eTable 1. Metabolic Derangements that May Confound BD/DNC Evaluation

Laboratory Result	Value[a]
Metabolic	
Ammonia[b]	>75 µmol/L
Blood urea nitrogen	>75 mg/dL
Calcium (or ionized calcium)	<7 mg/dL or >11 mg/dL (or <1 mmol/L or >1.3 mmol/L)
Glucose	<70 mg/dL or >300 mg/dL
Magnesium	<1.5 mg/dL or >4 mg/dL
Potassium	<3 mmol/L or >6 mmol/L
Sodium	<130 mmol/L or >160 mmol/L
Acid-Base	
pH	<7.3 or >7.5
Endocrine	
Total T4[b]	<3 mg/dL or >30 mg/dL
Free T4	≤ 0.4 ng/dL or >5 ng/dL

[a]The exact values at which the laboratory abnormality could affect the clinical evaluation are uncertain, and the values listed in this table are practical thresholds based on consensus only.

[b]Routine measuring of these values may not be necessary unless clinically indicated.

eTable 2. Common medications administered to critically ill patients and estimated half-lives[a]

Drug	Pharmacokinetics			Comments
Intravenous sedatives				
Dexmedetomidine[e32]	$t_{½}$	Infant ≤28d	3.2 hours	**Hepatic impairment** Compared to a baseline half-life of 2.5 hours in healthy adult patients, clearance in mild, moderate, and severe hepatic impairment was 3.9, 5.4, and 7.4 hours, respectively.[e33] Consider tapering rather than abrupt cessation for patients on >24 hours of therapy to avoid hemodynamic changes.
		Pediatric	<2 years: 2.3 hours 2-11 years: 1.6 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (95%)	

<table>
<tr><td rowspan="4">Etomidate[e34]</td><td rowspan="3">$t_{½}$</td><td>Infant ≤28d</td><td rowspan="3">2.6-3.5 hours</td><td rowspan="4">Continuous infusion: Plasma terminal half-life was found to be ~5.5 hours when administered as a continuous infusion.[e35]

Hepatic impairment: In patients with cirrhosis, the terminal half-life of continuous infusion can be prolonged up to 2-fold (~9 hours).[e36]</td></tr>
<tr><td>Pediatric</td></tr>
<tr><td>Adult</td></tr>
<tr><td colspan="2">Metabolism</td><td>Hepatic; plasma esterases</td></tr>
<tr><td colspan="2">Excretion</td><td>Urine (~75%), bile (10%)</td></tr>
<tr><td rowspan="4">Ketamine[e37, e38]</td><td rowspan="3">$t_{½}$</td><td>Infant ≤28d</td><td rowspan="3">~2.5 hours</td><td rowspan="4"></td></tr>
<tr><td>Pediatric[e39]</td></tr>
<tr><td>Adult</td></tr>
<tr><td colspan="2">Metabolism</td><td>Hepatic</td></tr>
</table>

	Excretion		Urine (91%)	
Midazolam[e40,b]	$t_{½}$	Infant ≤28d	4-12 hours	**Renal impairment:** With continuous infusions, half-life of the parent compound can increase up to 2-fold. Half-life of the active metabolite can increase significantly compared to control group.[e41] **Special populations with prolonged half-lives**: ● Elderly: Increased 2-fold ● Heart failure: Increased 2-fold ● Hepatic impairment: Increased 2.5-fold ● Obesity: increased 2-fold
		Pediatric	2.9-4.5 hours	
		Adult	~3 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	

Propofol[e42]	$t_{½}$	Infant ≤28d	Initial: 40 minutes Terminal: 4-7 hours	**Context sensitive half-time**: Prolonged infusions (>10 days) have been associated with a drug half-life of 1-3 days. **Elderly:** Clearance may be decreased.[e43]
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Intravenous narcotics				
Fentanyl[e44,b]	$t_{½}$	Infant ≤28d	5.5 ± 1.2 hours[e45]	**Continuous infusion:** Half-life prolongs with infusion duration. In children aged 6 months to 14 years, half-life reported as ~21 hours in long-term continuous infusions. **Special populations with prolonged half-lives:**
		Pediatric	5 months-4.5 years: 2.4 hours	
		Adult	2-4 hours	
	Metabolism		Hepatic	
	Excretion		Urine (75%)	

