Donor Human Milk for Low-Birthweight Infants: Effectiveness and Policies

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Overview

For this report, Center for Evidence-based Policy (Center) researchers examined the use of donor human milk for extremely and very premature (i.e., less than 28 and 28-32 weeks of gestation, respectively) and low (i.e., less than 2,500 grams) or very low birthweight (i.e., less than 1,500 grams) infants. The efficacy and effectiveness of donor human milk for these infants were compared to preterm formula for infants who did not have maternal breast milk to meet all or some of their nutritional needs for the following outcomes: incidence of necrotizing enterocolitis; neonatal intensive care unit (NICU) length of stay; retinopathy of prematurity; mode of feeding after hospital discharge; cost; and cost-effectiveness. Center researchers also searched for clinical practice guidelines and private and public payer policies on this topic.

Key Findings

Evidence Findings

Center researchers rated the strength of the evidence for the following critical outcomes using a modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach:

- Donor human milk could help to prevent necrotizing enterocolitis (*moderate strength of evidence*), and increase maternal breastfeeding at NICU discharge (*low strength of evidence*), but could also result in slower short-term growth (*low strength of evidence*).
- There is evidence that the use of donor human milk does not significantly change neurodevelopmental outcomes (*moderate strength of evidence*), the risk of death (*low strength of evidence*), or retinopathy of prematurity (*low strength of evidence)*.
- There were no eligible studies to determine the effect of donor human milk on NICU length of stay, costs, or cost-effectiveness.

Guidelines and Payer Policies

- No formal clinical practice guidelines on the use of donor human milk were identified, although two American Academy of Pediatrics (AAP) position papers recommend the use of donor human milk for preterm and low birthweight infants.
- Selected private payer policies do not provide publicly available coverage information or do not cover donor human milk. A few state Medicaid agencies cover donor human milk in specific situations such as for significant prematurity and low or very low birthweight infants.

Clinical Background

Breast milk is the preferred nutrition for infants as recommended by the American Academy of Pediatrics (2012). The AAP recommends exclusive breastfeeding for the first six months of life and continued breastfeeding for the second six months along with the gradual introduction of solid foods (AAP, 2012). This recommendation is based on data that infants who are exclusively breastfed for four to six months have a significantly lower risk of developing respiratory infections, otitis media, or diarrheal disease (AAP, 2012). Breastfeeding also appears to be

protective against the development of some allergic and autoimmune diseases, such as asthma, atopic dermatitis among infants of susceptible families, and diabetes (AAP, 2012). Infants who are breastfed have a lower risk of developing leukemia and dying of sudden infant death syndrome (AAP, 2012). Breast milk feeding could have even more substantial benefits for preterm infants and is recommended by the AAP for infants born at very low birthweight in particular (AAP, 2012, 2017). Despite these benefits, mothers of preterm infants often do not have sufficient breast milk to feed their infants, for whom early enteral nutrition has been shown to improve outcomes such as necrotizing enterocolitis (NEC), sepsis and meningitis, and early growth compared to parenteral nutrition (Quigley & McGuire, 2014; Underwood, 2013). When maternal breast milk is not available or available in sufficient quantity, the recommended options for preterm infant enteral feeding are fortified preterm infant formula or pasteurized donor human milk (Underwood, 2013).

Fortification of mother's milk or donor milk, and also of infant formula, is recommended to maximize preterm infant growth and development (American Academy of Pediatrics, 2012, 2017; Brown, Embleton, Harding, & McGuire, 2016; Underwood, 2013). Both bovine-derived and human-derived human milk fortifiers are available, but there are few data to support the use of one over the other (Underwood, 2013). A 2017 American Academy of Pediatrics position statement on the use of donor milk notes that both types of fortifiers have been shown to support appropriate growth when added to donor milk (American Academy of Pediatrics, 2017). However, there are questions about whether human milk and fortifiers derived from human milk are protective against necrotizing enterocolitis or whether components of bovine milk actually increase the chance of an infant developing the conditions (Underwood, 2013). Although beyond the scope of this main report, Center researchers also completed a supplemental evidence review on the outcomes associated with bovine- versus human-derived human milk fortifiers (King, Dion, Holup, & Harrod, 2017).

There are currently more than 20 nonprofit human milk banks in the U.S. and Canada that are part of the Human Milk Banking Association of North America (HMBANA, www.hmbana.org), and several unaffiliated commercial milk banks (AAP, 2017). HMBANA member milk banks adhere to rigorous safety standards for the donation, collection, processing, storage, and distribution of pasteurized donor human milk and undergo yearly accreditation review (American Academy of Pediatrics, 2012; Human Milk Banking Association of North America, n.d.). There is an insufficient national supply of donor human milk from milk banks to completely replace the use of infant formula, and HMBANA and the AAP both recommend prioritization of donor milk for infants who are at the highest risk when maternal milk is not available (AAP, 2017). This report reviews the evidence on the effectiveness of donor human milk compared to infant formula, as well as clinical practice guidelines and private and public payer policies regarding its use.

Prevalence

Approximately 8% of U.S. infants are born at low birthweight and about 1.4% are born at very low birthweight (Martin, Hamilton, Osterman, Driscoll, & Mathews, 2017). In New York, the proportion of low birthweight infants born in 2015 was 7.8% overall (6.4% non-Hispanic white, 12.0% non-Hispanic black, and 7.8% Hispanic) (Martin et al., 2017). The same racial and ethnic patterns apply to very low birthweight infants born in New York during 2015 (1.3% overall; 1.0% non-Hispanic white, 2.7% non-Hispanic black, and 1.4% Hispanic) (Martin et al., 2017).

PICO

This evidence review is guided by the following PICO statement:

Populations: Very low (i.e., less than 1,500 grams) and low birthweight infants (i.e., less than 2,500 grams) (usually corresponding to gestational age less than 32 weeks)

Intervention: Donor human milk (from an accredited milk bank)

Comparator: Infant formula

Efficacy and Effectiveness Outcomes: Incidence of NEC; NICU length of stay; retinopathy of prematurity; mode of feeding after hospital discharge; cost or cost-effectiveness

Methods

Center researchers searched Center core evidence sources and MEDLINE (Ovid) for systematic reviews (with or without meta-analysis) and technology assessments of donor human milk compared to infant formula for low birthweight or premature infants published within the last 10 years. To ensure that the most recent data were included, Center researchers also searched MEDLINE (Ovid) through March 21, 2017, for systematic reviews, individual randomized controlled trials, observational studies, and clinical practice guidelines on the use of donor human milk compared to infant formula for low birthweight or premature infants. We reviewed individual studies that were published after the search dates of the most recent systematic reviews of good or fair methodological quality that were included in this report. Center researchers evaluated the methodological quality of systematic reviews, individual studies, and clinical practice guidelines in this report using the quality assessment tools included with the New York State Department of Health dossier process (available on the New York State Department of Health website) and included systematic reviews, individual studies, and clinical practice guidelines of good and fair methodological quality. Search strategies and details on quality assessment tools are in Appendix A. Center researchers searched for donor human milk coverage policies from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physician's Health Plan, Centers for Medicare and Medicaid Services, Cigna, Emblem Health, Empire Blue Cross Blue Shield (BCBS), Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and

nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, WA). See Appendix A for a full list of payers searched.

