Calmark POC - Neo Platform

The first multiparameter POC for newborn babies – filling the gap and saving lives

Content

WP_Calmark_Neo_EN_v001

1. Executive Summary

Calmark POC Neo System is an innovative medical diagnostic device based on a unique blood filtering technology and allowing efficient, fast and easy measurement of blood glucose, lactate dehydrogenase and bilirubin levels – some of the most commonly performed blood tests in newborns.

Calmark's POC product will contribute to a reduction of newborn's morbidity and mortality as well as improve the care chain, setting a new standard for newborn's diagnosis.

Calmark Neo System fulfills a need in the market that no one has addressed so far, by specializing in tests for newborn babies. Estimates show that 20% of babies born every year would benefit from at least one of the three tests: bilirubin, glucose or LDH. Many of the newborns will benefit from more than one test.

The global POC market amounted to approximately USD 13.87 billion in 2017 and is expected to grow and reach USD 23.92 billion in 2026.[1]

Calmark aims to reduce neonatal mortality, improve treatment of neonatal diseases and decrease social-economic burden of neonatal diseases globally. As a result, the overall innovation effort is expected to take Calmark to a new level of competitiveness and growth. Most importantly, however, it will have an incredibly positive impact for the health care of millions of newborns worldwide.

2. Background

Newborn mortality is a serious global problem. According to World Health Organization (WHO) in 2017 around 2.5 million children died in the first month of life, about 1 million during the first day and close to 1 million within the next six days. Prevention of newborn mortality is one of the major societal challenges for global authorities and decision makers. It is part of the Sustainable Development Goals declared by WHO in 2015:

3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and under-5 mortality to at least as low as 25 per 1,000 live births.

Major causes of neonatal deaths are preterm birth, oxygen deficiency during birth (perinatal asphyxia), infections and birth defects among others. Some of the biomarkers of neonatal diseases are bilirubin, lactate dehydrogenase (LDH) and glucose. The abnormal concentration of these molecules in the blood can indicate hyperbilirubinemia, perinatal asphyxia or hypoglycemia and if undetected and untreated properly they can lead to irreversible brain damages or death.

Fast detection and precise measurement of the levels of these molecules in the blood could save many newborn lives, reduce the risk of serious diseases and lower the healthcare cost. However, today, in many parts of the world, detection of biomarkers for specific neonatal diseases is very difficult or even impossible. This is due to infrastructural, technical and economic limitations that result in lack of diagnostic laboratories in hospitals. Moreover, sending samples from newborns to clinical chemistry laboratories for analysis takes a lot of time, leads to delay in diagnosis, longer hospitalization time, requires a greater volume of blood and generates higher costs due to extra labor for laboratory staff.

3. Introduction of POC diagnostics

The solution to the previously mentioned problems is Point-Of-Care Tests (POCT) - medical diagnostic tests at the time and place of patient care. Unfortunately, currently there is no customized POC product for newborns that is able to measure blood bilirubin, LDH and glucose concentrations. The existing POC diagnostic technology is not suitable for testing of newborns, mainly due to differences between newborn's and adult's blood (higher percent of red blood cells and red blood cells disruption in newborns blood).

Cost analysis done in studies shows savings of between 8% and 25% of the total cost of the care chain. The studies also show that, on average, turn-around time for POC testing is 46 minutes less than for central laboratory analyzing. It is minimising transport times with clinically acceptable accuracy, even compared with the best settings. All time delay can be translated into economic impact, as each minute of waiting for a patient will result in increased need for staffing and delayed therapy.

Studies show that because POC testing delivers results 46 minutes earlier than central laboratory analysis, 20 decision pathways can be made more efficient and the chain of care improves substantially. This will lead to hospital resources being used more economically and reduces cost per patient.