				• Infants**:** half-life inversely proportional to gestational age • Elderly: Increased 5-fold[e46] • Transdermal route: 20-27 hours
Hydromorphone[e47,b]	*t*½	Infant ≤28d	2.3 hours	**Renal impairment:** Increased terminal half-life seen in patients with severe renal impairment compared to controls after oral administration immediate release hydromorphone (40 vs 15 hours).
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	
Morphine[e48,e49,b]	*t*½	Infant ≤28d[e50]	6.5 ± 2.8 hours	**Hepatic impairment:** 1. Children: extrahepatic

		Pediatric[e] [50]	2 ± 1.8 hours	metabolism may occur, minimal half-life changes 2. Adults with cirrhosis: delayed clearance **Elderly:** Reduced clearance
		Adult	2 hours	
	Metabolism		Hepatic	
	Excretion		Urine (90%)	
Remifentanil[e51, e52]	$t_{½}$	≤2 months	5.4 minutes	
		Pediatric	>2 months to <2 years: 3.4 minutes 2-6 years: 3.6 minutes 7- 2 years: 5.3 minutes 13 to <16 years: 3.7 minutes 16-18 years: 5.7 minutes	
		Adult	10-20 minutes	
	Metabolism		**Blood and tissue esterases**	

	Excretion		Urine (90%)	
Antiseizure Medications				
Clonazepam[e53,b]	$t_{½}$	Infant ≤28d	22-81 hours	**Hepatic impairment:** Clearance may be decreased **Elderly:** Hepatic clearance may be decreased
		Pediatric	28.7 hours	
		Adult[e54]	17-56 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Diazepam [e55,b]	$t_{½}$	Infant ≤28d	Parent: 33-45 hours Active metabolite: 87 hours	Terminal half-life prolonged with repeated dosing. **Hepatic impairment:** In mild and moderate cirrhosis, diazepam half-life is increased by 2-5 fold.[e56]
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	

				Elderly: In healthy patients >60 years, half-life of parent compound was ~79 hours.[e57]
Levetiracetam	$t_{½}$	Infant ≤28d[e58]	8.9 hours	**Renal impairment:** Renal clearance is directly proportional to creatinine clearance, reported half-lives[e59]: ● Mild impairment: 10.4 hours ● Severe impairment: 24.1 hours **Elderly:** Renal clearance may be decreased. ● Reported increases in half-life by 2.5 hours.
		Pediatric	<4 years: 5.3 ± 1.3 hours 4-12 years: 6 ± 1.1 hours	
		Adult	6-8 hours	
	Metabolism		Plasma hydrolysis (~24%)	
	Excretion		Urine	
Lorazepam[e60,b]	$t_{½}$	Infant ≤28d	40.2 ± 16.5 hours	**Renal impairment**: Half-life slightly prolonged in end

		Pediatric	5 months to <3 years: 15.8 hours 3 to <13 years: 16.9 hours 13 to <18 years: 17.8 hours	stage renal disease (~18 hours).[e61]
		Adult	~14 hours	
	Metabolism		Hepatic	
	Excretion		Urine (88%)	
Pentobarbital[e62]	$t_{½}$	Infant ≤28d	26 ± 16 hours	
		Pediatric		
		Adult	22 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Phenobarbital[e63]	$t_{½}$	Infant ≤28d	<10 days: 114.2 ± 43 hours	**Hepatic impairment:** Small changes in half-life

			11-30 days: 73.19 ± 24.17 hours	are seen in patients with cirrhosis (130 ± 15 hours) compared with the control group (86 ± 3 hours). There is large interpatient variability seen in hepatic impairment.[e64] **Therapeutic Range:** 10-40 mcg/mL
		Pediatric	2-3 months: 62.9 ± 5.2 hours 4-12 months: 63.2 ± 4.2 hours 1-5 years: 68.5 ± 3.2 hours	
		Adult	~79 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Phenytoin[e65] and fosphenytoin[e66, e67]	$t_{½}$	Infant ≤28d	0-2 days: 80 hours 3-14 days: 15 hours 15-150 days: 6 hours[e68]	**Michaelis-Menten**: Half-life increases with increasing phenytoin concentrations. **Hepatic impairment:** Active metabolite undergoes enterohepatic circulation and may prolong duration of action.[e69, e70]
		Pediatric	10-12 hours	
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine	