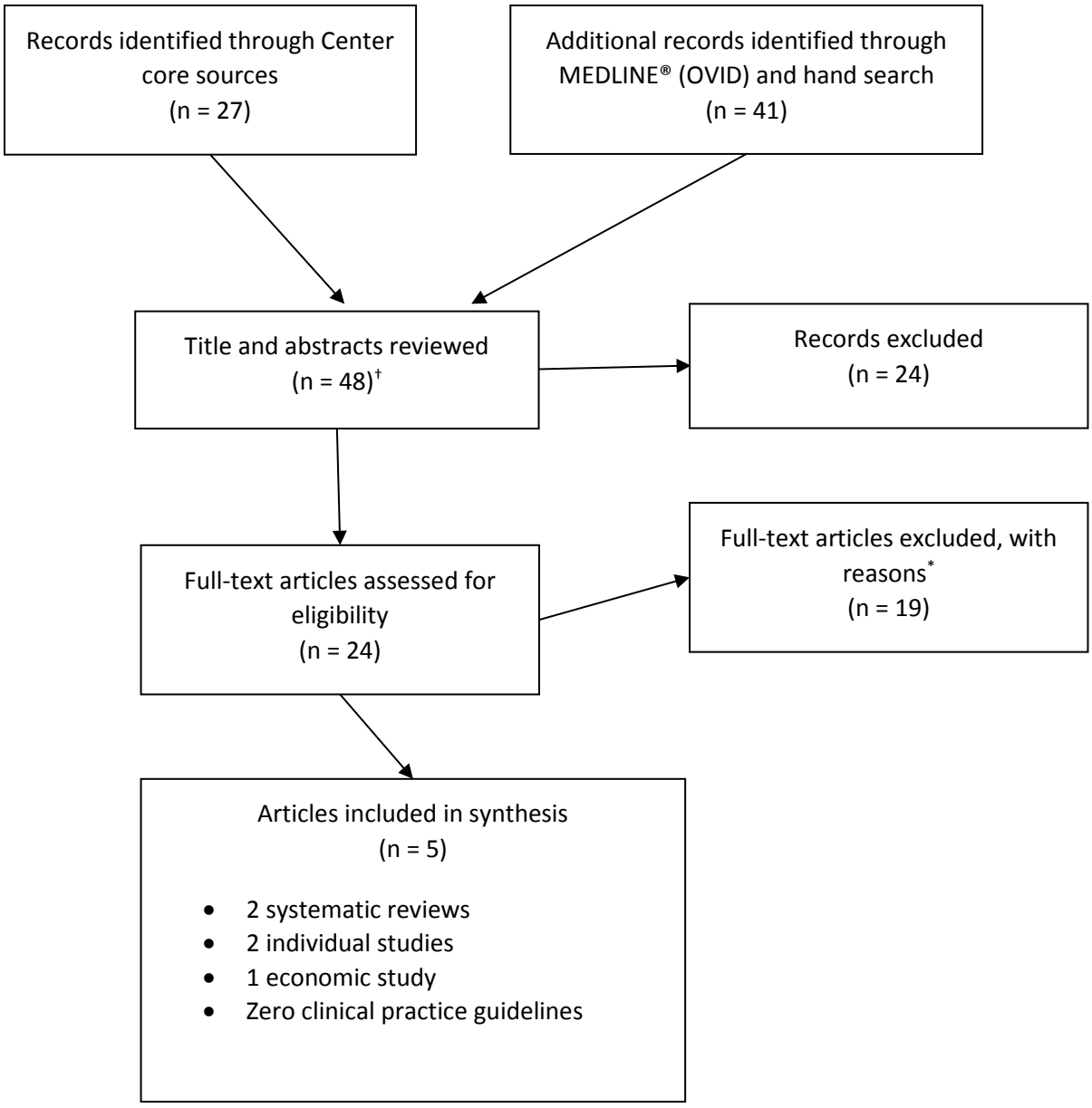
Center researchers excluded systematic reviews if all of the included studies were also summarized by a more comprehensive systematic review, a systematic review of a higher methodological quality, and/or a more recently published systematic review. All included studies were required to be published in English. In addition, only patient-important outcomes have relevance for the New York State Department of Health. Exclusion criteria were selected before review of the studies, and study methods were assessed before the review of outcomes to eliminate bias. See Appendix A for a full description of methods.

Evidence Review

Findings

From a search of Center core evidence sources, researchers identified six recent systematic reviews and seven individual studies that met inclusion criteria and were relevant to the effectiveness and/or harms of donor human milk for low birthweight and premature infants. The MEDLINE (Ovid) database search identified 41 studies, some of which were also identified through the Center search. Two additional studies were identified from a hand search of the bibliographies of studies identified by the MEDLINE (Ovid) and Center core evidence searches. Figure 1 shows the number of articles identified by each search and the total number of studies included in this evidence synthesis. The search strategies and list of studies reviewed in full with reasons for exclusion are included in Appendices A and B, respectively.

Figure 1. Study Flow Diagram



*Note. †Some duplication of articles between Center core source search results and MEDLINE® (Ovid) search results. *Exclusion rationale provided in Appendix B.*

Overview of Evidence Sources

Center researchers summarized the evidence as reported by the included systematic reviews, and did not review the individual studies within the systematic reviews unless necessary for clarification of information reported in the systematic review. In total, 19 individual studies, including both RCTs and observational studies, were identified across the two included systematic reviews. Table 1 provides an overview of findings from the systematic reviews and two additional, more recently published, RCTs.

Systematic Reviews

Quigley and McGuire (2014)

Center researchers assessed the Quigley and McGuire Cochrane review and meta-analysis as having good methodological quality. The review included nine RCTs published between 1976 and 2013 (Quigley & McGuire, 2014). The meta-analysis evaluated the benefits and harms of donor human milk versus formula for feeding preterm and low birthweight infants (Quigley & McGuire, 2014). Outcomes evaluated were growth parameters, neurodevelopment, mortality, NEC, invastive infection, and feeding intolerance (Quigley & McGuire, 2014). Only two of the included studies, published in 2005 and 2013, evaluated fortified donor human milk compared to fortified preterm infant formula, both of which represent the current state of practice in neonatology. The review conducted prespecified subgroup analysis of these two studies. This review used Cochrane's standard methodology, including an extensive search strategy, with no limits on date or language of publication (Quigley & McGuire, 2014).

Williams, Nair, Simpson, and Embleton (2016)

Williams and colleagues conducted a systematic review and meta-analysis of the use of donor human milk and its association with maternal breastfeeding rates that Center researchers assessed as having fair methodological quality. They included 10 observational studies (four from abstracts only) that were before-after type studies in which donor human milk was introduced to an NICU care setting at a particuar point in time (Williams et al., 2016). The authors used an extensive search strategy and did not exclude studies on the basis of publication date or language (Williams et al., 2016). The authors critically appraised the studies for methodological quality, and they assessed two as being low quality, seven as moderate quality, and one as high quality (Williams et al., 2016). Although there were not any RCTs in this review, the authors conducted a meta-analysis. No quantitative assesment of statistical heterogeneity was provided.

Individual Studies

Corpeleijn et al. (2016)

Center researchers assessed this multicenter RCT as having fair methodological quality. The RCT was conducted in the Netherlands and enrolled 377 preterm infants with an average gestational

age of 28 weeks and birthweight of slightly more than one kilogram (Corpeleijn et al., 2016). Infants were randomized to receive either fortified donor human milk or preterm formula if their mother did not have sufficient milk to meet their needs for the first 10 days of life (Corpeleijn et al., 2016). Outcomes were assessed during the first 60 days of life (Corpeleijn et al., 2016). The primary outcome was a composite of NEC, serious infection (sepsis or menningitis), or all-cause mortality between 72 hours and 60 days of life (Corpeleijn et al., 2016). Secondary outcomes were retinopathy of prematurity, brochopulmonary dysplasia, intraventricular hemorrhage, and persistent ductus arteriosus (Corpeleijn et al., 2016). There were high losses to follow-up in both groups (24.5% in the donor milk group and 27.5% in the formula group), and infants in both groups received more than 80% of their enteral nutrition from their own mother's milk (89.1% and 84.5%). The study was funded by an infant formula and fortifier manufacturer (Corpeleijn et al., 2016).

O'Connor et al. (2016)
This multicenter RCT was assessed as having good methodological quality by Center researchers. The RCT was conducted in Canada and enrolled 363 preterm infants with an average gestational age of 27.7 weeks and birthweight of just under one kilogram (O'Connor et al., 2016). Infants were randomized to receive either fortified donor human milk or preterm formula, when ther own mother's milk was not available, for their first 90 days of life or until discharge (O'Connor et al., 2016). The primary outcome was the cognitive composite score on the Bayley-III instrument at 18 months' corrected age (O'Connor et al., 2016). Secondary outcomes were mortality, and major morbidity (late-onset sepsis, NEC, chronic lung disease, retinopathy of prematurity, and severe brain injury) (O'Connor et al., 2016).

Assad et al. (2016)
This retrospective observational study was assessed as having fair methodological quality by Center researchers. It was conducted in a single U.S. community hospital with a level III NICU (Assad, Elliott, & Abraham, 2016). The primary study objective was to assess whether there were differences in length of stay, and feeding intolerance among 293 premature infants divided into four types of feeding groups: infants fed donor or maternal milk with human-derived fortifier (Group H); donor plus maternal milk with bovine-derived fortifier (Group B); mixed combinations of human milk with bovine-derived fortifier and formula (Group M); and preterm infant formula (Group F) (Assad et al., 2016). Secondary outcomes included development of necrotizing enterocolitis, and costs of care. Other outcomes reported included development of retinopathy of prematurity, sepsis, and bronchopulmonary dysplasia (Assad et al., 2016).

Quality and Limitations

Of the two included systematic reviews, Center researchers rated one as having good methodological quality (Quigley & McGuire, 2014) and the other as having fair methodological quality (Williams et al., 2016). Center researchers assessed the methodological quality of

included systematic reviews and meta-analyses and not the individual studies included within them. The individual studies included in the systematic reviews were assessed by the respective review authors. References to individual study quality are taken directly from the systematic reviews and are not the assessments of Center researchers. However, when appropriate, Center researchers have made comments about potential biases and the applicability of the individual studies included in the systematic reviews.