Table 1: Saving related to implementation of POC testing

Setting	Cost-reduction
ED, Sweden	€148.2/patient
Pretransfer, Canada	100 CDN/patient
ED, US	20% reduction in admission rate
CCU, US	25% reduction
Paediatric ED	18% reduction
ED, France	21.7% reduction, tetanus testing
Neonatal ICU	8.5% reduction
ED, Mozambique	US$500/life year saved HIV screening
GP + ED, Uganda	76.5% reduction in screening costs HIV and syphilis
Primary care, UK	Chlamydia and gonorrhea screening 10% reduction in total costs
Patient self-measuring, UK	International normalised ratio self-monitoring in coumarin therapy, reduction of £118.7/patient/year

Source: Ulf Martin Schilling MD PhD, The economic benefits of point-of-care testing, https://www.pointofcare.abbott/shared/static-assets/other/038655A_HHE2015ArticleMartinSchilling.pdf

Filling this market gap and responding to unmet needs, Calmark has developed the first multiparameter POC for newborns – Calmark Neo System. The most innovative and unique aspect of Calmark Neo lies in the revolutionary filter technology that allows to perform independent measurement of the biomarkers glucose, LDH and bilirubin. In addition, the product is safe, simple, easy to use, efficient, accurate and cost-effective.

4. Biomarkers

4.1 Bilirubin

Bilirubin is a compound found in the blood as a result of natural hemoglobin break down reaction in the aged red blood cells. In the perinatal period, the placenta, the organ that provides the baby with oxygen and nutrition, removes bilirubin from the baby's blood. After birth, the baby will by itself take care of this process. Although, it may take some time for the baby to do this efficiently because the liver function of newborns is immature and most of the degradation of bilirubin occurs in the liver. As a result, it is normal that newborns bilirubin levels increase the first days after birth and most newborns will develop physiological jaundice. For most babies, this does not cause any problem and disappears without treatment during the first two weeks in life. However, very high levels of bilirubin, called hyperbilirubinemia, can lead to irreversible brain damage (kernicterus) and/or even death if undetected and/or untreated.[2]

Treatment of hyperbilirubinemia is easily done by exposing the newborn's skin to a particularly blue-green light (phototherapy), it is an easy efficient way to reduce high levels of bilirubin in newborns.[3] In places where phototherapy devices is not avaliable it is possible to develop affordable adjustments, such as the use of filtered sunlight. Filtered sunlight phototherapy has been shown to be safe and effective method for reducing total bilirubin.[4]

Between 3-6 days after birth the serum or plasma bilirubin level reaches its peak in most newborns and the risk of hyperbilirubinemia is the greatest at this point. Timely detection, monitoring and treatment started during this time, is an effective way to prevent most bilirubin induced morbidity.[5]

Hyperbilirubinemia remains the most common cause of morbidity in the first week of life, affecting 60-80% of newborns worldwide[5]. The Global Burden of Disease report 2016 on the health of children younger than 5 years suggest that neonatal jaundice prevention is important in the first week of life in sub-Saharan Africa and south Asia.

Worldwide data shows that at least 481,000 term/near-term neonates are affected by hyperbilirubinemia each year, with 114,000 dying and an additional 63,000 surviving with neurological impairments, although these numbers may be underestimated due to limited data.[5]

In European and North American countries, the incidence of kernicterus varies from 0.44 to 2.7 cases per 100,000 live births.[5] In Sweden the incidence of kernicterus was two cases in 2017.[6]

The African region has the highest incidence of hyperbilirubinemia per 10,000 live births at 667.8 followed by Southeast Asian, Eastern Mediterranean, Western Pacific, American and European regions at 251.3, 165.7, 9.4, 4.4 and 3.7 respectively.[7]

Between 2010 and 2015 neonatal jaundice, in the early neonatal period (i.e day 0-6), was the seventh and eight leading cause of mortality in sub-Saharan Africa and south Asia,

the ninth leading cause in Western Europe and 13th in North America. Between day 7 and 27, the late neonatal period, it was ranked seventh in south Asia and 12th in Sub-Saharan Africa, 15th most common cause of mortality in Western Europe and 21st in North America.[5]

Hyperbilirubinemia is associated with a significant health burden especially in low-income and middle-income countries.[6] Estimated average lifetime economic costs for mental retardation after kernicterus amounts to 1,014,000 USD per person.[8]

During phototherapy the normal routine is to follow up the bilirubin levels 1-3 times per day and more often when the levels are higher or increases. When the treatment is terminated, the bilirubin levels is analyzed again and when needed even once more to evaluate possible rebound effect since the level of bilirubin can increase again after the terminated phototherapy, especially for pre-term babies.[3]

About 40% of all American children need to take at least one bilirubin test during their first days of life.[5] Year 2016, 3,853,472 babies were born in the United States,[9] which equals 1,541,388 tests/year.