			Renal impairment: Total phenytoin serum concentrations should be interpreted with caution. If available, recommend the use of free phenytoin concentrations.[e65] **Obesity:** Half-life may be prolonged in obese patients compared to controls (19.9 vs 12 hours, respectively).[e71] **Elderly:** Clearance decreases with increasing age **Therapeutic Range:** Total Phenytoin 10-20mcg/mL; Free Phenytoin 1-2 mcg/mL

Valproic acid[e72, e73]	$t_{½}$	Infant ≤28d	First week of life: 40-45 hours <10 days: 10-67 hours	**Liver impairment:** 18 hours[e73] **Elderly:** 15 hours[e74] **Therapeutic Range:** 50-100 mcg/mL
		Pediatric	>2 months: 7-13 hours 2-14 years: 9 hours	
		Adult	9-19 hours	
	Metabolism		Hepatic	
	Excretion		Urine	
Neuromuscular blocker agents				
Atracurium[e75, e76]	$t_{½}$	Infant ≤28d	Infants: 20 minutes Children: 17 minutes	
		Pediatric		
		Adult	20 minutes	
	Metabolism		Hofmann elimination and ester hydrolysis	
	Excretion		Urine (<5%)	

Cisatracurium[e7, e78]	$t_{½}$	Infant ≤28d	22-29 minutes	
		Pediatric		
		Adult		
	Metabolism		Hoffman elimination	
	Excretion		Urine (95%)	
Pancuronium[e79, b]	$t_{½}$	Infant ≤28d	89-140 min	**Renal impairment:** 257 minutes **Biliary obstruction:** 270 minutes **Hepatic cirrhosis:** 208 minutes **Hypothermia:** May prolong duration
		Pediatric		
		Adult		
	Metabolism		Hepatic	
	Excretion		Urine (40%), Bile (11%)	

Rocuronium[e80,b]	$t_{½}$	Infant ≤28d	3-12 months: 1.3 ± 0.5 hours 1 to <3 years: 1.1 ± 0.7 hours	**Hepatic impairment:** 4.3 hours **Renal impairment:** 2.4 hours **Elderly:** Duration prolonged in elderly patients compared with young adults (110 vs 78 minutes, respectively)[e81]
		Pediatric	3 to <8 years: 0.8 ± 0.3 hours	
		Adult	1.4-2.4 hours	
	Metabolism		Minimally hepatic	
	Excretion		Urine (26%)	
Succinylcholine[e82]	$t_{½}$	Infant ≤28d	<1 minute	**Pseudocholinesterase deficiency:** Prolonged clearance[e83]
		Pediatric		
		Adults		
	Metabolism		Plasma pseudocholinesterases	
	Excretion		Urine (10%)	

Vecuronium[e76, e84,b]	$t_{½}$	Infant ≤28d	Infants: 65 minutes Children: 41 minutes	**Hepatic impairment:** Half-life is prolonged in patients with cholestasis compared to controls (58 vs. 98 minutes, respectively)[e85]
		Pediatric		
		Adult	65-75 minutes	
	Metabolism		Hepatic	
	Excretion		Urine (30%)	**Hypothermia:** Clearance may be reduced[e86]

[a]The duration of time that medications should be held before neurologic examination to determine brain death is patient and medication specific. Providers should be aware that the metabolism and clearance of pharmacologic agents can be affected by patient-specific factors, including but not limited to hypothermia, organ dysfunction, obesity, and concomitant drug therapies. Typically, 3 to 5 half-lives will allow for adequate clearance of pharmacologic therapy; however, elimination half-life does not guarantee clearance of medications with active metabolites or enterohepatic recirculation. This table includes terminal half-life, which takes into account both volume of distribution and elimination rate, as well as information on specific populations that experience deviations in standard clearance when clinically significant data are available. Context-sensitive half-time was included when shown to be prolonged compared with reported half-life values. Whenever possible, providers should obtain drug levels to ensure that the levels are in a low to mild therapeutic range before neurologic examination.