Center researchers assessed the methodological quality of the studies not included in the systematic reviews using standard study design-specific quality assessment methods (see Appendix A for further details). Of the three additional included studies, two were RCTs (Corpeleijn et al., 2016; O'Connor et al., 2016) and one was a retrospective observational study (Assad et al., 2016). Center researchers rated one as having good methodological quality (O'Connor et al., 2016) and the other two as fair (Assad et al., 2016; Corpeleijn et al., 2016). An additional four systematic reviews, seven individual studies, and one economic modeling study were rated as having poor methodological quality and are excluded from this review (Boyd, Quigley, & Brocklehurst, 2007; Cacho, Parker, & Neu, 2017; Chowning et al., 2016; Herrmann & Carroll, 2014; Kantorowska et al., 2016; Lechner & Vohr, 2017; Mahon, Claxton, & Wood, 2016; Manzoni et al., 2013; Parker, Burnham, Mao, Philipp, & Merewood, 2016; Verd et al., 2015; Zhou, Shukla, John, & Chen, 2015).

There are several common characteristics and potential biases across the included studies. The majority of the studies were conducted in the U.S. and Europe. All but two of the nine RCTs in the Quigley and McGuire (2014) systematic review were conducted before the year 2000. Only these two RCTs conducted after 2000 compared fortified donor human milk and preterm formula, thus limiting the generalizability of most of the included RCTs to current practice in the U.S. health care system. The only evidence that addressed economic outcomes and length of stay was a single retrospective cohort study (Assad et al., 2016). Most potential economic studies identified in our search were excluded because of differences between this report's PICO and their interventions and comparators, as well as inability to extract data from some of these publications. Data about maternal breastfeeding rates after NICU discharge were derived from a systematic review of observational studies by Williams et al. (2016). These types of before-after studies are limited because they do not control for potential confounders that could influence breastfeeding practices such as lactation support for mothers, which could have been instituted concurrently with the availability of donor human milk. The authors assessed infant neurodevelopmental outcomes using the Bayley-III instrument which, although validated and widely used, is a screening instrument to assess the risk of developmental delay rather than a diagnostic measure of actual delay or disability. The studies generally excluded infants who had congenital anomalies, were small for gestational age, or had other major health conditions that could also affect studied outcomes.

Outcome #1 Incidence of Necrotizing Enterocolitis

Systematic Reviews

The Cochrane systematic review by Quigley and McGuire (2014) found that infant formula increased the risk of NEC among significantly low birthweight infants compared with donor human milk (relative risk [RR], 2.77; 95% CI, 1.40 to 5.46). However, seven of the included RCTs did not use fortified feeding preparations as is now common and recommended practice. Only two of the nine RCTs were conducted after 2005 and used fortified donor milk and fortified preterm formula as the comparators. Among these two RCTs, the risk was attenuated (RR, 2.40; 95% CI, 0.98 to 5.87) and was then only marginally statistically significant. Statistical heterogeneity was low for estimates of effect summarized in Table 1.

Individual Studies

Two additional RCTs have been published since the Quigley and McGuire (2014) systematic review that reported on the NEC outcome (Corpeleijn et al., 2016; O'Connor et al., 2016). In a fair methodological quality multicenter RCT conducted in the Netherlands, Corpeleijn et al. (2016) reported an adjusted hazard ratio for NEC of 0.98 (95% CI, 0.64 to 2.05) for fortified donor milk compared with fortified preterm formula for infants whose mothers did not have sufficient breast milk to meet all feeding requirements. However, both groups received most of their oral intake from mother's milk (84.5% for the donor human milk group and 89.1% for the formula group) and the intervention period lasted 10 days, although outcomes were assessed during the first 60 days.

A good methodological quality multicenter RCT performed in Canada by O'Connor et al. (2016) was conducted primarily to assess the neurobehavioral outcomes associated with the use of fortified donor human milk compared with fortified preterm formula given in the first 90 days of life, but reported on NEC as a secondary outcome. The incidence of NEC was statistically significantly lower in the donor human milk group (3.9% vs. 11.0%, risk difference, -7.1; 95% CI, -12.5 to -1.8]; p = 0.01).

The retrospective cohort study by Assad and colleagues reported a 1.10% rate of necrotizing enterocolitis among infants who received human milk (maternal and/or donor, with human-milk derived fortifier) (Assad et al., 2016). They did not report rates of necrotizing enterocolitis independently for each of the other groups in this study, but did give a rate of 10% for the combined bovine-based fortifier and mixed feeding groups (Assad et al., 2016). This outcome reporting is limited by the manner in which the authors did not report all four analysis groups separately.

Outcome #2 *NICU Length of Stay*

Systematic Reviews

None of the included systematic reviews reported on the outcome of NICU length of stay.

Individual Studies

The retrospective cohort study by Assad and colleagues (Assad et al., 2016) provided relative rather than absolute length of stay data for four groups of premature infants who received either donor plus maternal with human-derived fortifier (Group H); donor plus maternal with bovine-derived fortifier (Group B); mixed combinations of human milk with bovine-derived fortifier and formula (Group M); and preterm infant formula (Group F). Compared to Group H, the length of stay was longest for Group M (22.9 days longer), and a linear regression analysis controlled for gestational age was statistically significant for this comparison ($p<0.04$). Group B length of stay was 4.5 days longer and Group F was 7.26 days longer (Assad et al., 2016).

Outcome #3 Retinopathy of Prematurity

Systematic Reviews

No included systematic reviews reported retinopathy of prematurity as an outcome.

Individual Studies

The RCT by Corpeleijn et al. (2016) reported on retinopathy of prematurity (all stages) as a secondary outcome. In the donor human milk group, retinopathy was reported in 11.9% of infants; in the preterm formula group it was reported in 7.7% (OR, 1.77; 95% CI, 0.76 to 4.13).

The RCT by O'Connor et al. (2016) reported severe retinopathy as a secondary outcome. They did not find a significant difference between the donor milk and formula groups (3.9% vs. 4.4%, risk difference, -0.05; 95% CI, -4.6 to 3.6; $p = 0.80$) (O'Connor et al., 2016).

Assad and colleagues reported that rates of retinopathy of prematurity varied statistically significantly among feeding groups (Assad et al., 2016). The rate of retinopathy of prematurity was highest among infants exposed to mixed feeding (Group M: 40%), and equivalent among infants fed either formula (Group F) or human milk with human-derived fortifier (Group H) (14% in each group) (Assad et al., 2016). The group fed human milk with a bovine-derived fortifier (Group B) had a 30% rate of retinopathy of prematurity (Assad et al., 2016).

Outcome #4 Mode of Feeding After Hospital Discharge

Systematic Reviews

Williams and colleagues conducted a fair-quality systematic review including 10 non-randomized studies to determine whether the use of donor human milk had any effect on partial or exclusive maternal breast milk feeding of the infant upon hospital discharge (Williams et al., 2016). These studies were uncontrolled before-after studies comparing breastfeeding at discharge before and after the introduction of donor human milk into a hospital (Williams et al., 2016). Williams et al. (2016) reported that the introduction of donor human milk was associated with a 19% increase in the rate of any maternal breast feeding compared to the pre-introduction time period in the four studies that reported this outcome (Williams et al., 2016). The authors

did not find a statistically significant difference in the rate of exclusive breast feeding when they combined the two studies that reported this outcome (RR, 1.12; 95% CI, 0.91 to 1.40) (Williams et al., 2016). The systematic review authors rated most of the included studies as moderate quality. However, if these studies had been assessed with the Center's instruments, they would all have been rated as having poor methodological quality. We excluded four recently published studies with similar designs identified in the MEDLINE (OVID) search because of their poor methodological quality. These designs do not adequately control for confounding factors such as temporal changes in care in the before and after time periods.

Outcome #5 Cost

Individual Studies

No included systematic reviews reported economic outcomes. One retrospective cohort study, of fair methodological quality, by Assad and colleagues (Assad et al., 2016) reported on total costs of hospitalization (hospital and physician charges) and costs of physician services (with cost of human-derived fortifier added) for groups of premature infants who received either donor plus maternal with human-derived fortifier (Group H); donor plus maternal with bovine-derived fortifier (Group B); mixed combinations of human milk with bovine-derived fortifier and formula (Group M); and preterm infant formula (Group F). The authors reported that Group H had lowest total costs of hospitalization compared to the highest cost in Group M ($237,647 vs. $344, 618) (Assad et al., 2016). The difference was statistically significant in a linear regression analysis adjusted for gestational age (Assad et al., 2016). The analysis of physician charges followed a similar pattern (Assad et al., 2016).

Outcome #6 Other Reported Outcomes

Although the predefined outcomes for this review are listed in the PICO and detailed in outcomes #1 through #5 above, Center researchers observed several other reported outcomes in the included systematic reviews and individual studies that are worth noting.

Mortality

All-cause mortality was higher across the two RCTs of fortified preterm formula compared to fortified donor milk in the Quigley and McGuire (2014) systematic review, but the difference was not statistically different (RR, 1.53; 95% CI, 0.42 to 5.51) (Quigley & McGuire, 2014). This finding is similar to the risk difference in death between the donor milk and formula groups in the O'Connor RCT (9.4% vs. 11.0%; adjusted risk difference -1.0; 95% CI,-9.7 to 7.6; p = 0.82) (O'Connor et al., 2016).