4.2 LDH

LDH is an enzyme present in all human cells that catalyzes the conversion of pyruvate (the end product of glycolysis, basic energy producing pathway in cell) into lactic acid (lactate) when oxygen is absent or in short supply.

When newborn babies are in lack of oxygen, for example in prior to, during or immediately after delivery, failure of one or multiple organ systems is seen. This happens because the circulation to the tissues is insufficient. It will lead to cell damage and the cell membrane leaks LDH into plasma.[10]

The elevated LDH concentration in the newborn's blood has been associated with perinatal asphyxia,[11] [12] and other neonatal diseases.[13] Asphyxia or fetal distress during delivery is a risk factor for developing hypoxic ischemic encephalopathy (HIE).[10]

In an early stage of HIE and other critical conditions, elevated LDH has a high predictive value. Elevated LDH can be seen before diagnostic symptoms has developed since the LDH is increasing in such early stage, it also correlates with the severity of the disease.[10]

Perinatal asphyxia accounts for an estimated 900,000 deaths each year in the world and is one of the primary causes of early neonatal mortality.[14] In low-income countries 23% of all neonatal deaths occurred due to birth asphyxia.[15] South-central Asian countries stands for the highest numbers of neonatal deaths each year and the countries in this region, except some, have very little progress in reducing deaths in the last 10-15 years.[15]

Estimated average lifetime economic costs for mental retardation after for Cerebral palsy after for example asphyxia amounts to 921,000 USD per person.[8]

There is evidence that therapeutic hypothermia as treatment is beneficial for term and late preterm babies with HIE .[16] Therapeutic hypothermia means lowering the newborn's body temperature to 33–35 degrees for three days. This can be done by cooling the whole body or only the head. After finished treatment, the body temperature is slowly raised to normal again.[3]

It's been shown that cooling reduces mortality without increasing major disability in those who survives. If moderate to severe HIE is identified before six hours of age in term and late preterm infants, hypothermia should be instituted.[16]

Using POC-test to measure LDH could be a valuable support in the clinical assessment of newborns during their first week of life.[13]

4.3 Glucose

Glucose is a molecule that function as a main source of energy for the cells. Proper blood glucose level is especially important for brain activity. About 20% of newborns present low blood glucose level (hypoglycemia) during the first days of life. If left untreated it can be harmful. [17] [18]

The newborn baby's brain stands for approximately 50% of total glucose consumption. During the first days in life it's calculated that about 70% of the energy supply comes from glucose.[19]

Hypoglycemia is common among neonates and can lead to neurodevelopmental disorders, visual and hearing impairments, and disorders of the central nervous system, among other morbidities.

The key substrate for energy production during the perinatal, neonatal and postnatal period is glucose. In the perinatal period, the mother supplies the baby with glucose continuous. When the baby is born the glucose delivery from the mother is disrupted and a transitional phase of physiological low normal blood glucose levels occur and around 72 h after birth the levels are normalized. Important is that any pathological state which affect glucose production or utilization will lead to hypoglycemia.[20]

There are some groups of newborns that are at risk of developing hypoglycemia, for those it is important to monitor blood glucose in order to decrease the risk of neurological sequelae. These groups are among others; infants that are small or large for gestational age, infants of diabetic mothers, moderate to late preterm infants, perinatal acidosis, hypothermia, suspected/confirmed early sepsis.[21] Depending on the severeness of the hypoglycemia blood glucose levels are checked with different intervals and most often repeatedly.[22]