[b]Reversal agents can be considered after evaluating the risk vs benefit of their use.

eTable 3. Clinical Guidance for Performance of the Components of the BD/DNC Examination

Examination Component[a]	How to Perform the Examination Component	Response Consistent with BD/DNC	Clinical Considerations
Coma	• Visual response is determined by assessing for a blink to visual threat, taking care during the technique not to create a wind wave, thereby inadvertently testing a corneal reflex. • Auditory response is tested with clapping and loud yelling of the person's name, assuming that the patient is hard of hearing at baseline and a	• No evidence of arousal or awareness to maximal external stimulation (including noxious visual, auditory, and tactile stimulation)	• Drugs and metabolic derangements may cause reversible coma. Permanency must be established before performing a BD/DNC examination.

	loud stimulus is necessary.		

Motor responses of the face and limbs	• Apply deep pressure to all of the following:
	  ○ the condyles at the level of the temporomandibular joints
	  ○ the supraorbital notch bilaterally
	  ○ the sternum
	  ○ all 4 extremities, both proximally and distally
	• Insert a cotton swab on a stick in each nostril to perform “nasal tickle” testing.
		• Noxious stimuli should not produce grimacing, facial muscle movement, or a motor response of the limbs other than spinally mediated reflexes.
		• Noxious stimuli above the foramen magnum should not produce any movement in the face or body.
		• Noxious stimuli below the
			• The clinical differentiation of spinal responses from brain-mediated motor responses requires expertise. Consultation with an experienced practitioner is recommended if the origin of a response is unclear. Alternatively, if interpretation is unclear, ancillary testing is recommended.
			• Ancillary testing is recommended if a person has a pre-existing severe neuromuscular disorder, such as amyotrophic lateral sclerosis or a pre-existing severe sensory neuropathy.
			• Ancillary testing is not required if a person does not have all 4 limbs. Painful

		foramen magnum should not produce any movement in the face but may elicit spinally mediated peripheral motor reflexes.	stimulation can still be provided centrally and on the torso as close to the termination of the limb as possible. • Severe facial trauma and swelling may preclude evaluation of facial motor response, so ancillary testing is recommended in this setting.
Pupillary reflex	• Dim the room light for several minutes before testing to maximize responsiveness • A bright (e.g., LED) light can be used • Shine a bright light into each of the person's eyes, looking for pupillary constriction and measuring the diameter of the pupils. Use of a magnifying glass	• Ipsilateral and contralateral pupillary response should be absent in both eyes. Pupils in both eyes should be fixed in a midsize or dilated position.	• Pupils can be any shape (round/oval/irregular). • Corneal trauma or prior ophthalmic surgery may influence pupillary reactivity and preclude adequate evaluation, necessitating ancillary testing. • Ocular instillation of drugs (e.g., anticholinergic) may artificially produce transiently nonreactive

	may be considered.	Constricted pupils (<2 mm) are not consistent with BD/DNC and suggest possibility of intoxication or locked-in syndrome.	pupils. • In the setting of anophthalmia or inability to see the pupils, ancillary testing is recommended. • Automated pupillometers may be a useful adjunct in the examination,[e87] as this may detect responsiveness not appreciated by the naked eye. However, automated pupillometers are not validated for use in isolation in BD/DNC. If performed, it must be consistent with no pupillary responses to light bilaterally. In some patients younger than 6 months, the pupillary border may not be formed sufficiently for an automated pupillometer to obtain an accurate measurement.

			• Any pupillary reactivity, whether to bright light or dimming of the ambient light, is not consistent with BD/DNC.
Corneal reflex	• Touch the cornea of each eye with a cotton swab on a stick at the external border of the iris, applying light pressure and observing for any eyelid movement. • Effective stimulus location is at the border of the iris; testing farther out on the sclera/conjunctiva is less sensitive.[e88]	• No eyelid movement should be seen, other than that directly caused by the stimulus.	• Care should be taken to avoid damaging the cornea. • In the setting of anophthalmia, severe orbital edema, prior corneal transplantation, or scleral edema or chemosis, ancillary testing is recommended.
Gag and cough reflexes	• Stimulate the posterior pharyngeal wall bilaterally with a tongue depressor or rigid suction device. • Stimulate the tracheobronchial wall to the	• Absence of cough and gag.	• The efferent limb for the cough reflex includes the phrenic nerve, which may be injured in persons with high cervical cord injuries, so ancillary testing is