Neurodevelopment

The primary outcome of interest in the O'Connor RCT described above was the Bayley-III composite score at 18 months of age (O'Connor et al., 2016). There were no differences between the fortified donor human milk and preterm infant formula groups (O'Connor et al., 2016). There were also no differences in the language and motor subscales of the Bayley-III, which were

reported as secondary outcomes (O'Connor et al., 2016). The Quigley and McGuire (2014) systematic review did not report neurodevelopmental outcomes for studies comparing fortified donor human milk and preterm infant formula, and did not note any differences in either neurological or developmental outcomes of infants in the general meta-analysis of donor human milk versus formula (Quigley & McGuire, 2014).

Growth

Particularly among studies conducted using preterm rather than term formula, the Quigley and McGuire (2014) systematic review found significant differences in short-term weight gain (expressed in grams per kilogram per day, or g/kg/d) favoring the formula group over the donor human milk group (term formula vs. donor human milk: mean difference 1.74 g/kg/d; 95% CI, 0.96 to 2.53). For preterm formula vs. donor human milk the mean difference was 3.71 g/kg/d; 95% CI, 2.79 to 4.63 (Quigley & McGuire, 2014). For any formula vs. any donor human milk, the mean difference was 2.58 g/kg/d; 95% CI, 1.98 to 3.17 (Quigley & McGuire, 2014). When the analysis was restricted to the two RCTs that compared fortified feeding with preterm formula versus fortified donor human milk, the results for short-term weight gain were similar, favoring formula (mean difference 2.80 g/kg/d; 95% CI, 1.20 to 4.39) (Quigley & McGuire, 2014). Patterns were similar for other short-term growth parameters such as length and head circumference. The only studies that examined longer term growth used preterm infant formula, but did not use fortified donor human milk. Nevertheless, they found no significant differences in growth at 9 and 18 months of corrected age and at 7.5 to 8 years of age (Quigley & McGuire, 2014).

Cost-Effectiveness

Center researchers identified no eligible systematic reviews or individual studies that conducted a formal cost-effectiveness analysis on the use of donor human milk for the feeding of low birthweight infants. Costs of donor milk compared to other alternatives were reported in the retrospective cohort study by Assad and colleagues (Assad et al., 2016) and are described above and in Table 1.

Summary of the Evidence

The included systematic reviews and s are summarized in Table 1. Individual study methodological quality discussed in the context of included systematic reviews is taken directly from the review authors and is not the Center's original assessment of the work.

Table 1. Overview of Included Studies

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Systematic Reviews (with meta-analyses)			
Quigley and McGuire (2014) Search Dates Inception to March 2014 Included Study Designs Randomized and quasi-randomized studies were eligible for inclusion; only RCTs were included Methodological Quality Good	k = 9 RCTs total n = 1,070 infants Studies generally included infants born at <32 weeks (i.e., very preterm birth) gestational age and/or <1,800 g birthweight Intervention duration from studies in SR: Cristofalo (2013): PIF vs. MM or DHM with human milk-based fortifier for <=91d. Davies (1977): unfortified term formula vs. DHM for <=2m. Gross (1983): unfortified term formula vs. DHM until infant reached 1800g or was withdrawn from study Lucas (1984a and 1984b): PIF vs. DHM (1984a used	Groups DHM and IF, either as sole diet or as a supplement to mother's own milk Outcomes (IF vs. DHM) NEC (all studies): RR, 2.77; 95% CI, 1.40 to 5.46, I^2 = 0% NEC (fortified IF vs. fortified DHM): RR, 2.4; 95% CI, 0.98 to 5.87; I^2 = 8% All-cause mortality (all studies, k = 4): RR, 1.33; 95% CI, 0.79 to 2.25; I^2 = 0% All-cause mortality (fortified IF vs. fortified DHM, k = 2): RR, 1.53; 95% CI, 0.42 to 5.51; I^2 = 21% Short-term weight gain (g/kg/d) (fortified IF vs. fortified DHM, k = 2): mean difference 2.80; 95% CI, 1.20 to 4.39; I^2 = 0% Other outcomes Neurodevelopmental outcomes not reported for studies comparing fortified preterm IF to fortified DHM Retinopathy of prematurity not reported in any study Continuation of maternal breast milk feeding after hospital discharge not reported in any study	Only 2 RCTs (n = 219), conducted after 2000, compared fortified donor human milk and preterm formula, which are the current recommended options for feeding or supplementing preterm and low birthweight infants whose mothers do not produce sufficient maternal breast milk. Most studies excluded infants who were small for gestational age, had congenital anomalies, or gastrointestinal or neurological problems.

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
	primarily "drip" milk and 1984b used banked DHM) until infant reached 2000g or discharge Raiha (1976): term formula or unfortified DHM until infant reached 2.4kg or was withdrawn from study Schanler (2005): PIF vs. fortified DHM until 90d. or discharge Schultz (1980): term formula vs. DHM for at least 4 wks. *SR's quality assessment of individual studies:* Low to high risk of bias for assessed items, generally equating to fair to good methodological quality		
Williams et al. (2016) Search Dates Inception to October 2014 Included Study Designs	k = 10 non-randomized studies (8 retrospective and 2 prospective) Total n = 2381, of these n = 859 evaluated	Outcomes Any breastfeeding at discharge (after introduction of DHM vs. no availability of DHM in NICU) (k = 4, moderate to high methodological quality of studies as rated by systematic review authors) RR, 1.19; 95% CI, 1.06 to 1.35; no I^2 provided	Studies with varying infant inclusion criteria (<1 to <2 kg birthweight; outcome was exclusive breast milk feeding at discharge in 1 study)

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
Non-randomized studies Methodological Quality Fair	maternal breastfeeding (full or partial) at discharge Studies conducted in NICUs in U.S., U.K., Spain, and Australia Most infants were born at <32 weeks and under 1500g *SR's quality assessment of individual studies:* Low (2), moderate (7), high (1)	Exclusive breastfeeding at discharge (after introduction of DHM vs. no availability of DHM in NICU) (k = 2, low- to moderate-quality); RR, 1.12; 95% CI, 0.91 to 1.40; no I^2 provided	
Randomized Controlled Trials			
Corpeleijn et al. (2016) Study Length 2 months Location The Netherlands Methodological Quality Fair	n = 373 Mean birthweight 1,066 g Mean gestational age 28.4 weeks	Groups Fortified donor human milk vs. fortified preterm infant formula, either given in addition to any available maternal breast milk, for the first 10 days of life. Outcomes Combined outcome (NEC, sepsis or meningitis, death, from 3 to 60 days after birth): 42.1% vs. 44.7% Mean difference, 2.6%; 95% CI, -12.7% to 7.4% Adjusted HR, 0.87; 95% CI, 0.63 to 1.19	Babies in both groups received the vast majority of their total oral intake from their own mothers (IF group 89.1% and DHM group 84.5%). The intervention was short-term (10 days), further decreasing differences between actual treatment of subjects. There were relatively high losses to follow-up in this study (24.5% of the donor human milk group and 27.5% of the formula group). The study was

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		Secondary outcomes NEC: adjusted HR, 0.98; 95% CI, 0.64 to 2.05 Retinopathy of prematurity: 11.9% vs. 7.7%; adjusted OR, 1.77; 95% CI, 0.76 to 4.13	funded by a manufacturer of infant formula and fortifier.
O'Connor et al. (2016) Study Length 18 (corrected) months Location Canada Methodological Quality Good	n = 363 (299 for neurodevelopmental outcomes) Mean birthweight 996 g Mean gestational age 27.7 weeks	Groups Donor breast milk vs. preterm formula for 90 days or until discharge, when mother's milk not available Outcomes (at 18 months of corrected age) Neurodevelopment as measured by Bayley-III composite score, mean score: 92.9 vs. 94.5 Adjusted mean difference: -2; 95% CI, -5.8 to 1.8); p = 0.31 Secondary outcomes Bayley-III language, mean score: 87.3 vs. 90.3 Adjusted mean difference: -3.1; 95% CI,-7.5 to 1.3; p = 0.17 Bayley-III Motor, mean score: 91.8 vs. 94.0 Adjusted mean difference: -3.7; 95% CI,-7.4 to 0.09; p = 0.06 Mortality and morbidity index 43.1% vs. 40.1%, adjusted risk difference 5; 95% CI, -2.7 to 12.7; p = 0.20	5 points on the Bayley-III 100-point scale is considered the minimal clinically important difference. The Bayley-III scale is designed to screen for neurodevelopmental risk and is not a diagnostic tool.