The risk of developing neurodevelopmental disorders increases with the time that the baby is exposed to hypoglycemia, therefore it's important to detect low blood glucose levels and initiate treatment as soon as possible.[19] When confirming hypoglycemia, the infants are managed with increased breast feeding, being given supplemental infant formula or intravenous dextrose. Research also shows that dextrose gel is a simple and inexpensive treatment which can be administered directly to the buccal mucosa for rapid correction of hypoglycemia and that this should be first line treatment.[23]

Available blood monitors on the market are well developed for adults but not optimized for the neonatal blood glucose range. High hematocrit levels in the newborn's blood often leads to incorrect readings in the available blood monitors.[16]

To decrease morbidity and mortality it's important to enable rapid diagnosis and initiate treatment when needed. Many low-resource health care centers do not have access to sophisticated laboratories, at these places POC diagnostic provides a great solution and enables the health care staff to detect illness.[16]

5. References

1. Global Point-of-Care Testing Market - Focus on Application, Market Share, Product Mapping and Country - Analysis and Forecast (2017-2026)
2. Govaert, P., Lequin, M., Swarte, R., Robben. S., De Coo, R., Weisglas-Kuperus, N., ... Barkovich, J. (2003). Changes in globus pallidus with (pre) term kernicterus. *Pediatrics. 112*(6), 1256–1263. DOI: https://pediatrics.aappublications.org/content/112/6/1256.long
3. Svenska Barnläkarföreningens Neonatalsektion. (2008). *Neonatal Hyperbilirubinemi.* (1). Retrieved from http://www.blf.net/neonatol/images/pdf/Vpm_bili.pdf
4. Slusher, T.M., Olusanya, B.O., Vreman, H.J., Brearley, A.M., Vaucher, Y.E., Lund, T.C., ... Stevenson, D.K. (2015). A Randomized Trial of Phototherapy with Filtered Sunlight in African Neonates. *The New Enlgand Journal of Medicine, 2015*(373), 1115-1124. DOI: 10.1056/NEJMoa1501074
5. Olusanya, B.O., Teeple, S., & Kassebaum, N.J. (2018). The Contribution of Neonatal Jaundice to Global Child Mortality: Findings From the GBD 2016 Study. *Pediatrics, 141*(2), 1-5. DOI: 10.1542/peds.2017-1471
6. Swedish Neonatal Quality Register. (2017). *Årsrapport 2017*. Retrieved from https://www.medscinet.com/pnq/Uploads/SNQ%20Årsrapport%202017_180909.pdf
7. Slusher, T.M., Zamora, T.G., Appiah, D., Stanke, J.U., Strand, M.A., Lee, B.W., ... Olusanya, B.O. (2017). Burden of severe neonatal jaundice: a systematic review and meta-analysis. *BMJ Paediatrics Open*, 1(1), 1-10. DOI:10.1136/bmjpo-2017-000105
8. Centers fo Disease Control and Prevention. (2004). *Economic Costs Associated with Mental Retardation, Cerebral Palsy, Hearing Loss, and Vision Impairment,* (53 03). Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5303a4.htm
9. Centers for Disease Control and Prevention. (2018). *Births: Provisional Data for 2017.* (004). Retrieved from https://www.cdc.gov/nchs/data/vsrr/report004.pdf
10. Karlsson, M., Wiberg-Itzel, E., Chakkarapani, E., Blennow, M., Winbladh, B., & Thoresen, M. (2010). Lactate dehydro-genase predicts hypoxic ischaemic encephalopathy in newborn infants: a preliminary study. *Acta Paediatrica, 99*(8),1139-44). DOI.org/10.1111/j.1651-2227.2010.01802.x
11. Thoresen, M., Liu, X., Jary, S., Brown, E., Sabir, H., Stone, J., ... Karlsson, M. (2012). Lactate dehydrogenase in hypothermia-treated newborn infants with hypoxic-ischaemic encephalopathy. *Acta Paediatrica, 101*(10). 1038–1044. DOI: 10.1111/j.1651-2227.2012.02778.x
12. Yum, S.K., Moon, C-J., Youn. Y.A, Sung, I.K., Changes in lactate dehydrogenase are associated with central gray matter lesions in newborns with hypoxic-ischemic encephalopathy. (2017). *The Journal of Maternal-Fetal & Neonatal Meidcine, 30*(10). 1177–1181. DOI: 10.1080/14767058.2016.1208745
13. Karlsson,M., Dung,K.T., Thi, T.L., Borgström, E., Jonstam, K., Kasström, L., & Winbladh, B. (2012). Lactate dehydrogenase as an indicator of severe illness in neonatal intensive care patients: a longitudinal cohort study. *Acta Paediatrica, 101*(12), 1225–1231. DOI: 10.1111/apa.12014
14. Lawn, J.E., Manandhar A, Haws, R.A., & Darmstadt, G.L. (2007). Reducing one million child deaths from birth asphyxia: a survey of health systems gaps and priorities. *Healt Reserach Policy and Systems, 5*(4), 1-10. DOI.org/10.1186/1478-4505-5-4
15. Lawn, J.E., Cousens, S., Zupan. J. (2005). 4 million neonatal deaths: When? Where? Why? *Lancet, 365*(9462), 891–900. https:// DOI.org/10.1016/S0140-6736(05)71048-5
16. Jacobs, S.E., Berg, M., Hunt, R., Tarnow-Mordi, WO., Inder, T.E., Davis, P.G. (2013). Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database of Systematic Reviews, 2013*(1). DOI 10.1002/14651858.CD003311.pub3
17. McKinlay, C.J.D., Alsweiler. J,M., Ansell, J.M., Ansitce, N.S., Chase, G.J., Gamle, G.D., ... Harding, J.E. (2015). CHYLD Study Group. Neonatal glycemia and neuro-developmental outcomes at 2 years. *New England Journal of Medicine, 373*(16), 1507–1518. DOI: 10.1056/NEJMoa1504909