	level of the carina with deep endotracheal placement of a suction catheter.		recommended in this setting.
OCR and OVR reflexes	• OCR: Confirm integrity of the cervical spine and skull base, securing the endotracheal tube to prevent accidental dislodgement. • Rotate the head briskly horizontally to both sides. There should be no movement of the eyes relative to head movement. Testing vertically is optional. • OVR: Examine the auditory canal to ensure patency and the integrity of the tympanic membrane. Presence of a ruptured tympanic membrane does not negate the clinical testing. • Evaluate the head to 30^{o} to	• There should be absence of extraocular movements (i.e., the eyes follow the head movement exactly, staying mid-position the entire time). • Detection of any extraocular movements is not compatible with BD/DNC.	• If the OCR cannot be performed, but the OVR is performed bilaterally and there are no extraocular movements, ancillary testing is not required. • A fracture of the base of the skull or petrous temporal bone may obliterate the response on the side of the fracture, and ancillary testing is recommended in this instance. • Severe orbital or scleral edema or chemosis may affect the free motion of the globes, and ancillary testing is recommended in this instance.

	place the horizontal semicircular canals in the correct vertical position. Irrigate with ≥50-60mL of ice water for at least 60 seconds using a syringe or a syringe attached to a catheter placed inside the canal. Test both sides separately, with a 5-minute interval between to allow the endolymph temperature to equilibrate.		• In the setting of anophthalmia, ancillary testing is recommended. • If present, the OVR can lead to vomiting, posing a risk for aspiration.
Sucking and rooting reflexes	• Sucking reflex: A gloved finger is placed inside the baby's mouth. • Rooting reflex: The external surface of both cheeks and corners of the mouth are stroked with a finger.	• Sucking: The lips do not close around the finger and there is no rhythmic squeezing of the finger between the tongue and	• These reflexes are present at birth. • The rooting reflex extinguishes between 3 and 6 months of life. • The sucking reflex transitions from a primitive reflex to a voluntary movement around 4 months of life.

		palate. • Rooting: No movement of the head.	

Abbreviations: BD/DNC = brain death/death by neurologic criteria; LED = light-emitting diode; OCR = oculocephalic reflex; OVR = oculovestibular reflex

[a]The oculocardiac reflex and/or atropine testing are not standard parts of the BD-DNC examination and need not be performed.

eTable 4. Described Spinal Reflexes in BD/DNC*

Reflex	Description
Decerebrate-type movements[27]	Spontaneous extension of the extremities
Extensor-like posturing[27]	Back arching to the left or right
Eyelid opening[27]	Opening of the eyelids after nipple stimulation
Fasciculation[e89]	Twitching of contiguous groups of muscle fibers
Head turning[27, e90-e92]	Intermittent head turning from side to side every 10-30 seconds with or without extension of the upper extremities
Hugging[27]	Flexion of the trunk and movement of the arms in a hugging-like manner
Lazarus sign[27, e89, e93-e98]	Bilateral arm flexion, shoulder adduction, and hand raising to chest, face, or endotracheal tube with dystonic posturing of the fingers
Limb elevation[27]	Raising of limbs off the bed
Myoclonus[e89]	Twitching or contraction of a muscle or group of muscles
Plantar response[e89]	Plantar flexion
Pronator-extension[e89]	Pronation and extension of the upper extremity

Respiratory-like movements[27]	Adduction of both shoulders followed by a slow cough-like movement
Repetitive leg movements[e99]	Slight flexion of the leg and foot
Thumbs Up sign[e100]	Isolated thumb extension
Triple flexion[e89]	Flexion of the thigh, leg, and foot
Undulating toe[27]	Slow flexion then extension of the toes

* The terminology for the reflex and description included in this table are directly reproduced from the World Brain Death Project, which took them directly from the literature. Because it can sometimes be challenging to determine if a movement is cerebrally or spinally mediated, if there is any uncertainty, as per Rec 16b, determination of BD/DNC should include an ancillary test.