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		Death 9.4% vs. 11.0%, adjusted risk difference -1.0; 95% CI, -9.7 to 7.6; p = 0.82 NEC 3.9% vs. 11.0%, risk difference -7.1; 95% CI, -12.5 to -1.8); p = 0.01 Severe retinopathy of prematurity 3.9% vs. 4.4%, risk difference -0.05; 95% CI, -4.6 to 3.6; p = 0.80	
Other Individual Studies			
Assad et al. (2016) (Retrospective cohort study) Study Length Data collected between 2009 and 2014, no data given about duration of feeding Location U.S. Methodological Quality Fair	n = 293 total, Mean birthweight not given, range was 490 to 1700g Mean gestational age given by group: H: 27.7 weeks B: 28.3 weeks M: 27.6 weeks F: 29.8 weeks	Groups Group H: Fortified donor human milk (human derived fortifier) vs. Group B: fortified donor human milk (bovine derived fortifier) vs. Group M: mixed feeding of maternal or donor milk (bovine fortifier)/formula vs. Group F: fortified preterm infant formula Outcomes Length of stay Compared to H group, M group had 22.9d. longer LOS (p<0.04); F group was 7.26 d. longer; B group was 4.5 d. longer (no absolute duration given, only relative figures; no statistical testing provided for the F and B groups compared to H group) Secondary outcomes	H group born March 2012 to 2014 Other groups born March 2009 to 2012. Epoch of birth not controlled in regression analyses. Authors state care and feeding protocols did not significantly change between 2009 and 2014. Study internally funded by hospital.

Citation, Study Details	# of Studies (k) Population (n) *Individual Study Quality*[a]	Study Summary and Findings	Comments
		NEC H group: 1.10% B plus M groups: 10.0% (p<0.01) F group: not reported Total cost of hospitalization (hospital plus physician charges—charges unavailable for 10 infants) H group: $237,647 B group: $265,035 M group: $344,618 F group: $266,825 Linear regression analysis adjusted for gestational age, difference between H and M groups p<0.001 Costs (physician charges plus cost of human derived fortifier in H group) H group: $91,112 B plus M groups: $116,878 F group: $105,603 Retinopathy of prematurity H group: 14% B group: 32% M group: 40% F group: not reported	

Abbreviations: IF is infant formula; DHM is donor human milk; HR is hazard ratio; LOS is length of stay; NEC is necrotizing enterocolitis; OR is odds ratio

Clinical Practice Guidelines

Center researchers identified no clinical practice guidelines that address the use of donor human milk for the treatment of low birthweight infants who do not have access to any or sufficient maternal breast milk. However, we did identify two policy statements from AAP that are relevant to this topic (AAP, 2012, 2017). If Center researchers had applied the Center's clinical practice guideline assessment instrument to these documents, they would have been rated as having poor methodological quality. Table 2 provides a summary of key statements regarding the use of donor human milk from these two position statements (AAP, 2012, 2017).

Table 2. Summary of American Academy of Pediatrics Policy Statements

Citation, Type of Document	Statement
AAP Policy Statement *Breastfeeding and the Use of Human Milk* (AAP, 2012)	"Mother's own milk, fresh or frozen, should be the primary diet, and it should be fortified appropriately for the infant born weighing less than 1.5 kg. If mother's own milk is unavailable despite significant lactation support, pasteurized donor milk should be used." (p. e831).
AAP Policy Statement *Donor Human Milk for the High-Risk Infant: Preparation, Safety, and Usage Options in the United States* (AAP, 2017)	From section on usage, Infants <1,500 g birthweight: "The supply of donor human milk currently available in the United States and Canada is less than optimal. Although a goal of providing donor milk to supplement the mother's milk for all preterm infants has been described, this goal may not be achievable for a period of time; thus, prioritization may be needed for infants weighing <1500 g. Relatively few data are available on whether this would include small for gestational age infants, such as those who are >32 to 33 weeks' postmenstrual age at birth who also weigh <1500 g; but, in general, the primary guide for use is birth weight, not gestational age, in prioritizing donor milk use. There are no clear guidelines for discontinuing the use of donor human milk in an infant <1500 g birth weight when the volume of mother's milk is not adequate. A range of postmenstrual ages from 32 to 36 weeks is commonly usedin the United States, because this range covers the highest risk period for necrotizing enterocolitis. Further research is needed to clarify the optimal timing of discontinuing donor human milk. Breastfeeding should be encouraged during hospitalization for these infants to enhance the likelihood of successful breastfeeding after hospital discharge" (p. 3). From Summary of Key Points: "Although a mother's own milk is always preferred, donor human milk may be used for high-risk infants when the mother's milk is not available or the mother cannot provide milk. Priority should be given to providing donor human milk to infants <1500 g birth weight" (p. 4).

Payer Policies

Center researchers searched for payer policies on the coverage of donor human milk from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physician's Health Plan, Cigna, Emblem Health, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare, Centers for Medicare & Medicaid Services, and nine state Medicaid agencies (CA, FL, MA, NJ, NY, OR, PA, TX, WA).

Private Payers

None of the 10 private payers searched had a policy covering donor human milk, and three explicitly excluded coverage (Aetna, 2017; Cigna, 2016; Tufts Health Plan, 2016) (Table 4). Cigna's nutritional support coverage policy excludes donor human milk because of uncertainty about adequate screening and associated risks of infectious disease and contamination (Cigna, 2016). Additionally, Cigna does not consider breast milk a medical food because it is not necessary for the dietary management of a disease or condition (Cigna, 2016). Aetna and Tufts Health Plan list banked breast milk under the excluded products in their oral formula (Tufts Health Plan, 2016) and nutritional support (Aetna, 2017) policies.

Center staff identified one private payer that covers donor human milk. AmeriHealth Caritas (2017) considers donor human milk medically necessary for infants at risk of necrotizing enterocolitis, at risk for malabsorption, or for whom the mother's breast milk is contraindicated or otherwise unavailable (Table 4).

Public Payers

Medicare

Center researchers identified no national or local coverage determinations on donor human milk.

Medicaid

Five states (California, Missouri, Kansas, Texas, and Utah) and the District of Columbia had Medicaid coverage for donor human milk in 2016 (National Conference of State Legislatures, 2016).

Of the nine state Medicaid agencies searched from the group of New York's comparator states (CA, FL, MA, NJ, NY, OR, PA, TX, WA), only California and Texas cover donor human milk (Table 3). California Medicaid's policy is not publicly available, but staff from the Mother's Milk Bank of San Jose provided Center researchers information on eligibility, documentation, and billing for donor human milk (P. Sakamoto, personal communication, April 12, 2017), and confirmed coverage of donor human milk in a publication from the California Women, Infants, and Children's (WIC) Program (California WIC Association, 2012). Texas Medicaid's policy has different eligibility, documentation, and prior authorization for inpatient and outpatient use of

donor human milk (Texas Medicaid & Healthcare Partnership, 2017). Both states require donor human milk to be medically necessary, but the specific medical necessity criteria are not included in the publicly available policies. Center researchers identified donor human milk policies from three additional state Medicaid agencies (Kansas, Missouri, and Utah) and the District of Columbia (Table 3) (District of Columbia Medicaid Program - Department of Health Care Finance, 2014; Kansas Medicaid Drug Utilization Review Board, 2015; Missouri General Assembly, 2016; Utah Division of Medicaid and Health Financing, 2016).

Eligibility

The Medicaid policies vary in the patients and settings under which they cover donor human milk. Kansas (Kansas Medicaid Drug Utilization Review Board, 2015) and Missouri (Missouri General Assembly, 2016) only cover infants 3 months or younger who are in the NICU, whereas Utah (Utah Division of Medicaid and Health Financing, 2016) and the District of Columbia (District of Columbia Medicaid Program - Department of Health Care Finance, 2014) provide coverage only for infants in the home setting, for up to one year. Texas (Texas Medicaid & Healthcare Partnership, 2017) covers hospitalized infants under 6 months old and outpatients up to one year, with outpatient coverage extended for children up to age 21 with documentation of medical necessity. Texas (outpatients only) and the District of Columbia require a feeding trial of an appropriate nutritional product every 180 days, or documentation that an infant is too fragile to attempt a trial (District of Columbia Medicaid Program - Department of Health Care Finance, 2014; Texas Medicaid & Healthcare Partnership, 2017).

Documentation

All of the Medicaid policies required a prescription by a licensed health care provider and documentation of medical necessity. The specifics of medical necessity varied somewhat, but in general require that the physician explain why the infant cannot survive and grow on any appropriate formula and that the mother cannot supply the breast milk. The policies also require informed consent with documentation that the risks of donor human breast milk have been discussed with the parent or guardian.

Milk Bank Requirements

Policies specified that donor milk must be obtained from a milk bank meeting quality standards established by each state, such as certification by the Human Milk Bank Association of North America.

Prior Authorization

Prior authorization is required by all of the Medicaid agencies. Texas requires prior authorization for outpatients but not inpatients (Texas Medicaid & Healthcare Partnership, 2017). The agencies that cover donor breast milk in the home settings (Texas, Utah, and DC) require reauthorization every 180 days (District of Columbia Medicaid Program - Department of Health Care Finance, 2014; Texas Medicaid & Healthcare Partnership, 2017; Utah Division of Medicaid and Health Financing, 2016).

