kayexalate, *i.e.*, that he didn't consider whether that course of action was necessary or appropriate in Mr. Allen's particular case, given his renal failure and the availability of dialysis, a safer and more effective alternative. Moreover, the evidence that Dr. Burks misrepresented during his deposition testimony that he had given an oral order to Nurse Frock to substitute calcium chloride in place of the calcium gluconate, despite no entry in Mr. Allen's medical record to substantiate that that occurred, was relevant to his credibility. *See, e.g.*, *Hill v. Wilson*, 134 Md. App. 472, 480 (2000) (a "witness's credibility is always relevant") (citation omitted).

Of course, the court had discretion to exclude the evidence pursuant to Rule 5-403 if its "probative value [was] substantially outweighed by the danger of unfair prejudice, confusion of the issues, or misleading the jury . . . ." Dr. Burks maintains that the court abused its discretion by not excluding the evidence pertaining to calcium gluconate and calcium chloride because it was both highly prejudicial and misleading. He relies primarily on *Lai v. Sagle*, 373 Md. 306 (2003). In that case, the Court of Appeals held

that a trial court abused its discretion by not granting a mistrial in a medical malpractice action after plaintiff's counsel mentioned in opening statements that the defendant physician had been sued for medical malpractice on five prior occasions. Analogizing that evidence to "prior bad acts" evidence, the Court reasoned that the jury could use the evidence that a defendant had been sued previously to infer, improperly, that the defendant was negligent in those cases *and* that he or she had a propensity to be negligent.

In the instant case, the challenged evidence concerned Dr. Burks's treatment of Mr. Allen, not prior medical malpractice suits. It did not create, as Dr. Burks suggests, a mini-trial on a collateral issue because, as we have explained, evidence that neither calcium gluconate nor calcium chloride was ordered/administered was relevant to a central issue at trial: the propriety of Dr. Burks's treatment decisions in the immediate aftermath of Mr. Allen's bradycardia. For all these reasons, the court did not err or abuse its discretion by denying Dr. Burks's motion *in limine* or by admitting the challenged evidence.

(b)

At trial, Dr. Burks testified that when he arrived on the floor on the morning of March 18, 2013, between 7:00 a.m. and 8:00 a.m., he learned that the results of Mr. Allen's routine blood tests were not back. He asked Nurse Frock about this, and she told him that Mr. Allen "may have refused" to have his blood drawn that morning. Dr. Burks believed that he then gave an oral order for the labs to be drawn that morning but acknowledged that there was no notation in Mr. Allen's medical record to that effect and

the labs were not drawn. He acknowledged that if the lab results had been available they likely would have revealed an elevated potassium level and he would have ordered a nephrology consult, which would have resulted in dialysis that morning. Had that happened, Mr. Allen would not have experienced a cardiac event and Kayexalate would not have been prescribed.

On appeal, the appellants contend the Allens should not have been permitted to elicit testimony that Dr. Burks "did not request a blood draw after learning that Mr. Allen's blood work had not been completed" earlier that morning because that evidence had no tendency to prove a breach in the standard of care that caused injury to Mr. Allen. We conclude that this issue is waived.

All the challenged testimony was elicited on direct examination of Dr. Burks, who, as mentioned, was called adversely.[19] During the entire line of questioning pertaining to the blood draw, which spans thirteen pages of the trial transcript, counsel for Dr. Burks did not lodge any objections directed at the substance of the questions and never argued to the court that, in his view, the subject of the questions was irrelevant and prejudicial. Having failed to object to the challenged testimony, Dr. Burks has waived this contention of error. *See* Md. Rule 2-517(a) ("An objection to the admission of

[19] When Dr. Burks testified, he was asserting an affirmative defense of contributory negligence based upon Mr. Allen's alleged refusal of a blood test during the early morning hours of March 18, 2013. After Dr. Burks testified, his attorney withdrew that defense. As a result, the court ruled that the issue as to whether Mr. Allen actually had refused his blood draw was collateral and precluded further evidence on that subject.

evidence shall be made at the time the evidence is offered or as soon thereafter as the grounds for objection become apparent. Otherwise, the objection is waived.").

CROSS APPEAL

I.

In their cross-appeal, the Allens contend the trial court violated their constitutional rights by reducing the $10,000,000 verdict to $906,250, consistent with the statutory cap on noneconomic damages in actions for medical malpractice ("the cap") codified at CJP section 3-2A-09.[20] They argue that the cap creates a discriminatory classification scheme prohibited by the Equal Protection Clause of the Fourteenth Amendment to the federal constitution, and Article 24 of the Maryland Declaration of Rights because it "discriminates against the most severely injured" and against "larger families," such as the Allens. They assert that the cap cannot survive rational basis scrutiny and must be struck down.

It is not within this Court's purview to revisit the constitutionality of the cap, which the Court of Appeals repeatedly has upheld in the face of challenges premised on the same arguments made by the Allens in the instant appeal.[21] *See Murphy v. Edmonds*,

[20] When Mr. Allen died in 2013, the cap on noneconomic damages in a wrongful death action premised upon medical malpractice brought by "two or more claimants or beneficiaries" was 125% of $725,000 ($906,250) for "all claims for personal injury and wrongful death arising from the same medical injury[.]" CJP § 3-2A-09(b)(2).

[21] Most of the appellate cases consider the constitutionality of the cap on non-economic damages codified at CJP section 11-108, which, in its current form, applies to all personal injury and wrongful death actions that are not premised on medical

Continued…

325 Md. 342, 367–70 (1992) (holding that the constitutionality of the cap is scrutinized under the deferential rational basis test and that the "legislative classification drawn . . . between tort claimants whose noneconomic damages are less than [the cap] and tort claimants whose noneconomic damages are greater than [the cap], and who are thus subject to the cap, is not irrational or arbitrary"); *DRD Pool Serv., Inc. v. Freed*, 416 Md. 46, 66-67 (2010) (holding that the cap "does not create a classification between affected parties, and certainly not a classification subject to heightened scrutiny"); *Dixon v. Ford Motor Co.*, 433 Md. 137, 169 (2013) (holding that by capping the total gross award in wrongful death actions, the legislature did not "create irrational classifications among the claimants"); *Martinez v. The Johns Hopkins Hospital*, 212 Md. App. 634, 656 n.19 (2013) ("it is well settled that the [c]ap is constitutional. The Court of Appeals has consistently upheld the constitutionality of the [c]ap, explaining that it has become 'embedded in the bedrock of Maryland law.'") (quoting *DRD Pool*, 416 Md. at 68). We are bound by the direct precedent governing this issue and decline to further address it.

JUDGMENT AFFIRMED. COSTS TO BE PAID BY THE APPELLANTS.

…cont'd
malpractice. As all the parties agree, the reasoning of those cases is equally applicable to CJP section 3-2A-09, which applies only to medical malpractice actions.