eTable 5. Clinical Guidance for Performance of the Apnea Test

Prerequisites

1. Ensure the patient is not hypercarbia, hypotensive, hypovolemic, or hypothermic
2. Determine if the patient has baseline CO_2 retention due to pre-existing disease and whether the baseline $PaCO_2$ is known
    a. In a patient without known baseline CO_2 retention, adjust the ventilator to achieve a normal $PaCO_2$ (35-45 mm Hg) and pH (7.35-7.45)
    b. In a patient with known baseline CO_2 retention due to pre-existing disease for whom the baseline $PaCO_2$ is known, adjust the ventilator to achieve baseline pH/ $PaCO_2$
    c. In a patient with known baseline CO_2 retention due to pre-existing disease for whom the baseline $PaCO_2$ is not known, adjust the ventilator to achieve estimated baseline pH/ $PaCO_2$ (This patient will also require an ancillary test if they do not breathe during the apnea test)

Prior to procedure

1. Preoxygenate for at least 10 minutes with 100% FIO_2, aiming for PaO_2 > 200 mm Hg
2. Check ABG to establish baseline pH, PaO_2, $PaCO_2$ within above parameters
3. Ensure respiratory therapist and/or nurse; staff with appropriate expertise in managing the potential cardiopulmonary complications of apnea testing; supplies for multiple ABGs; and vasopressors, inotropes, and/or intravenous fluids are readily available

Disconnect the patient from intermittent mandatory ventilation and provide apneic oxygenation

Techniques for providing apneic oxygenation

1. Tracheal insufflation for patients ≥18 years old
    a. Place a catheter inside the endotracheal or tracheostomy tube such that it approximately terminates just above the level of the carina.
    b. The catheter diameter should be <70% of the diameter of the endotracheal or tracheostomy tube.
    c. Deliver 100% F_{IO_2} at a flow rate of 4-6 L/min.
2. Continuous positive airway pressure for all patients using 100% F_{IO_2} and the same PEEP the patient required prior to the apnea test. The following are acceptable ways to provide CPAP during the apnea test:
    a. Flow inflating bag with functioning PEEP valve
    b. T-piece with functioning PEEP valve
    c. Mechanical ventilator in CPAP mode
        i. Disable default backup apnea ventilation
        ii. Disable apnea alarm or lengthen to maximum allowable limit and assign provider to manually silence alarm
        iii. Remove all condensation from the inspiratory and expiratory limbs of ventilator circuit
        iv. Position the ventilator circuit away from the patient's body to allow for close examination of the chest and abdomen
        v. Adjust the trigger sensitivity to a level that avoids auto-triggering but is sensitive enough to detect a true spontaneous respiratory effort. Auto-triggering may falsely indicate a patient is initiating respiratory effort.

d. T-piece resuscitator (e.g., Neopuff ventilator for infants)

These techniques may need modification in patients with communicable respiratory illness[e101,e102]

Monitoring during the apnea test

1. Monitor the patient's cardiopulmonary status via an invasive arterial catheter, 3-5 lead ECG, and pulse oximeter
    a. If unable to obtain invasive arterial access, use blood pressure cuff with frequent cycling
    b. Visual (bare chest and abdomen) and tactile observation of the patient's chest for movement and abdominal musculature for contraction or evidence of spontaneous breathing. Some chest wall movement, which must be distinguished from respiratory effort, can be observed due to cardiac pulsation or contraction of the intercostal muscles due to acidosis
2. If using a flow inflating bag, monitor for respiratory effort by feeling and watching the bag
3. If using the ventilator in CPAP mode, monitor the flow waveforms for a patient-initiated breath
4. Transcutaneous CO_2 monitoring can be used to follow the rise in partial pressure of CO_2 and guide the timing of ABG sampling

Performance of serial arterial blood gasses

1. PaCO_2 increases by approximately 2-3 mm Hg per minute during apnea

2. If point of care blood gas testing is available, perform serial ABG's (approximately every 2 minutes) beginning at approximately 8 minutes of apnea, if the patient does not have hemodynamic instability or hypoxemia, until the ABG results are consistent with the criteria below.
3. If point of care blood gas testing is not available, send an ABG after approximately 8 minutes of apnea, but continue apnea testing/repeat the ABG every 2-3 minutes if the patient is hemodynamically stable until the ABG results are consistent with the criteria below. The duration of testing is typically 10-15 minutes but can be carried out for longer if the patient is stable.