Billing and Reimbursement

The HCPCS code T2101 (human breast milk processing, storage, and distribution only) is used for reimbursement for donor human breast milk. For inpatients, Texas requires that hospitals bill revenue code 220 (special charges) with the procedure code T2101; code B9998 (enteral nutrition, not otherwise classified) is used for outpatients (Texas Medicaid & Healthcare Partnership, 2017). Reimbursement rates per ounce ranged from $2.20 (Texas) to $3.30 (District of Columbia).

Table 3. Donor Human Milk Policies in State Medicaid Programs

State	Policy Details
California	Eligibility Information on Medicaid eligibility requirements not available. Donor milk usually used for infants in neonatal intensive care units, or infants who are: • Failing to thrive on formula • Facing life-threatening diseases or conditions with failing immune systems or catastrophic diseases • Whose mothers can't keep up the milk to nourish multi-birth babies • Whose mothers aren't producing enough milk during the first week of life • Whose mothers aren't able to produce enough milk for their baby's demand • Adopted by families who believe in the value of breast milk • Born to mothers whose breast milk isn't suitable for consumption, either because of disease or prescription medications that pass through the milk Documentation • Inpatients: Prescribing doctors submit a Hospital Request Form to Mothers' Milk Bank. • Outpatients: Prescription to Mothers' Milk Bank, including o Name of infant, address and diagnoses o Parent name and phone number or email o Request "donor human milk" o How many ounces per day, week, or month is needed o Prescriptions must be written on a prescription notepad and signed off by the doctor or nurse practitioner Milk Bank Requirements Only one milk bank operates in the state (Mother's Milk Bank of San Jose) Reimbursement • HCPCS code T2101 • $2.94 per ounce
District of Columbia	Eligibility Infants, age 0 through 11 months of age, provided all of the criteria are met:

State	Policy Details
	• The requesting physician is the infant's treating physician and has documented medical necessity. The documentation must address all of the following criteria: o Why the particular infant cannot survive and grow as expected on any other formula (e.g., elemental, special, or routine formulas or food) or any enteral nutritional product other than donor human milk o Why donated human milk must be used to correct or ameliorate a documented condition or defect o That a clinical feeding trial of an appropriate nutritional product has occurred every 180 days. If the infant is too fragile for a feeding trial, documentation must support the illness that makes the infant too fragile to test. o That the informed consent details for the parent or guardian the risks and benefits of using banked donated human milk • The requesting physician has addressed the benefits and risks of using donated human milk, such as HIV, freshness, effects of pasteurization, nutrients, and growth factors to the parent/guardian. The physician also must address donor screening, pasteurization, milk storage, and transport of the donated milk. The physician may obtain this information from the donor milk bank. • The parent or guardian has signed and dated an informed consent form indicating the risks and benefits of using banked donated human milk have been discussed with them. Documentation The treating physician must submit the Donor Human Milk Request Form every 180 days documenting the infant's medical necessity for breast milk. Copies of the Donated Human Milk Request Form must be maintained in the infant's records of both the ordering physician and the providing milk bank. The information submitted to establish that donated human breast milk is medically necessary must be substantiated by written documentation in the infant's clinical record maintained by the treating physician. Records are subject to retrospective review by DHCF or its designee. Milk Bank Requirements Enrolled as a Medicaid Provider in the District of Columbia and is certified by the Human Milk Bank Association of North America or meets such other standards as may be adopted by DHCF. Prior Authorization A request for authorization must be completed and signed by the treating physician every 180 days and expires on the infant's first birthday. A request for authorization must specify the quantity and time frame. Reimbursement Donated human milk is reimbursed only to a DHCF Medicaid-enrolled donor milk bank and only for infants in the home setting. • Procedure code T2101 • $3.30 per ounce

State	Policy Details
Kansas	Eligibility • Infant is under three months of age, critically ill, and in the neonatal intensive care unit of a hospital and o The milk was ordered by a person licensed to practice medicine and surgery; o KDHE determined the milk was medically necessary for the infant; o An informed consent form indicating the risks and benefits of using banked milk was signed and dated by the infant's parent or legal guardian; and o The milk was obtained from a milk bank that meets the quality requirements established by KDHE. Prior Authorization The KDHE is required to utilize an electronic prior authorization system that uses the best medical evidence and care and treatment guidelines consistent with national standards to determine medical necessity. In addition, the KDHE is required to promulgate rules and regulations deemed necessary to administer the provisions regarding reimbursement for prescribed milk prior to July 1, 2016
Missouri	Eligibility • The participant is an infant under the age of three months • The participant is critically ill • The participant is in the neonatal intensive care unit of the hospital • A physician orders the milk for the participant • The department determines that the milk is medically necessary for the participant Documentation Requirements The parent or guardian signs and dates an informed consent form indicating the risks and benefits of using banked donor human milk Milk Bank Requirements The milk is obtained from a donor human milk bank that meets the quality guidelines established by the department. Prior Authorization An electronic web-based prior authorization system using the best medical evidence and care and treatment guidelines consistent with national standards shall be used to verify medical need.
Texas	Eligibility Inpatients: Age 6 months and younger Outpatients: Age through 11 months; may be extended through 20 years with documentation of medical necessity

State	Policy Details
	Documentation Inpatients: • Hospitals must follow clinical recommendations for administering donor human milk to inpatient clients and maintain all applicable and appropriate medical necessity documentation in the client's medical record Outpatients: • Requesting physician documents medical necessity and appropriateness, including why the particular client cannot survive and gain weight on any appropriate formula (e.g., elemental, special, or routine formula or food), or any enteral nutritional product other than donor human milk. • A clinical feeding trial of an appropriate nutritional product has been considered with each authorization. • Parent or guardian consent form detailing the risks and benefits of using banked donor human milk • The physician must address the benefits and risks of using donor human milk, such as HIV, freshness, effects of pasteurization, nutrients, and growth factors to the parent. The physician also must address donor screening, pasteurization, milk storage, and transport of the donor milk. The physician can obtain this information from the donor milk bank. Milk Bank Requirements • Texas Medicaid-enrolled donor milk bank • Adheres to quality guidelines consistent with the Human Milk Bank Association of North America or other standards that may be adopted by Texas Health and Human Services Commission Limits • Maximum 6 months per authorization • Can be extended with documentation of medical necessity Prior Authorization • Inpatients: Not required • Outpatients: Required. Providers must complete a Prior Authorization Request Form and a Donor Human Milk Request Form every 180 days Reimbursement Inpatients: • The hospital must bill revenue code 220 (special charges) with procedure code T2101 as an outpatient hospital service with the most appropriate outpatient type of bill. • Must indicate number of ounces

State	Policy Details
	• $2.00 per ounce Outpatients: • Procedure code B9998 • Reimbursed at a maximum fee determined by HHSC or manual pricing • Donor human milk is only reimbursed to a Texas Medicaid-enrolled donor milk bank and only for children who are in the home setting
Utah	Eligibility Medicaid coverage for donor human milk applies to members residing in a home setting. All of the following criteria must be met: • Member is Medicaid eligible and age birth through 11 months • The requesting prescriber is the infant's treating practitioner • Completed feeding trial • The requesting prescriber has addressed with the parent or guardian the benefits and risks of using donated milk, such as HIV, freshness, effects of pasteurization, nutrients, growth factors • The prescriber has given the parent or guardian information concerning donor screening, pasteurization, milk storage, and transport of the donated milk. (The prescriber may obtain this information from the donor milk bank.) • An informed consent signed and dated by the parent or guardian, outlining the risks and benefits using banked donor human milk. (The consent is usually signed in the hospital.) Milk Bank Requirements The provider must be a donor human milk bank certified by the Human Milk Bank Association of North America and enrolled as a Utah Medicaid provider. Prior Authorization To request a PA, the infant's treating physician will submit: • Request for Prior Authorization form • Donor Human Milk Request Form [https://medicaid.utah.gov/utah-medicaid- forms] • Documentation supporting the finding that donated human breast milk is medically necessary for the intended recipient and why the mother cannot supply the breast milk The request must be resubmitted every 180 days.