18. McKinlay, C.J.D., Alsweiler, J.M., Anstice, N.S., Burakevych, N., Chakraborty, A., Chase, J.G. (2017). Children with hypoglycemia and their later develop-ment (CHYLD) study team. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. *JAMA Pediatrics, 171*(10),972–983. DOI:10.1001/jamapediatrics.2017.1579

19. Wackernagel, D., Edstedt-Bonamy, A-K., Gustafsson, A., Remis, A., Hansen-Pupp, I., Ahlsson, F., ... Domellöf,M. (2017). *Nationellt vårdprogram: Neonatal hypoglykemi hos nyfödda med gestationsålder ≥35v.* Retrieved from http://neo.barnlakarforeningen.se/wp-content/uploads/sites/14/2017/12/Nationellt_postnatal_hypoglykemi_vårdprogram_final.pdf

20. Güemes, M., Rahman, S.A., & Hussain, K. (2016). What is a normal blood glucose? *Archives of Disease in Childhood, 101*(6),569-574. DOI:10.1136/archdischild-2015-308336

21. British Association of Perinatal Medicine. (2017). *Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant. Framework for Practice.* Retrieved from https://www.bapm.org/sites/default/files/files/Identification%20and%20Management%20of%20Neonatal%20Hypoglycaemia%20in%20the%20%20full%20term%20infant%20-%20A%20Framework%20for%20Practice%20revised%20Oct%202017.pdf

22. Stark. J., Simma, B. & Blassing-Ezeh, A. (2019). Incidence of hypoglycemia in newborns infants identified as at risk. *The journal of Maternal-Fetal & Neonatal Medicine, 27*, 1-6. DOI.org/10.1080/14767058.2019.1568985

23. Weston, P.J., Harris, D.L., Battin, M., Brown, J., Hegarty, J.E., & Harding, J.E. (2016). Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *Cochrane Database of Systematic Reviews, 2016*(5). DOI 10.1002/14651858.CD011027.pub2.

Office: Stockholm
Calmark Sweden AB
Greenhouse labs
Teknikringen 38A
S-114 28 Stockholm

Phone
+46 70 214 98 93
Email
info@calmark.se
Website
www.calmark.se

Residence: Karlstad
Calmark Sweden AB
Sommargatan 101A
S-656 37 Karlstad

WP_Calmark_Neo_EN_v001