The apnea test is consistent with BD/DNC if these conditions are met

1. No respirations or effort occurs, and
2. The arterial pH level is <7.30, and

3a. In patients who are known NOT TO HAVE chronic CO_2 retention, the $PaCO_2$ level is ≥60 mm Hg AND ≥20 mm Hg above the patient's pre-apnea test baseline level.

3b. In patients who are KNOWN TO HAVE chronic CO_2 retention, and the baseline $PaCO_2$ is KNOWN, the $PaCO_2$ level is ≥60 mm Hg AND ≥20 mm Hg above the patient's known chronic elevated premorbid baseline level.

3c. In patients who are SUSPECTED TO HAVE chronic CO_2 retention, but the baseline $PaCO_2$ is UNKNOWN, the $PaCO_2$ level is ≥60 mm Hg AND ≥20 mm Hg above the patient's pre-apnea test level, and an ancillary test is required.

Terminate the apnea test for:

1. Spontaneous respirations or effort
2. Hemodynamic instability or hypoxemia
    a. SBP ≤100 mm Hg or MAP ≤75 mm Hg in adults, or SBP or MAP ≤5th percentile for age in children, despite titration of vasopressors, inotropes, and/or intravenous fluids
    b. Decrease in oxygen saturation below 85%
    c. Cardiac arrhythmia with hemodynamic instability
    d. In infants, bradycardia (<60 BPM), since it can occur before hypotension or hypoxemia
3. Unless the test is being aborted due to spontaneous respirations, obtain an ABG before reconnecting the patient to the ventilator if able. If the arterial pH and $PaCO_2$ criteria (as included above) are achieved, the apnea test is consistent with BD/DNC.
4. After resuming mechanical ventilation, transiently increase minute ventilation to achieve normoxia, normocapnia and a normal acid-base status.
5. If the test is aborted but the completion conditions are not met, the apnea test may be repeated for a longer duration if the patient was stable during testing, or an ancillary test may be performed.

eTable 6. Ancillary testing: Tests of cerebral blood flow and perfusion[8]

Test	Diagnostic criteria	Advantages	Disadvantages	Sensitivity/ specificity	Comments
Digital subtraction angiography /conventional 4-vessel angiography	Absence of contrast within the intracranial arterial vessels	• Gold standard for ancillary tests	• Requires transport to imaging suite • Invasive (requires technical skills) • Renal susceptibility to contrast • Stasis filling–false negative	100%/ 100%[a] e103, e104	Persistence of flow does not contradict comprehensive competent clinical diagnosis; Equipment and operator dependence limits practical use–still used as calibration standard;
Radionuclide angiography	Absence of radiologic activity upon imaging of the	• Can be performed at bedside	• Limited evaluation of brainstem • Limited availability	98.5%/56 %[e105]	Persistence of flow does not contradict comprehensive competent clinical diagnosis

	intracranial vault	• No renal susceptibility to contrast	• Results can vary based on technique used		
Radionuclide perfusion scintigraphy	Absence of radiologic activity indicating metabolic uptake upon imaging of the intracranial vault	• Can be performed at bedside (planar imaging)	• Limited availability • Planar imaging may limit brain-stem evaluation • SPECT requires patient transport to scanner	Planar: 77.8%/100% SPECT: 88.4%/100%[a, e106]	Uptake of isotope indicates metabolic activity.
Transcranial doppler ultrasound	Reciprocating flow or small systolic spikes with absent or reversed diastolic flow on initial	• Easily performed at bedside • No contrast required	• Operator expertise required • 10% of patients have	90%/98%[59]	Persistence of flow does not contradict comprehensive competent clinical diagnosis

(adult patients)	assessment of intracranial arterial supply, confirmed or proceeding to absent flow velocity signal on second assessment	• Can assess carotid and basilar circulations	no acoustic windows		

[a]Specificity is *assumed* on basis of experimental data but should be interpreted with caution[e107] given the limitation of studies that reported only on clinically confirmed BD/DNC.

Adapted with permission from Greer DM, Shemie SD, Lewis A, et al. Determination of brain death/death by neurologic criteria: The world brain death project. JAMA 2020;324:1078-1097(suppl 5).