Claims 1, 2, 4, 6, 7, 9, 11-13, 15, 18, 20, 21, 23, and 25 of the '163 patent are unpatentable under 35 U.S.C. § 103(a) as Obvious Over *Bernasconi* in View of *INOMAX label*, *Loh*, and *Goyal*.

U.S. Pat. No. 8,431,163	*Bernasconi*, *INOMAX label*, *Loh*, and *Goyal*
CLAIM 1	
A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:	See Sections (a)-(c) of Claim 1 below.
(a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;	*Bernasconi* teaches that echocardiography is essential to identify and treat pediatric patients with conditions that may be treated with inhaled nitric oxide ("iNO"). PPHN is a syndrome associated with diverse neonatal cardiopulmonary disorders, which are characterised by a high pulmonary vascular resistance with right to left shunt of deoxygenated blood across the ductus arteriosus and/or the foramen ovale. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Ex. 1004 at 8. *Bernasconi* further teaches the FDA recommended dose for treating neonatal hypoxic respiratory failure is 20 ppm iNO. The appropriate dose of iNO to assess pulmonary vascular resistance or treat pulmonary hypertension is not completely defined. Dose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN) and ARDS[41–46] and in congenital heart disease.[47,48] Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Ex. 1004 at 3. *INOMAX label* teaches identifying neonates with hypoxic respiratory failure associated with echocardiographic evidence

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	of pulmonary hypertension that may be treated with iNO. INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation. Ex. 1014 at 4. *INOMAX label* further teaches the FDA recommended dose for iNO treatment is 20 ppm. The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. Ex. 1014 at 6. *INOMAX label* further teaches that iNO should not be used in patients dependent on right-to-left shunting of blood. **CONTRAINDICATIONS** INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood. Ex. 1014 at 4.
(b) determining that the patient identified in (a) has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and	*Bernasconi* teaches that there are negative effects of iNO in patients with left ventricular dysfunction ("LVD") including a risk of causing pulmonary edema. There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.[103–108] Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.[108] This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.[103] Ex. 1004 at 8. *Loh* teaches measuring a baseline wedge pressure prior to administering iNO. (Wedge pressure may also be called pulmonary capillary wedge pressure ("PCWP"), pulmonary arterial wedge pressure ("PAWP"), or merely "wedge." All the terms refer to the same concept). *Loh* further teaches that patients with LVD have a baseline wedge pressure that is greater than 20 mm Hg.

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studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with moderate to severe heart failure secondary to LV dysfunction from idiopathic or ischemic dilated cardiomyopathy.

Ex. 1006 at 2780.

To establish baseline conditions, patients inhaled room air (F_{IO_2}, 21%; N_2, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (F_{IO_2}, 21%; N_2, 79%)

Ex. 1006 at 2781.

TABLE 1. Hemodynamic Effects of Inhaled NO in Patients With Congestive Heart Failure (n=19)

	Room Air	NO	P
HR, bpm	90±3	93±3	NS
MAP, mm Hg	79±3	81±3	NS
SVR, dyne · s · cm^{-5}	1102±104	1041±97	NS
PA, mm Hg	35±4	37±4	NS
PAWP, mm Hg	25±3	31±4	<.001
LVEDP, mm Hg; n=10	28±4	34±5	.02
PVR, dyne · s · cm^{-5}	226±30	119±13	<.001
PA−PAWP, mm Hg	11±1	6±0.5	<.001
SVI, mL/m^2	26±2	24±2	.03
CI, L · min^{-1} · m^{-2}	2.3±0.2	2.1±0.2	.03

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery measure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index; and CI, cardiac index.

Ex. 1006 at Table 1.

Additionally, *Goyal* teaches measuring wedge pressure in infants.

During cardiac catheterization study, baseline heart rate, systolic, diastolic and mean systemic as well as PA pressures, right atrial pressure and pulmonary capillary wedge pressure (PCWP) were recorded for all the patients

Ex. 1007 at 209.

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	Table 1 Patient characteristics. Data are expressed as median (range) or absolute numbers. BSA, body surface area; Hb, haemoglobin; VSD, ventricular septal defect Age (months) 33 (8–54) M:F 12:7 Weight (kg) 11 (5–17) Height (cm) 89(64–115) BSA (m^2) 0.52 (0.29–0.75) Hb (gm dl^{-1}) 11.2 (10–14) Type of VSD Perimembranous 15 Muscular 2 Multiple muscular 1 Perimembranous with muscular 1 Ex. 1007 at Table 1.
(c) excluding the patient from inhaled nitric oxide treatment, based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.	*Bernasconi* teaches that patients with LVD treated with iNO are at risk of pulmonary edema. There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.[103–108] Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.[108] This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.[103] Ex. 1004 at 8.
CLAIM 2	
The method of claim 1, wherein the determination in (b) comprises performing echocardiography.	**All the elements of the independent claim from which this claim depends are disclosed in Bernasconi, INOMAX label, Loh, and Goyal as outlined above in Claim 1.** *Bernasconi* teaches that echocardiography may be used to confirm a diagnosis and conduct therapy with iNO, as well as to exclude a condition that may contraindicate the use of iNO. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO.

U.S. Pat. No. 8,431,163	*Bernasconi*, *INOMAX label*, *Loh*, and *Goyal*
	Ex. 1004 at 8. *Bernasconi* further teaches that patients with LVD treated with iNO are at risk of pulmonary edema. There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.[103–108] Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.[108] This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.[103] Ex. 1004 at 8.
CLAIM 4	
The method of claim 1, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide.	**All the elements of the independent claim from which this claim depends are disclosed in Bernasconi, INOMAX label, Loh, and Goyal as outlined above in Claim 1.** *Bernasconi* teaches that negative effects of iNO treatment in patients with LVD can include not only pulmonary edema, but also rapid left heart failure. There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.[103–108] Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.[108] This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.[103] Ex. 1004 at 8.

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