Sources: (California WIC Association, 2012; District of Columbia Medicaid Program - Department of Health Care Finance, 2014; Kansas Medicaid Drug

Utilization Review Board, 2015; Missouri General Assembly, 2016; Texas Medicaid & Healthcare Partnership, 2017; Utah Division of Medicaid and Health Financing, 2016)

Table 4. Payer Policies on Donor Human Milk

Payer	Information Identified
Medicare	
National coverage database	No local or national coverage determinations identified
Private Payers	
Aetna (*last review 3/3//2017)*	Aetna does not cover banked breast milk, food supplements, specialized infant formulas, vitamins, and/or minerals taken orally (i.e., by mouth). Aetna does not cover nutritional support that is taken orally (i.e., by mouth), unless mandated by state law. Oral nutrition is not considered a medical item.
AmeriHealth Caritas	AmeriHealth Caritas Northeast considers the use of donor human milk to be clinically proven and, therefore, medically necessary when any of the following criteria are met: A. Infant at risk for necrotizing enterocolitis, i.e., fulfills at least one of the following criteria: • Very low birth rate equal to or less than 1500g • Infant born at or before 28 weeks of gestation, and is under six months old infant suffers from gastrointestinal anomaly, metabolic/digestive disorder, or is recovering from intestinal surgery where digestive needs require additional support. C. Infant at risk for malabsorption. D. If mother's breast milk is contraindicated or otherwise unavailable Limitations: All other uses of donor human milk are not medically necessary Alternative covered services: Lactation specialists within network
Anthem	No information identified
Blue Shield of Northeastern New York	No information identified
Capital District Physician's Health Plan	No information identified
Cigna (*effective 9/15/2016*)	Breast milk is a standard food for infants and young children including premature and sick newborns. In some cases human breast milk may be recommended for the infant of a mother who is unable to use or produce her own breast milk. Donor milk

Payer	Information Identified
	banks have been established to meet these needs when maternal milk is unavailable. According to the U.S. Food and Drug Administration (FDA), "When human milk is obtained directly from individuals or through the Internet, the donor is unlikely to have been adequately screened for infectious disease or contamination risk" (FDA, 2015). The FDA stated that there are potential risks associated with disease transmission, contamination, or exposure to untoward substances contained within donor milk. Aside from the safety issues, breast milk is non-medical food. As such, it is not considered to be necessary for the dietary management of a disease or condition.
Emblem Health	No information identified
Empire BCBS	No information identified
Excellus BCBS	No information identified
Tufts Health Plan (*effective 9/14/2016*)	Tufts Health Plan may not authorize oral formula for any of the following: Banked breast milk
UnitedHealthcare	No information identified
State Medicaid	
California (5/2014)	No Medicaid policy identified. Information from Mother's Milk Bank of San Jose detailed in Table 3 above
District of Columbia	See detailed information in Table 3 above
Florida	No information identified
Kansas	See detailed information in Table 3 above
Massachusetts	No information identified
Missouri	See detailed information in Table 3 above
New Jersey	No information identified
New York	Assembly bill vetoed November 2016
Oregon (5/2016)	No information identified
Pennsylvania	No information identified
Texas	See detailed information in Table 3 above
Utah	See detailed information in Table 3 above
Washington	Found only "Sunrise Review" performed in 2015: (explained here): http://www.doh.wa.gov/AboutUs/ProgramsandServices/HealthSystemsQualityAssurance/SunriseReviews) http://www.doh.wa.gov/Portals/1/Documents/2000/ApplicantReport-BankedMilk.pdf

Payer	Information Identified
	http://www.doh.wa.gov/Portals/1/Documents/2000/DonorMilkSunriseReq.pdf No department coverage policy identified

Conclusion

Significantly preterm and low birthweight infants are susceptible to health conditions such as NEC, retinopathy of prematurity, death, disability, and neurodevelopmental problems. Feeding has an important role to play in the care of these babies in the NICU. Fortified breast milk has been demonstrated to improve many outcomes compared to formula feeding (Quigley & McGuire, 2014). Many mothers of premature infants will not be able to produce enough of their own breast milk to be used as the sole nutrition source for their infant. Pasteurized fortified donor human milk and preterm infant formula are both used to feed infants who have insufficient maternal milk available to meet their needs or for whom no maternal milk is available. This review addresses the question of comparative effectiveness of these interventions. Donor human milk could help to prevent NEC and could have a beneficial effect on the rate of maternal breast feeding at NICU discharge. Current evidence does not support a difference between donor milk and formula for retinopathy of prematurity or other outcomes such as neurodevelopment or mortality. There is very low strength of evidence that the use of donor milk decreases the length of stay based on one retrospective cohort study of fair methodological quality. It is possible that donor human milk decreases the short-term growth rate of preterm and low birthweight infants, but there is not adequate evidence from contemporary studies to examine longer-term growth. Center researchers did not locate any eligible data on the cost-effectiveness of donor human milk, but one retrospective, single institution study found that donor milk decreased total costs and NICU length of stay. There are no clinical practice guidelines that address the use of donor human milk in the NICU setting, but two AAP position papers recommend its use. Some state Medicaid programs cover donor human milk, but Center researchers found only one private insurer that did so.

Strength of Evidence

The Center uses the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group approach to enhance consistency in rating the strength of evidence. RCTs are initially categorized as having high strength of evidence and observational studies are categorized as having low strength of evidence. The strength rating is downgraded one or two levels based on limitations including inconsistency of results, uncertainty of directness of measurement or population, imprecise or sparse data, and high probability of reporting bias. The rating is upgraded one or two levels from the starting point of low for evidence from observational studies if there is a strong association,[1] a very strong association,[2] or a dose-response gradient. The rating is also upgraded if all plausible confounders would have reduced

[1] Significant relative risk of >2 or <0.5 with no plausible confounders in two or more observational studies.

[2] Significant relative risk of >5 or <0.2 based on direct evidence with no major threats to validity.

the effect (Guyatt et al., 2008; Schünemann, Brozek, Guyatt, & Oxman, 2014). Table 5 provides an overview of the strength of evidence by outcome and associated rationale for the strength of evidence rating.

Table 5. Strength of Evidence for Donor Human Milk for Low Birthweight Infants

Outcome	Strength of Evidence Assessment	Rationale
Primary outcomes		
Necrotizing enterocolitis	Moderate	Use of donor milk rather than preterm formula may be protective against development of NEC based on a systematic review that included 2 RCTs comparing currently used interventions and 2 additional RCTs. Only one of the RCTs (O'Connor et al., 2016) found a statistically significant difference favoring donor human milk. The systematic review (Quigley & McGuire, 2014) did not find a statistically significant benefit, and the other RCT (Corpeleijn et al., 2016) found a small increased risk that was not statistically significant. In this RCT (Corpeleijn et al., 2016) the intervention was given for only 10 days and rates of maternal milk use were high. These factors may also contribute to indirectness. When the results of the 2 more recent RCTs (Corpeleijn et al., 2016; O'Connor et al., 2016) are incorporated into the Cochrane review (Quigley & McGuire, 2014), it is likely that the combined evidence would definitively favor donor human milk for prevention of NEC. However, given that findings were somewhat inconsistent, strength of evidence is downgraded one level.
NICU length of stay	Very low	Limited evidence from one retrospective cohort study of fair methodological quality favoring donor milk.
Post-hospitalization breastfeeding rate	Low	Limited evidence in fair-quality SR of low to high methodological quality primary studies that the use of donor milk appears to increase rates of maternal breast milk feeding at NICU discharge.
Retinopathy of prematurity	Low	No difference identified between interventions.
Cost/Cost-effectiveness	Very low (cost) None (cost-effectiveness)	Limited evidence, favoring donor milk, from one retrospective cohort study of fair methodological quality regarding relative cost, but no evidence identified on cost-effectiveness.
Other outcomes		
Mortality	Low	No differences identified between interventions.
Neurodevelopment	Moderate	No differences identified between interventions.

Outcome	Strength of Evidence Assessment	Rationale
Growth	Moderate (short term) Very low (long term)	Short-term growth is slightly decreased in infants who are fed donor breast milk. There are no long-term studies of infants receiving fortified donor milk vs. preterm formula, but older studies that did not use fortified donor milk did not find differences in growth.

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Appendix A. Methods

General Search Strategy

Evidence

A full search of the Center's core clinical evidence primary sources was conducted to identify systematic reviews and meta-analyses and technology assessments using search terms for donor human milk. Searches of core sources were limited to citations published after 2007. Center researchers also searched the MEDLINE (Ovid) database for relevant systematic reviews and meta-analyses or technology assessments, and for individual studies published after the search dates of the identified systematic reviews, and cost-effectiveness studies published after 2007.

The core sources searched included:

Agency for Healthcare Research and Quality (AHRQ)

BMJ Clinical Evidence

Cochrane Library (Wiley Interscience)

National Institute for Health and Care Excellence (NICE)

PubMed Health

Tufts Cost-Effectiveness Analysis Registry

Veterans Administration Evidence-based Synthesis Program (ESP)

Washington State Health Technology Assessment Program

Clinical Practice Guidelines

Center researchers conducted a full search of Center clinical practice guidelines primary sources to identify clinical practice guidelines using the terms *donor milk* and *breast milk or breastfeeding*. Searches were limited to citations published within the last five years.

The guideline sources included:

Australian Government National Health and Medical Research Council (NHMRC)

Centers for Disease Control and Prevention (CDC) – Community Preventive Services

Institute for Clinical Systems Improvement (ICSI)

National Guidelines Clearinghouse

National Institute for Health and Care Excellence (NICE)

New Zealand Guidelines Group

Scottish Intercollegiate Guidelines Network (SIGN)

United States Preventive Services Task Force (USPSTF)

Veterans Administration/Department of Defense (VA/DOD)

American Academy of Pediatrics (AAP)

Academy of Breastfeeding Medicine (ABM)

Coverage Policies

Center researchers searched for policies on the coverage of donor human milk for the treatment of preterm and low birthweight infants from Aetna, Anthem, Blue Shield of Northeastern New York, Capital District Physician's Health Plan, Centers for Medicare and Medicaid Services, Cigna, Emblem Health, Empire BCBS, Excellus BCBS, Tufts Health Plan, UnitedHealthcare, and nine state Medicaid programs (CA, FL, MA, NJ, NY, OR, PA, TX, WA).

General Exclusion Criteria

Center researchers excluded studies that were not systematic reviews, meta-analyses, technology assessments, or individual studies that were published before 2007, or were published in a language other than English. Studies and guideline citations, abstracts, and full-text were reviewed independently by two Center researches for inclusion or exclusion.

Quality Assessment

Two Center researchers assessed the methodological quality of the included studies using standard instruments developed and adapted by the Center that are modifications of the systems in use by the Campbell Collaboration, Cochrane, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN) (Campbell Collaboration, 2015; Cochrane Collaboration, 2011; Guyatt et al., 2008; Moher, Liberati, Tetzlaff, & Altman, 2009; National Institute for Health and Care Excellence, 2014; Scottish Intercollegiate Guidelines Network, 2009). Two Center researchers independently rated all studies. In cases where there was not agreement about the quality of a study, consensus was reached through discussion.

Each rater assigned the study a rating of good, fair, or poor, based on its adherence to recommended methods and potential for biases. In brief, good methodological -quality systematic reviews include a clearly-focused question, a literature search sufficiently rigorous to identify all relevant studies, criteria used to select studies for inclusion (e.g., RCTs) and assess study quality, and assessments of heterogeneity to determine if a meta-analysis would be appropriate. Good methodological quality RCTs include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good methodological quality systematic reviews and RCTs also have low potential for bias from conflicts of interest and

funding source(s). Fair methodological quality systematic reviews and RCTs have incomplete information about methods that might mask important limitations. Poor methodological quality systematic reviews and RCTs have clear flaws that could introduce significant bias.

Specific Search Details

The search terms *donor milk*, and *breastfeeding* were used in the remaining core source searches. Archived government reports were not included.

Inclusion Criteria

Populations: Very low (i.e., less than 1,500 grams) and low birthweight infants (i.e., less than 2,500 grams) (usually corresponding to gestational age less than 32 weeks)

Intervention: Donor human milk (from an accredited milk bank)

Comparator: Infant formula

Efficacy and Effectiveness Outcomes: Incidence of NEC; NICU length of stay; retinopathy of prematurity; mode of feeding after hospital discharge; cost or cost-effectiveness

Exclusion Criteria

The following were the study exclusion criteria:

- Studies published before 2007
- Studies published in languages other than English
- Duplicate information from a research study published in more than one source (only the highest quality, most recent publication with outcome of interest was included)
- Systematic reviews (SR) that included only studies that were summarized by more comprehensive SRs or SRs of higher quality and/or that were more recently published
- Individual studies identified that were included in a summarized SR or technology assessment (TA)
- SR or TA, or individual study of poor methodological quality

MEDLINE (Ovid) Search

The MEDLINE search strategy was adapted from the Cochrane systematic review (Quigley & McGuire, 2014). Eligible primary studies published after the search dates (2014 and later) of the Cochrane systematic review (Quigley & McGuire, 2014) were included to update the existing systematic reviews.

1 Infant, Very Low Birth Weight/ or Infant, Premature/ or Infant, Low Birth Weight/ or Infant, Newborn/
2 (infan$ or neonat$ or preterm or prem$).mp.

3 1 or 2
4 exp Infant Nutritional Physiological Phenomena/
5 Infant Formula/
6 (milk or formula).mp.
7 4 or 5 or 6
8 3 and 7
9 limit 8 to english language
10 limit 9 to yr="2014 -Current"
11 limit 10 to (case reports or comment or editorial or interview or lectures or letter or news or newspaper article or webcasts)
12 10 not 11
13 limit 12 to (meta analysis or systematic reviews or technical report)
14 (systematic review$ or meta analys$ or technology assessment).mp.
15 12 and 14
16 13 or 15
17 ((randomi$ adj3 trial) or RCT).mp.
18 limit 12 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or randomized controlled trial)
19 12 and 17
20 18 or 19
21 (donor adj3 milk).mp.
22 16 and 21
23 20 and 21

Economic Studies (search conducted 4-26-17)
1 economic* or cost*.m_titl.
2 (donor$ adj5 milk) or human milk.mp.
3 1 and 2
4 limit 3 to english language
5 limit 4 to yr="2007 -Current"

Appendix B. Articles Selected for Full Text Review and Inclusion/Exclusion Rationale

Table B1. Articles Selected for Full Text Review

Citation	Inclusion/Exclusion Rationale
Systematic Reviews	
Quigley and McGuire (2014)	Include (eligible SR)
Williams et al. (2016)	Include (eligible SR)
Boyd et al. (2007)	Exclude (SR): Superseded by more recent and/or comprehensive systematic reviews
Cacho et al. (2017)	Exclude (narrative SR of all study designs): Superseded by more comprehensive systematic reviews (1 recent retrospective cohort study, Chowning et al. (2016), retrieved from bibliography for individual study review)
Chowning et al. (2016)	Exclude: Data not extractable
Lechner and Vohr (2017)	Exclude: Narrative review
Johnson, Patel, Bigger, Engstrom, and Meier (2014)	Exclude: Narrative review
Manzoni et al. (2013)	Exclude: Data not extractable
Smith (2013)	Exclude: narrative review; does not discuss DHM
Zhou et al. (2015)	Exclude (SR): Intervention (4 of 5 included cohort studies used EMM and in the 5th there was no separation of EMM vs. DHM use)
Individual Studies	
Assad et al. (2016)	Include (eligible observational study)
Corpeleijn et al. (2016)	Include (RCT published after Quigley SR)
O'Connor et al. (2016)	Include (RCT published after Quigley SR)
Herrmann and Carroll (2014); Unger, Gibbins, Zupancic, and O'Connor (2014)	Protocol for O'Connor RCT, included, but not as separate study
Kantorowska et al. (2016)	Exclude after full text review and QA: poor methodological quality
Mahon et al. (2016)	Exclude after full text review and QA (economic modeling study): poor methodological quality
Parker et al. (2016)	Exclude after full text review and QA: poor methodological quality

Citation	Inclusion/Exclusion Rationale
Parker, Krueger, Sullivan, Kelechi, and Mueller (2012)	Exclude: Not clear whether includes use of DHM, data not extractable
Patel et al. (2013)	Exclude: Data not extractable
Renfrew et al. (2009)	Exclude: Interventions do not include DHM
Johnson, Patel, Bigger, Engstrom, and Meier (2015)	Exclude: Non-comparative
Jegier, Meier, Engstrom, and McBride (2010)	Exclude: does not discuss DHM
Jegier et al. (2013)	Exclude: does not discuss DHM
Butler, Szekely, and Grow (2013)	Exclude: Interventions do not include DHM
Verd et al. (2015)	Exclude after full text review and QA: poor methodological quality

Abbreviations: SR is systematic review; RCT is randomized controlled trial.

Appendix C. List of Ongoing Trials

Search terms used for www.clinicaltrials.gov database: 1) "breast milk" and condition: weight; exclude trial with publications; 2) "donor milk" condition: Weight.

For the two studies listed with completion dates of 2014 and 2016, no published results were available.

Registered Clinical Trial Number	Title of Study	Study Completion Date indicated on https://clinicaltrials.gov/
NCT01534481 (U.S.)	Donor milk vs. formula in extremely low birth weight (ELBW) infants	June 2018
NCT02216292 (Austria)	Impact of preterm single donor milk in very low birth weight infants	June 2014
NCT01204983 Non-randomized study (U.S.)	Quality improvement project – Evaluation of current standard of care for feeding practices in the NICU	July 2018
NCT01390753 (Argentina)	Role of human milk bank in the protection of severe respiratory disease in very low birth weight premature infants	December 2016

About the Center for Evidence-based Policy and the Medicaid Evidence-based Decisions Project

The Center for Evidence-based Policy (Center) is recognized as a national leader in evidence-based decision making and policy design. The Center understands the needs of policymakers and supports public organizations by providing reliable information to guide decisions, maximize existing resources, improve health outcomes, and reduce unnecessary costs. The Center specializes in ensuring that diverse and relevant perspectives are considered and appropriate resources are leveraged to strategically address complex policy issues with high-quality evidence and collaboration. The Center is based at Oregon Health & Science University in Portland, Oregon.

The Medicaid Evidence-based Decisions Project (MED) is housed at the Center. Its mission is to create an effective collaboration among Medicaid programs and their state partners for the purpose of making high-quality evidence analysis available to support benefit design and coverage decisions made by state programs. Further information about MED and the Center is available at http://centerforevidencebasedpolicy.org/.

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